

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022416Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 022416

SUPPL #

HFD # 120

Trade Name Aptiom

Generic Name eslicarbazepine acetate

Applicant Name Sunovion Pharmaceuticals Inc.

Approval Date, If Known November 8, 2013

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(1) NDA

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

YES NO

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

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

d) Did the applicant request exclusivity?

YES NO

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

5 years; new molecular entity

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

YES NO

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

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

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

YES NO

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES NO

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES NO

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

NDA#

NDA#

NDA#

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

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If

the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

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

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

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

YES NO

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

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

YES NO

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

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently

demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

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

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

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

Investigation #1 YES NO

Investigation #2

YES

NO

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

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

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

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

Investigation #1

IND #

YES

!

!

! NO

! Explain:

Investigation #2

IND #

YES

!

!

! NO

! Explain:

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

/s/

SU-LIN SUN
11/08/2013

ELLIS F UNGER
11/14/2013

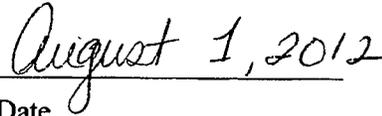
1.3. Administrative Information

3. DEBARMENT CERTIFICATION

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



Karen Joyce
Director, Regulatory Affairs



Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 022416 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Aptiom Established/Proper Name: eslicarbazepine acetate Dosage Form: tablets (200mg, 400mg, 600mg, 800mg)		Applicant: Sunovion Pharmaceuticals Inc. Agent for Applicant (if applicable): Ms. Karen Joyce
RPM: Su-Lin Sun, PharmD		Division: Neurology Products
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>	<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>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.</p>	
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is November 11, 2013 	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR	
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 	<input checked="" type="checkbox"/> Incomplete Response (11/02/2012) <input checked="" type="checkbox"/> CR (04/30/2010)	

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

² For resubmissions, (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).

<p>❖ 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 _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics ³</p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard (6months for resubmission) + 3 months major amendment extension <input type="checkbox"/> Priority Chemical classification (new NDAs only): 1</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC </p> <p> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies </p> <p> <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request </p> <p> BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies </p> <p> REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required </p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input checked="" type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

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. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>CONTENTS OF ACTION PACKAGE (section # 1)</p>	
<p>❖ Copy of this Action Package Checklist⁴</p>	<p>11/08/2013</p>
<p>Officer/Employee List (section # 2)</p>	
<p>❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)</p>	<p><input checked="" type="checkbox"/> Included</p>
<p>Documentation of consent/non-consent by officers/employees</p>	<p><input checked="" type="checkbox"/> Included</p>
<p>Action Letters (section #3)</p>	
<p>❖ Copies of all action letters (<i>including approval letter with final labeling</i>)</p>	<p>Approval letter 11/08/2013 Review extension-Major Amendment 5/8/13 Acknowledge-class 2 response-2/22/2013 Acknowledge Incomplete Response 11/02/2012 Complete Response 04/30/2010 Major amendment extension-12/4/09 (first cycle) Filing communication—6/12/2009 (first review cycle) NDA Acknowledgement letter-05-2009</p>

⁴ Fill in blanks with dates of reviews, letters, etc.

Labeling (section # 4)	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	11/7/2013 (final agreed PI) 10/25/2013
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	02/10/2013 (2 nd resubmission) 09/04/2012 (1 st resubmission)
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	n/a
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input checked="" type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	Same as package insert section
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	Same as package insert section
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	n/a
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
<ul style="list-style-type: none"> • Most-recent draft labeling 	11/07/2013 (final agreed carton and container labels) 02/10/2013 (2 nd resubmission) 09/04/2012 (1 st resubmission)
❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i> • Review(s) <i>(indicate date(s))</i> • <i>Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.</i> 	Proprietary Name request conditionally acceptable letter—11/1/2013 Proprietary name request unacceptable letter—8/4/2013 Memorandum of teleconference: 07/30/2013 Acknowledge Proprietary name withdrawal: 05/15/2013 Memorandum of Teleconference -050813 Review—10/23/2013; 8/14/2013 Proprietary name Granted – 07/10/09 (first cycle review) 7/2/09 (first cycle)
❖ Labeling reviews <i>(indicate dates of reviews and meetings)</i>	<input checked="" type="checkbox"/> RPM 5/9/13 <input checked="" type="checkbox"/> DMEPA 10/31/13; 09/13/13 2/28/10 (first cycle review) <input checked="" type="checkbox"/> DMPP/PLT (DRISK) 10/18/13 <input checked="" type="checkbox"/> ODPD (DDMAC) 10/24/13; 05/30/13; 11/21/12; (Advisory for Launch Professional Letter)

	<input checked="" type="checkbox"/> SEALD 11/5/2013 <input checked="" type="checkbox"/> CSS -see CSS review memo
Administrative / Regulatory Documents (section #5)	
<ul style="list-style-type: none"> ❖ Administrative Reviews (e.g., RPM Filing Review⁵/Memo of Filing Meeting) (indicate date of each review) ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (indicate date) 	3/16/2010 RPM filing review (first cycle) <input type="checkbox"/> Not a (b)(2) <input type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (signed by Division Director) 	<input checked="" type="checkbox"/> Included 11/14/13
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm <ul style="list-style-type: none"> • Applicant is on the AIP • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (indicate date) ○ If yes, OC clearance for approval (indicate date of clearance communication) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (approvals only) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>10/16/2013</u> If PeRC review not necessary, explain: • Pediatric Page/Record (approvals only, must be reviewed by PERC before finalized) 	PeRC meeting minute 10/29/13 Pediatric record # 2145 <input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (include certification) 	<input checked="" type="checkbox"/> Verified, statement is acceptable
<ul style="list-style-type: none"> ❖ Outgoing communications (letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons) 	11/08/13; 11/07/13; 11/06/13; 11/05/13; 11/05/13; 11/01/13; 10/31/13; 10/31/13; 10/29/13; 10/25/13; 10/24/13; 10/24/13; 10/22/13; 10/17/13' 10/8/13; 10/04/13; 9/24/13; 9/23/13; 9/13/13 ;9/13/13; 8/26/13; 8/23/13; 8/23/13; 8/12/13; 8/7/13; 8/2/13; 7/24/13; 7/11/13; 6/28/13; 6/27/13; 6/17/13; 6/17/13; 6/17/13; 6/13/13; 6/13/13; 6/7/13; 6/6/13; 5/31/13; 5/15/13; 5/14/13; 5/3/13; 5/2/13; 4/25/13; 4/24/13; 4/17/13; 4/17/13; 4/16/13; 4/4/13; 3/28/13; 3/27/13; 3/21/13; 3/19/13 ;3/18/13; 3/13/13; 3/8/13; 3/8/13; 2/25/13; 2/22/13; 2/15/13; 12/18/12; 12/14/12; 12/12/12; 12/11/12; 12/4/12; 11/29/12; 11/27/12; 9/25/12; 9/19/12; 9/18/12; 6/2/12; 1/12/12; 12/20/11;

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

	12/13/11/10/5/11; 9/15/11; 6/2/11;4/28/11; 1/31/11; 10/22/10; 4/16/2010; 3/31/2010; 7/22/2009; 3/24/2009; 10/28/09; 8/31/2009; 5/8/2009
❖ Internal memoranda, telecons, etc.	9/27/13; 5/1/13; 11/6/2012
❖ Minutes of Meetings	
<ul style="list-style-type: none"> Regulatory Briefing (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> 12/14/2011; 09/23/2011; 06/07/2011 Meeting denied: 08/07/2013; 12/20/2011
<ul style="list-style-type: none"> If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> end of review 07/30/2010
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	7/6/2011
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg
<ul style="list-style-type: none"> Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date(s) of Meeting(s) 48-hour alert or minutes, if available (<i>do not include transcript</i>) 	
Decisional and Summary Memos (section # 6)	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> 11/08/13 4/30/2010 (first cycle)
Division Director Summary Review (<i>indicate date for each review</i>)	11/06/13 4/29/2010 (first cycle)
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	11/5/13 4/30/2010 (first cycle)
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> PMR # 2099-1 to PMR# 2099-11/12/13
Clinical Information (section # 7)	
❖ Clinical Reviews	
<ul style="list-style-type: none"> Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	Same as CDTL review memo for both cycles
<ul style="list-style-type: none"> Clinical review(s) (<i>indicate date for each review</i>) 	10/11/13; 6/3/2011 4/30/2010 (first cycle) 6/7/2009 (filing review-first cycle)
<ul style="list-style-type: none"> Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See clinical review memo 10/11/13
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Safety Team Leader Reviews	9/16/2013
Safety review	10/24/13; 10/22/13; 9/9/2013

OPE pre-marketing safety review	10/08/2013
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	9/19/2013 7/27/2010 (first cycle) 3/19/2010 (first cycle)
CSS Statistical Review	5/31/2013
QT Study Review	10/2009 (first cycle)
PMHS Review	12/15/2011
Pharmacovigilance Review	04/12/13
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	09/29/13 (REMS review by DRISK) 10/29/12 (REMS Retraction Memo) 3/4/2010 (first cycle) 10/21/09 REMS memo (first cycle) 11/4/2009
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	10/10/13 clinical inspection summary 10/10/13; 10/8/13 10/7/13 (5 inspections); 9/27/13; 9/23/13 First cycle: 10/12/11; 5/21/10; 4/27/10; 4/27/10; 4/9/2010; 3/2/2010
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics (section # 8) <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	Same document as primary reviewer's memo
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	Same document as primary reviewer's memo
Statistical Review(s) (<i>indicate date for each review</i>)	9/10/13 3/16/2010 (first cycle)
Clinical Pharmacology (section # 9) <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	Same document as the primary reviewer's memo
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	9/16/2013 12/26/12 filing review 3/8/2010 (first cycle) 7/16/2009 (first cycle)
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	1/20/2010 (first cycle)

Nonclinical (section# 10)		<input type="checkbox"/> None
❖ Pharmacology/Toxicology Discipline Reviews		
• ADP/T Review(s) <i>(indicate date for each review)</i>		11/07/2013 4/29/2010 (first cycle)
• Supervisory Review(s) <i>(indicate date for each review)</i>		9/17/2013 4/28/2010 (first cycle)
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>		9/6/2013 2/22/13 ---filing review 4/14/2010 (first cycle) 10/9/2009 (first cycle) 5/11/2009 –filing review (first cycle)
❖ Carcinogenicity Study		07/22/2009 (first cycle)
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> No
❖ ECAC/CAC report/memo of meeting		10/07/2009
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>		<input checked="" type="checkbox"/> None requested
Product Quality (section # 11)		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>		10/21/2013
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>		Same document as primary reviewer's document
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>		10/21/2013; 08/29/13; CMC 4/16/2010 (first cycle) CMC 3/3/2010 (first cycle) CMC 10/26/2009 (first cycle) CMC 4/16/09--filing review-first cycle 10/17/2013; 08/27/13-- Biopharmaceutics
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		<input checked="" type="checkbox"/> Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>		<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>		See CMC 8/29/13 review memo (page 84)
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>		See CMC 8/29/13 review memo (page 84)
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>		See CMC 8/29/13 review memo (page 84)

❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report) (date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites ⁶)	Date completed: 10/18/2013 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (check box only, do not include documents)	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review) see CMC 8/29/13 (page 55-68)

⁶ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

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

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

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

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

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

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

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

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

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

/s/

SU-LIN SUN
11/16/2013

Sun, Su-Lin

From: Karen.Joyce@sunovion.com
Sent: Friday, November 08, 2013 4:04 PM
To: Sun, Su-Lin
Cc: Amy.Schacterle@sunovion.com
Subject: RE: NDA 022416 approval letter

Dear Sulin,

I am confirming receipt of the electronic copy of the approval letter with the final agreed PI/MG, carton and container labeling.

Thanks and have a wonderful weekend!

Karen

Karen Joyce
Director, Regulatory Affairs
Sunovion Pharmaceuticals Inc.
84 Waterford Drive | Marlborough, MA 01752
Office: 508-357-7856 | Fax 508-357-7491 | karen.joyce@sunovion.com

From: Sun, Su-Lin [<mailto:Su-Lin.Sun@fda.hhs.gov>]
Sent: Friday, November 08, 2013 3:54 PM
To: Joyce, Karen
Cc: Schacterle, Amy
Subject: NDA 022416 approval letter
Importance: High

Dear Karen:

Attached is an electronic approval letter for your NDA 022416 APTIOM, you will receive the official document via mail in few days.

Please send me an e-mail confirmation to acknowledge the receipt of an electronic copy of approval letter with the final agreed PI/MG, carton and containers labeling.

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service
Senior Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4200
10903 New Hampshire Ave
Silver Spring, MD 20993

Office: 301-796-0036
Fax: 301-796-9842
Email: Su-Lin.Sun@fda.hhs.gov

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48 Pages Have Been Withheld As A Duplicate Copy Of The "Approval Letter and Labeling" dated November 8, 2013 Which Are Located In The Approval Letter and Labeling Sections Of This NDA Approval Package

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

/s/

SU-LIN SUN
11/08/2013

From: Doi, Mary
To: [Hershkowitz, Norman](#)
Cc: [Yasuda, Sally](#); [Bastings, Eric](#)
Subject: FW: Finalized - NDA-22416 General Consult Review (CONSULT REV-CSS-01)
Date: Tuesday, October 22, 2013 6:24:00 PM
Attachments: [Eslcarbazepine_NDA22416_10172013-CSS_Amendment-Final.pdf](#)
[Sponsor's_Sept_5_rsp-to-2013-08-26-div-info-rqst.pdf](#)

Hi Norm,

I sent this information to Sally but I wanted to respond to your email below regarding the information in Alicja's addendum. I finished reviewing Alicja's addendum regarding the Sponsor's Safety Information Amendment submitted on September 5, 2103 (attached to this email) in response to the following CSS information request:

"Please provide CRFs for all cases of overdoses, medication errors, poisoning and toxicity for period covered by NDA and all new post-marketing cases. If the CRF is already in the data base provide a link."

Of note – earlier in the review cycle, I had sent an R to the Sponsor on 6/19/13 with the following request:

"Provide a tabular listing of all cases of overdose in the entire ESL clinical database (all studies pool), ongoing studies, postmarketing database."

The Sponsor submitted a Safety Information Amendment on 7/1/13 in which the Sponsor defined overdoses as "any reports greater than the maximum recommended dose or any report characterized by the word 'overdose' regardless of specified dose." The Sponsor reported a total of 24 postmarketing cases of overdose. *[Interestingly, this is a lower number than what the Sponsor had already reported in the ISS- a total of 35 cases that included 11 new cases that occurred after 8/31/12 but prior to the data cutoff date of 10/21/12.]*

Below, I have compared the Sponsor's information submitted in the 9/5/13 amendment and the information in my review and Alicja's addendum specifically regarding cases of overdoses that were not identified in the ISS.

In summary, in this amendment, I did not identify any new clinical trial cases of ESL "overdose."

However, **in the postmarketing data submitted by the Sponsor in this amendment, I did identify a substantial number of ESL "overdose" cases (as defined by the Sponsor as patients taking >1200 mg of ESL) that were not previously reported by the Sponsor in the ISS or prior amendments.** Therefore, I agree with Alicja's statement that there is a discrepancy between the numbers of overdoses reported in the ISS and in this amendment (although I do not agree with her specific calculations).

I identified 1 important and worrisome case of overdose (BIAL 01172 who took 32 000 mg of ESL) that was not previously reported as an overdose by the Sponsor or identified by me (although the case was identified in the section on suicidality). However, not enough information was provided in this case report regarding associated adverse events, hospital course, treatment required, labs, etc. Therefore, no new safety signals were identified in this case.

In the Sponsor's listing of "medication error" cases, I identified 62 postmarketing cases of "overdose" that were not reported in the ISS or in the earlier Safety Information Amendment (dated 7/1/13). Serious adverse events were reported in these patients (e.g., decrease in sodium to 117, cardiac arrest [in the setting of a possible seizure, described in my review]). Most of the associated adverse events were consistent with those reported in the clinical trials at the indicated doses (≤ 1200 mg): hyponatremia, seizures, and neurologic adverse reactions (however, I have not read all of these narratives).

Today, we sent an information request to the Sponsor inquiring about these discrepancies.

Thanks,
Mary

Safety Information Amendment submitted on September 5, 2103

1.1 Overdoses

1.1.1 Clinical Trial Cases – all of the Sponsor's cases were identified in my review

1.1.2 Postmarketing Cases

The Sponsor "expanded the search from [their] previous response to include cases of suicide as potentially representing overdose." This expanded search identified an additional case, BIAL 01172, (b) (6) with a suicide attempt with 32,000 mg (40 tablets of 800 mg ESL along with diazepam and alcohol). Patient was hospitalized and recovered (the CRF reported that "no further information could be obtained"). This case was coded only to "suicide attempt" and not to "overdose" – which is **an additional coding omission (not noted in my review)**. Thus, this subject was reported in the ISS only in the suicidality section (without reference to the dosage) but not in the overdose section. In the ISS, the Sponsor noted that the "highest dose reported was 3200 mg" referring to an overdose in the setting of a suicide attempt (BIAL 01792).

Otherwise in this amendment, the cases that the Sponsor lists that occurred prior to the ISS data cutoff date of October 21, 2012, were indeed reported previously by the Sponsor (and included in my review).

Additionally, the Sponsor reported 7 postmarketing cases that occurred after the ISS data cutoff date, that were coded to "overdose": BIAL 01864, 02131, 01913, 02023, 02122, 02028 (subject with loss of consciousness described in my review), 02160.

1.2 Toxicity

1.2.1 Clinical Trial Cases – the Sponsor searched for the word "toxicity" in any part of the verbatim or preferred terms (different from my review in which I searched for all of the AEs coded to "drug toxicity" as the preferred term). The Sponsor did not identify any new cases of toxicity due to ESL overdose. However, the **Sponsor missed the ESL overdose case that I identified in my review** using my search strategy: 301-141-90171 (subject had taken double doses of ESL and other concomitant medications). In this amendment, the Sponsor listed this case as "toxicity was reported related to concomitant medications."

1.2.2 Postmarketing Cases – Two toxicity cases were identified and discussed by the Sponsor: BIAL 01037 with SJS (discussed in my review) and BIAL 02122 (after the ISS data cutoff date, see Section 1.1.2 above).

1.3 Poisoning

1.3.1 Clinical Trial Cases – the Sponsor searched for the word "poison" in any part of the verbatim or preferred terms (different from my review in which I searched for all of the AEs coded to "poisoning" as the preferred term). The Sponsor did identify the same subject that I identified as an overdose: subject 301-124-90357 (noted in my review as a coding omission and was not originally included by the Sponsor in the ISS in their list of overdoses).

1.3.2 Postmarketing Cases – no "poisoning" cases were identified by the Sponsor.

1.4 Medication Error

1.4.1 Clinical Trial Cases - the Sponsor searched for any medication errors reported as protocol violations and had any sequelae reported as adverse events. Only one event was identified by the Sponsor (BIAL 02048 who was dispensed an out-of-date package of ESL and reported headache/fatigue).

1.4.2 Postmarketing Cases - the Sponsor searched for reports labeled as "medication error" when the pattern of use was outside the approved labeling (in Europe), even when such use may have been as prescribed by the physician.

[Of note - in the ISS, the Sponsor noted that "according to BIAL convention, the term 'overdose' is coded whenever a patient, for whatever reason, is prescribed or takes more ESL than the maximum recommended 1200 mg/day, and 'medication error' is coded whenever ESL is prescribed or used in a manner not in accordance with approved prescribing information.]

The Sponsor identified 151 cases of "medication error." Alicja notes in her review addendum (dated 10/17/13) that the majority of the cases (n=138, 91%) occurred prior to the October 2012 cut-off date. *[Of note, in the ISS, the Sponsor reported only 30 cases of "medication errors."]* Furthermore, Alicja notes that 90 events (out of the 151 cases) were coded as "overdose."

I reviewed Table 6 and also counted 90 cases classified by the Sponsor as "overdose." Excluding the cases that were previously reported in the ISS, I counted a total of **62 cases that were classified by the Sponsor as "overdose" and not reported in the ISS**. I reviewed a few of these narratives and the majority of these cases were literature reports of patients prescribed doses above the European labeled maximum dose of 1200 mg per day (generally at doses of 1600 mg or 2000 mg daily). However, of note – I did not read all of these narratives – so some of these may have been after the data cut-off or labeled as "overdose" for other reasons.

For these 62 cases, the following associated adverse events were listed in Table 6 as the "most important diagnosis as MedDRA preferred terms": no adverse event (n=18), hyponatremia/blood sodium decreased (n=31), convulsion/partial seizures/grand mal seizures/status epilepticus (n=6), ataxia, constipation, diarrhea, tachycardia, diplopia, cardiac arrest/asystole (BIAL 00504, described in my review), and suicide attempt (BIAL 01172, described above in Section 1.1 2).

Of note, many of these serious postmarketing adverse events were included in the ISS and prior amendments by Sponsor (but were not coded to "overdose"). So I have noted and described a lot of these serious cases in my review – in sections other than the overdose section.

From: Hershkowitz, Norman
Sent: Thursday, October 17, 2013 5:28 PM
To: Yasuda, Sally; Doi, Mary
Cc: Bastings, Eric
Subject: FW: Finalized - NDA-22416 General Consult Review (CONSULT REV-CSS-01)

Guys,

Can I ask you to look at Alicja's addendum. She lists the following serious sequela:

"For these "medication errors," many were serious AEs which required hospitalizations and included, among others, 1 asystole, 1 hepato-renal syndrome, 1 suicide attempt, multiple cases of convulsions/seizures, 1 non-convulsive status epilepticus with cardiopulmonary failure and 49 cases of hyponatremia, 20 of which were <125 mmol/L.

Sounds to me we identified all these cases and/or at least these were very common events. Mary do you know if overdose was a substantial cause of these event?

Norm

From: Sun, Su-Lin
Sent: Thursday, October 17, 2013 2:03 PM
To: Hershkowitz, Norman
Cc: Bastings, Eric
Subject: FW: Finalized - NDA-22416 General Consult Review (CONSULT REV-CSS-01)

CSS amendment for NDA 22416 eslicarbazepine

From: qasfda@fda.gov [<mailto:qasfda@fda.gov>]
Sent: Thursday, October 17, 2013 1:46 PM
To: Salis, Olga; Ngan, Kelly; Li, Hongshan; Zerislassie, Ermias; Bouie, Teshara; Ling, Xiang; Chikhale, Elsbeth G; Lerner, Alicja; Yu, Bei; Sun, Su-Lin; Podruchny, Teresa; Jewell, Charles; Moody, Corinne P; Toscano, Christopher; Saltz, Sandra; Neshiewat, Julie; IntegrityServices; Klein, Michael
Subject: Finalized - NDA-22416 General Consult Review (CONSULT REV-CSS-01)

■

(b) (4)



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

/s/

MARY DOI
11/05/2013

From: Doi, Mary
To: [Yasuda, Sally](#); [Hershkowitz, Norman](#); [Bastings, Eric](#)
Subject: FW: NDA 22416 urgent IR
Date: Thursday, October 24, 2013 5:02:00 PM
Attachments: [1.11 FDA RFI - Overdose tables Final 23Oct2013.pdf](#)

Hello –

I reviewed the Sponsor's response (attached to this email) to our information request regarding overdoses.

In summary, the Sponsor listed 61 cases as “postmarketing cases of overdose reported prior to 10/21/12” (the ISS data cut-off date for postmarketing information) which were newly reported in the 9/5/13 amendment but NOT reported previously (in the ISS or prior amendments).

The Sponsor stated that these extra cases (9/5/13) were identified because Bial used a “conservative” convention that records overdose when patients are prescribed doses outside the recommended dosing in the European labeling (>1200 mg) in addition to identifying accidental and intentional overdose cases. *[Of note, in the ISS, the Sponsor had used the same definition – and originally reported that the term “overdose” is coded whenever a patient, for whatever reason, is prescribed or takes more ESL than the maximum recommended 1200 mg/day].*

In terms of adverse events, we had requested that the Sponsor review all of these 61 narratives in order to fill in the column labeled “List all TEAEs described in the narrative of the case report” in addition to the column “List all TEAEs coded to PTs in the case report.” I asked for this information to obtain a comprehensive list of adverse events (knowing that there have been many coding omissions in this NDA). However, the Sponsor did not fill in the “requested column of ‘All TEAEs described in the narrative’...as it is not coded in the database.”

I reviewed all of these coded TEAEs for the 61 cases. Most of these TEAEs were consistent with those already included in labeling: hyponatremia (blood sodium decreased), seizure related (status epilepticus/convulsion/partial seizures/grand mal convulsion), ataxia, diplopia, vertigo, vomiting, diarrhoea, fatigue/asthenia, rash pruritic, and suicide attempt.

Additionally, there were 5 patients with the following adverse events: cardiopulmonary failure/dyspnoea/oedema peripheral after an episode of status epilepticus (BIAL 00468, ESL 1600 mg), aura (BIAL 01174, ESL 2400 mg), tachycardia/chills/headache (BIAL 01217, ESL 2400 mg), constipation/mictuition urgency/weight decreased (BIAL 00532, ESL 1600 mg), and cardiac arrest (BIAL 00504 likely due to ictal asystole, described in my review).

Thanks,
Mary

From: Sun, Su-Lin
Sent: Wednesday, October 23, 2013 6:40 PM
To: Doi, Mary; Yasuda, Sally
Cc: Lerner, Alicja; Podruchny, Teresa; Hershkowitz, Norman
Subject: FW: NDA 22416 urgent IR

FYI

From: Amy.Schacterle@sunovion.com [<mailto:Amy.Schacterle@sunovion.com>]
Sent: Wednesday, October 23, 2013 6:34 PM
To: Sun, Su-Lin
Cc: Karen.Joyce@sunovion.com
Subject: RE: NDA 22416 urgent IR

Dear Sulin,

Please find attached our response to the urgent IR regarding overdoses from yesterday.

We will submit this formally tomorrow.

Best regards,

Amy

Amy L. Schacterle, Ph.D.

Vice President, Regulatory Affairs

Sunovion Pharmaceuticals Inc.

84 Waterford Drive, Marlborough, MA 01752

Tel: 508.787.4025

Email: amy.schacterle@sunovion.com

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/s/

MARY DOI
11/05/2013

From: Sun, Su-Lin
To: Karen.Joyce@sunovion.com
Cc: Amy.Schacterle@sunovion.com; [Toure, Hamet](#)
Subject: NDA 22416 Aptiom --FDA's labeling comments
Date: Friday, November 01, 2013 3:51:00 PM
Attachments: [NDA 22416--FDA's labeling comments--11-1-13.doc](#)
[NDA 22416--eslicarbazepine acetate 22416 MedGuide -FDA's MG labeling comments--11-1-13.doc](#)
Importance: High

Dear Karen:

Attached are our labeling comments for PI and MG, please accept track changes if you agree, insert your counter-proposal with track changes.

Below are additional comments for the Forrest plots:



Please send your counter-proposed documents back to us as soon as possible, no later than COB on Monday 11/4/13.

I will be out of office on 11/4 and 11/5, please contact LCDR Hamet Toure if you have any question for your NDA 22416 application. Please cc me on all correspondences, I will try to monitor my email intermittently during those 2 days.

Thanks,

Sulin

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/s/

SU-LIN SUN
11/01/2013



NDA 022416

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Sunovion Pharmaceuticals Inc.
84 Waterford Drive
Marlborough, MA 01752

ATTENTION: Karen Joyce, Director Regulatory Affairs

Dear Ms. Joyce:

Please refer to your New Drug Application (NDA) dated March 29, 2009, received March 30, 2009, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Eslicarbazepine Acetate, Tablets 200mg, 400mg, 600mg, and 800mg.

We also refer to your August 22, 2013 correspondence received August 23, 2013 requesting review of your proposed proprietary name, Aptiom. We have completed our review of the proposed proprietary name, Aptiom and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your August 23, 2013 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 Ermiias Zerisslassie, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0097. For any other information regarding this application contact Su-Lin Sun, the Office of New Drugs (OND) Regulatory Project Manager at 301-796-0036.

Sincerely,

{See appended electronic signature page}

Carol Holquist, 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

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/s/

TODD D BRIDGES on behalf of CAROL A HOLQUIST
11/01/2013

From: Sun, Su-Lin
To: Karen.Joyce@sunovion.com
Cc: Amy.Schacterle@sunovion.com
Subject: NDA 22416 PMR request & carton container review status update
Date: Thursday, October 31, 2013 11:03:00 AM
Importance: High

Dear Karen:

Below are our review team's request for your NDA# 22416 one of the PMR. Please send your response back to us as soon as possible, no later than COB today. We are still waiting for this information –so we can forward the draft PMRS for Safety Review Team's review—which needs 1-2 week clearance.

[Please provide your agreement on the milestone dates for the revised PMR related to thyroid function tests.](#) (b) (4)

[Redacted]

An ex vivo study to determine whether eslicarbazepine interferes with assays for free T3 and T4 as well as total T3, T4, and TSH. Collect a blood sample from 30 subjects who have taken a daily dose of at least 1200 mg ESL for at least 6 weeks as well as a blood sample from 30 non-ESL exposed age-matched subjects. Subjects must not be taking phenytoin, carbamazepine, or oxcarbazepine (or any other drugs known to displace T4 or T3 from binding proteins). Blood samples collected from ESL subjects will be assayed utilizing the clinical trial methods and the most suitable physical separation methodology (e.g., equilibrium dialysis, ultrafiltration, gel filtration) for comparison for serum free T4 and serum free T3 measurements. Blood samples from non-ESL exposed subjects will be spiked with a range of eslicarbazepine and R-licarbazepine concentrations both above and below the known exposures of patients receiving at least ESL 1200 mg and assayed utilizing the clinical trial methods and the most suitable physical separation methodology to determine the effect on serum free T3 and T4 as well as on serum total T3, T4, and TSH. Results will be evaluated to determine if there is an artifact in the method.

We recommend that you seek consultation with technical experts who are familiar with the artifactual effects of certain drugs (e.g., carbamazepine, phenytoin) on decreasing serum free T4 and free T3 with non-physical separation methodologies (e.g., analog immunoassays) to determine the most suitable physical separation method (e.g., equilibrium dialysis, ultrafiltration, gel filtration) for your study.

Final Protocol Submission: 06/2014

Study Completion: 06/2015

Final Report Submission: 12/2015

** Also from my previous email, can you clarify the final report submission for your juvenile tox study—is listed on your counter-proposal date as 01/2014, do you mean 01/2015.

So far it's listed as

A juvenile dog toxicology study under PREA to identify and characterize the unexpected serious risk of adverse effects of eslicarbazepine acetate on the immune system of the developing organism. The study should utilize animals of an age range and stage(s) of development that are comparable to the intended pediatric population.

Final Protocol Submission: 03/2014

Study Completion: 09/2014

Final Report Submission: 01/2014

I double checked with our OPDP and DMEPA team regard to your 10/29/13 revised carton and container labeling submission, so far there are no additional comments from them.

Thanks,

Sulin

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/s/

SU-LIN SUN
10/31/2013

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Wednesday, October 30, 2013 7:44 PM
To: 'Amy.Schacterle@sunovion.com'; Karen.Joyce@sunovion.com
Subject: RE: FDA's comments

Importance: High

Dear Amy and Karen:

The review team prefer to provide their comments to your proposed labeling comments via email instead of Tcon.

Below are the comments from our review team for your counter-proposed labeling comments:

1. Your proposed labeling comments for section 2.3 and section 4 are acceptable.
2. Your proposal for replacing (b) (4) with quartiles is acceptable. However, the Division does not agree with the statement of (b) (4)

Please insert your counter-proposed comments as track changes. If you make changes to the PI, please also make corresponding changes on the Med Guide.

If you have any question, please feel free to contact me.

Thanks,
Sulin

From: Sun, Su-Lin
Sent: Wednesday, October 30, 2013 6:05 PM
To: Amy.Schacterle@sunovion.com
Cc: Karen.Joyce@sunovion.com
Subject: Re: FYI

I can check w DMEPA team first then follow up w you later.

From: Amy.Schacterle@sunovion.com [<mailto:Amy.Schacterle@sunovion.com>]
Sent: Wednesday, October 30, 2013 04:59 PM
To: Sun, Su-Lin
Cc: Karen.Joyce@sunovion.com <Karen.Joyce@sunovion.com>
Subject: RE: FYI

Thank you. We appreciate your efforts.

To help manage availability of our team, when would we expect to see the carton/container labeling back again?

Thanks,
Amy

From: Sun, Su-Lin [<mailto:Su-Lin.Sun@fda.hhs.gov>]
Sent: Wednesday, October 30, 2013 4:56 PM

To: Schacterle, Amy
Cc: Joyce, Karen
Subject: FYI

FYI—still have not receive Dr. Basting's response yet. I just sent him another reminder. I will continue monitor my email throughout the evening hours, as soon as I receive his recommendation, I will follow up with you.

Thanks,
Sulin

From: Amy.Schacterle@sunovion.com [<mailto:Amy.Schacterle@sunovion.com>]
Sent: Wednesday, October 30, 2013 1:30 PM
To: Sun, Su-Lin
Cc: Karen.Joyce@sunovion.com
Subject: RE: NDA 22-416 - Follow-up information to request for Telecon

Thank you!

From: Sun, Su-Lin [<mailto:Su-Lin.Sun@fda.hhs.gov>]
Sent: Wednesday, October 30, 2013 1:18 PM
To: Joyce, Karen
Cc: Schacterle, Amy
Subject: RE: NDA 22-416 - Follow-up information to request for Telecon

OK, thank you, I forwarded your email to our review team.
FYI—We are still waiting for Dr. Basting's response regard to your Tcon request. He is in meetings back to back till 5pm. As soon as I receive his recommendation, I will follow up with you.

Thanks,
Sulin

From: Karen.Joyce@sunovion.com [<mailto:Karen.Joyce@sunovion.com>]
Sent: Wednesday, October 30, 2013 12:53 PM
To: Sun, Su-Lin
Cc: Amy.Schacterle@sunovion.com
Subject: NDA 22-416 - Follow-up information to request for Telecon
Importance: High

Dear Sulin,

Below is background information on the three points that Sunovion proposed for discussion during the teleconference.

1. Use with oxcarbazepine (Section 2.3)

We noted FDA's comment to include the statement APTIOM should not be taken concurrently with oxcarbazepine. We are concerned that this statement, as worded, may preclude the potential to transition from oxcarbazepine to APTIOM or vice versa for appropriate patients. We recognize that this would not be the Division's intent and suggest that the wording should be clarified to reflect the concern regarding use as an adjunctive therapy to oxcarbazepine. As such, we propose the following alternate text below:

APTIOM should not be taken as an adjunctive therapy with oxcarbazepine

The suggestion to replace “concurrently” with “as an adjunctive therapy” is in keeping with the context of the overall adjunctive indication for the product while still allowing for a brief transition period of concurrent administration if the prescriber wants to convert from oxcarbazepine adjunctive therapy to APTIOM adjunctive therapy or vice versa.

2. **Statement regarding (b) (4) (Section 14)**

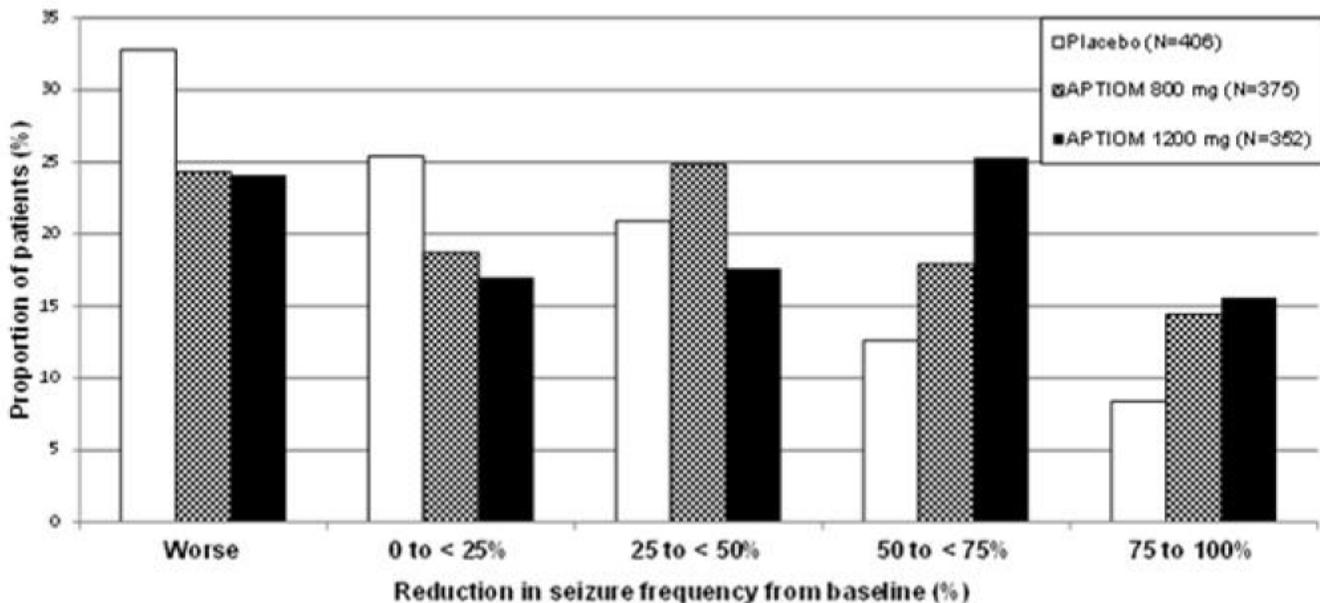
As follow-up to our request for a teleconference, we note in the Division’s communication of September 23, 2013 (e-mail from Dr. Sun) that the Division is considering new ways to generate data that represents the proportion of patients by category of seizure response.

We fully agree that the presentation of the graph greatly facilitates communication of the data and is important to convey the distribution of response to the product. We propose that presentation of the data by quartiles would further accomplish what we believe are the Division’s objectives.

We received advice from opinion leaders and practicing epileptologists that it is important to convey standard endpoints (b) (4) that are traditionally discussed and widely cited in the literature and presented in the prescribing information for numerous recently approved AED labels (eg, Fycompa, Vimpat, Trokendi XR, Sabril). It is also an important consideration in the assessment of formulary status by payors and a frequently requested endpoint. (b) (4)

(b) (4) We understand that the expert advice to us is in part driven by how physicians counsel patients about the benefit/risk associated with the use of the product.

(b) (4) Therefore, alternatively we propose the below figure.



(b) (4)

(b) (4)

(b) (4)

3. **Use of the word eslicarbazepine versus eslicarbazepine acetate (Section 4)**

We noted the Division deleted the word acetate from Section 4 (contraindications) and similar text in the highlights section and medication guide. It is necessary from our perspective to reinsert the word acetate as the product delivered to the patient is eslicarbazepine acetate.

We note that the final Guidance for Industry (October 2011) entitled “Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format” states the following “A contraindication in patients with hypersensitivity reactions should be included in labeling only when there are demonstrated cases of hypersensitivity with the **product...**” [emphasis added]. From this guidance it is clear that the hypersensitivity should concern the product that is delivered to the patient, which in this case is eslicarbazepine acetate, and should not be confused with the metabolite eslicarbazepine.

Kind regards,

Karen

Karen Joyce

Director, Regulatory Affairs

Sunovion Pharmaceuticals Inc.

84 Waterford Drive | Marlborough, MA 01752

Office: 508-357-7856 | Fax 508-357-7491 | karen.joyce@sunovion.com

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/s/

SU-LIN SUN
10/31/2013

From: Sun, Su-Lin
To: ["Karen.Joyce@sunovion.com"](mailto:Karen.Joyce@sunovion.com)
Cc: ["Amy.Schacterle@sunovion.com"](mailto:Amy.Schacterle@sunovion.com)
Subject: RE: NDA 22416 submission request for carton and container labels
Date: Tuesday, October 29, 2013 9:37:00 AM
Importance: High

Dear Karen:

Per our review team's request, please submit as a single submission which contains ALL of the container labels and carton labeling (both commercial and professional sample presentations that Sunovion intend to market) as soon as possible, no later than 12noon on 10/30/13 Wednesday.

Thanks,
Sulin

From: Sun, Su-Lin
Sent: Monday, October 28, 2013 10:48 PM
To: 'Karen.Joyce@sunovion.com'
Cc: Amy.Schacterle@sunovion.com
Subject: RE: NDA 22416 Sunovion's comments for PI/MG + PMRs comments 28Oct13

Dear Karen:

Maybe wait till I double checked with DMEPA and OPDP team again before you officially submit the carton and container labels tomorrow as 1 single submission. As soon as I receive their recommendation, I will follow up with you—probably will be tomorrow 10/29/13 since it's kind of late now.

Thanks,
Sulin

From: Karen.Joyce@sunovion.com [<mailto:Karen.Joyce@sunovion.com>]
Sent: Monday, October 28, 2013 10:41 PM
To: Sun, Su-Lin
Cc: Amy.Schacterle@sunovion.com
Subject: FW: NDA 22416 Sunovion's comments for PI/MG + PMRs comments 28Oct13
Importance: High

Dear Sulin,

Please note that Sunovion did not propose any changes to the trade labels as discussed in Section 2.2 of the labeling history submitted this afternoon (please see text below from Section 2.2). As requested, Sunovion will resubmit the submission in the morning with all revised carton and container labeling in 1 single submission.

2.2. Proposed Labeling Text

Changes since the last proposed text (eCTD sequence 0122 submitted on October 2, 2013) are summarized in [Table 2](#). Changes were made to the sample wallet and sample

carton labels. There were no changes made to the trade labels (i.e., oblong bottle, round bottle, and round bottle carton).

Kind regards,

Karen

Karen Joyce

Director, Regulatory Affairs

Sunovion Pharmaceuticals Inc.

84 Waterford Drive | Marlborough, MA 01752

Office: 508-357-7856 | Fax 508-357-7491 | karen.joyce@sunovion.com

From: Sun, Su-Lin [<mailto:Su-Lin.Sun@fda.hhs.gov>]

Sent: Monday, October 28, 2013 9:52 PM

To: Joyce, Karen

Cc: Schacterle, Amy

Subject: RE: NDA 22416 Sunovion's comments for PI/MG + PMRs comments 28Oct13

Our DEMPAs team just informed me that it looks like this afternoon's official submission—does not include the revised container labels. Please submit those as soon as possible, so DMEPA and OPDP can review them and provide our review team with their recommendation.

They also requested—that all revised carton and container labeling—to be send via 1 single submission.

Thanks,

Sulin

From: Karen.Joyce@sunovion.com [<mailto:Karen.Joyce@sunovion.com>]

Sent: Monday, October 28, 2013 8:43 PM

To: Sun, Su-Lin

Cc: Amy.Schacterle@sunovion.com

Subject: RE: NDA 22416 Sunovion's comments for PI/MG + PMRs comments 28Oct13

Hi Sulin,

Yes, we received confirmation that the carton/container submission went through the gateway this afternoon. Please let me know if you did not receive and I can forward the files via e-mail this evening.

Kind regards,

Karen

Karen Joyce

Director, Regulatory Affairs

Sunovion Pharmaceuticals Inc.

84 Waterford Drive | Marlborough, MA 01752

Office: 508-357-7856 | Fax 508-357-7491 | karen.joyce@sunovion.com

From: Sun, Su-Lin [<mailto:Su-Lin.Sun@fda.hhs.gov>]

Sent: Monday, October 28, 2013 6:12 PM

To: Joyce, Karen

Cc: Schacterle, Amy

Subject: RE: NDA 22416 Sunovion's comments for PI/MG + PMRs comments 28Oct13

Yes, we will try to aiming to send you our comments hopefully by Oct 29, 2013 5pm.

FYI—just want to double check that you also submitted your revised carton and container this afternoon via gateway, right?

Thanks,

Sulin

From: Karen.Joyce@sunovion.com [<mailto:Karen.Joyce@sunovion.com>]

Sent: Monday, October 28, 2013 4:12 PM

To: Sun, Su-Lin

Cc: Amy.Schacterle@sunovion.com

Subject: FW: NDA 22416 Sunovion's comments for PI/MG + PMRs comments 28Oct13

Importance: High

Dear Sulin,

Attached are Sunovion's comments (in tracked changes) on the package insert/medication guide and PMRs (with 2 references to support the PMR comments). Based on your e-mail of October 10, 2013, the Division's comments are due back to Sunovion by 5 PM (or early evening) Tuesday, October 29th with Sunovion's counter-proposal due back to Division by COB Thursday, October 31th. Are you still planning on sending the Division's comments back on the 29th?

Kind regards,

Karen

Karen Joyce

Director, Regulatory Affairs

Sunovion Pharmaceuticals Inc.

84 Waterford Drive | Marlborough, MA 01752

Office: 508-357-7856 | Fax 508-357-7491 | karen.joyce@sunovion.com

From: Sun, Su-Lin [<mailto:Su-Lin.Sun@fda.hhs.gov>]

Sent: Friday, October 25, 2013 6:19 PM

To: Joyce, Karen

Cc: Schacterle, Amy

Subject: RE: NDA 22416 FDA's comments for PI/MG + PMRs comments

FYI for PMR—the juvenile tox study—please double check your proposed dates, our review team think the timeline seem pretty tight. 😊

PeRc recommendation that juvenile tox study has to been completed. If there is no safety signal concerned, then the 2 PKs studies may start.

Thanks,
Sulin

From: Karen.Joyce@sunovion.com [<mailto:Karen.Joyce@sunovion.com>]
Sent: Friday, October 25, 2013 6:10 PM
To: Sun, Su-Lin
Cc: Amy.Schacterle@sunovion.com
Subject: RE: NDA 22416 FDA's comments for PI/MG + PMRs comments

Thank you Sulin

Karen Joyce
Director, Regulatory Affairs
Sunovion Pharmaceuticals Inc.
84 Waterford Drive | Marlborough, MA 01752
Office: 508-357-7856 | Fax 508-357-7491 | karen.joyce@sunovion.com

From: Sun, Su-Lin [<mailto:Su-Lin.Sun@fda.hhs.gov>]
Sent: Friday, October 25, 2013 5:47 PM
To: Joyce, Karen
Cc: Schacterle, Amy
Subject: NDA 22416 FDA's comments for PI/MG + PMRs comments
Importance: High

Dear Karen:

Attached 3 documents for NDA 22416, please use track changes to insert your counter-proposal comments.

For MG---the font and format are specific per DMPP and OPDP's request.

For PI—I double checked with SEALD team that the reference bracket (bracket itself as well as the text inside the bracket will need to be italic).

You may insert MG at the end of the PI (make sure MG has its recommended font and format)

For PMR comments—please insert your counter-proposed comments to the document.

Please send your counter-proposed comments back to us as soon as possible, no later than COB on Monday 10/28/13.

If you have any question, please feel free to contact me.

Thanks,

Sulin

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/s/

SU-LIN SUN
10/29/2013

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Friday, October 25, 2013 5:47 PM
To: Karen.Joyce@sunovion.com
Cc: Amy.Schacterle@sunovion.com
Subject: NDA 22416 FDA's comments for PI/MG + PMRs comments

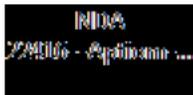
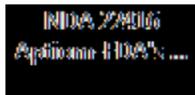
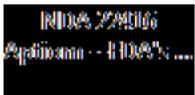
Importance: High

Dear Karen:

Attached 3 documents for NDA 22416, please use track changes to insert your counter-proposal comments.
For MG---the font and format are specific per DMPP and OPDP's request.
For PI—I double checked with SEALD team that the reference bracket (bracket itself as well as the text inside the bracket will need to be italic).

You may insert MG at the end of the PI (make sure MG has its recommended font and format)
For PMR comments—please insert your counter-proposed comments to the document.

Please send your counter-proposed comments back to us as soon as possible, no later than COB on Monday 10/28/13.
If you have any question, please feel free to contact me.



Thanks,

Sulin

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/s/

SU-LIN SUN
10/25/2013

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Thursday, October 24, 2013 4:45 PM
To: Karen.Joyce@sunovion.com
Cc: Amy.Schacterle@sunovion.com
Subject: NDA 22416 PMRs

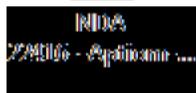
Importance: High

Dear Karen:

There will be total 7 PMRs, please insert your counter-proposed comments (as track changes) & proposed timeline dates on this document, and send it back to me as soon as possible, no later than 10AM on 10/25/13. Please remind your team to standby on 10/25/13 from 12 noon to 12:30PM (EST) for possible PMR Tcon discussion.

For PMR # 6, there are internal change request 30mins ago and it's currently routing for approval process. Since it's already 4:40pm now, so I think it may be good idea to send you the other 6 PMRs now, so your team has some time to review those while waiting for PMR #6 internal approval.

As soon as PMR# 6 is approved internally, I will send it to you.



FYI—there will be cartoon and container change request also. I am currently waiting for internal approval. As soon as it's ready, I will send it to you.

Thanks,
Sulin

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

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/s/

SU-LIN SUN
10/24/2013

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Thursday, October 24, 2013 6:58 PM
To: 'Karen.Joyce@sunovion.com'
Cc: Amy.Schacterle@sunovion.com
Subject: RE: NDA 22416 draft PMR# 6

Importance: High

Dear Karen:

Below is our draft PMR #6, I am still waiting for Dr. Bastings and Dr. Unger's approval. We will probably send you our revised version tomorrow AM. Or as soon as I receive their approval, I will send it to you.

(b) (4)

Thanks,
Sulin

From: Karen.Joyce@sunovion.com [<mailto:Karen.Joyce@sunovion.com>]
Sent: Thursday, October 24, 2013 4:49 PM
To: Sun, Su-Lin
Cc: Amy.Schacterle@sunovion.com
Subject: RE: NDA 22416 PMRs

Sorry, I just noticed that in your previous e-mail.

Karen Joyce
Director, Regulatory Affairs
Sunovion Pharmaceuticals Inc.
84 Waterford Drive | Marlborough, MA 01752
Office: 508-357-7856 | Fax 508-357-7491 | karen.joyce@sunovion.com

From: Sun, Su-Lin [<mailto:Su-Lin.Sun@fda.hhs.gov>]
Sent: Thursday, October 24, 2013 4:49 PM
To: Joyce, Karen
Cc: Schacterle, Amy
Subject: RE: NDA 22416 PMRs

Yes PMR # 6 is still pending approval currently, since there are change request after our internal meeting.

There are several people need to approve the new change requests, it may take a while or even possible tomorrow. Instead of waiting for that single PMR and hold up the entire document, so I send you the document contains PMR (1-5) and PMR 7 first, so your team has sometimes to review this.

As soon as PMR# 6 is approved internally, I will send it to you.

Thanks,
Sulin

From: Karen.Joyce@sunovion.com [<mailto:Karen.Joyce@sunovion.com>]
Sent: Thursday, October 24, 2013 4:46 PM
To: Sun, Su-Lin
Cc: Amy.Schacterle@sunovion.com
Subject: RE: NDA 22416 PMRs

Hi Sulin,

There is no #6 in the document that you sent?

Thanks-

Karen

Karen Joyce
Director, Regulatory Affairs
Sunovion Pharmaceuticals Inc.
84 Waterford Drive | Marlborough, MA 01752
Office: 508-357-7856 | Fax 508-357-7491 | karen.joyce@sunovion.com

From: Sun, Su-Lin [<mailto:Su-Lin.Sun@fda.hhs.gov>]
Sent: Thursday, October 24, 2013 4:45 PM
To: Joyce, Karen
Cc: Schacterle, Amy
Subject: NDA 22416 PMRs
Importance: High

Dear Karen:

There will be total 7 PMRs, please insert your counter-proposed comments (as track changes) & proposed timeline dates on this document, and send it back to me as soon as possible, no later than 10AM on 10/25/13. Please remind your team to standby on 10/25/13 from 12 noon to 12:30PM (EST) for possible PMR Tcon discussion.

For PMR # 6, there are internal change request 30mins ago and it's currently routing for approval process. Since it's already 4:40pm now, so I think it may be good idea to send you the other 6 PMRs now, so your team has some time to review those while waiting for PMR #6 internal approval.

As soon as PMR# 6 is approved internally, I will send it to you.

FYI—there will be cartoon and container change request also. I am currently waiting for internal approval. As soon as it's ready, I will send it to you.

Thanks,
Sulin

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/s/

SU-LIN SUN
10/24/2013

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Tuesday, October 22, 2013 11:30 AM
To: Karen.Joyce@sunovion.com
Cc: Amy.Schacterle@sunovion.com
Subject: NDA 22416 urgent IR

Importance: High

Dear Karen:

Below is the information request from our review team for your NDA 22416:

In reference to NDA 22-416, provide the following information by COB today (10/22/13):

In the amendment submitted on 9/5/13 in response to the information request dated 8/26/13, CRFs were provided for all cases of overdoses, medication errors, poisoning, and toxicity. In Table 6 of that amendment, 90 postmarketing cases were classified as “overdose.” However, in the ISS, it is reported that there were a total of 35 postmarketing cases of “overdose.” Furthermore, in the amendment submitted on 7/1/13 to provide a listing of all cases of overdose, only 24 postmarketing cases were listed. In the ISS and in these amendments, overdose has been defined as “whenever a patient, for whatever reason, is prescribed or takes more ESL than the maximum recommended 1200 mg/day.” Explain these discrepancies in the number of postmarketing “overdose” cases. Provide a listing of all postmarketing cases of overdose – using the following table shell (make 2 separate tables for cases reported prior to 10/21/12 and for cases reported after 10/21/12). This needs to be a comprehensive listing of all postmarketing cases of overdose that have been reported (so narratives and case reports will need to be reviewed to identify cases that were not originally coded to overdose). The definition of overdose should be consistent with the ISS.

Subject ID	Listed in 9/5/13 Amendment (Y or N)	Listed in ISS 2/10/13 (Y or N)	Listed in 7/1/13 Amendment (Y or N)	Case Originally Coded to Preferred Term of Overdose (Y or N)	Source of the Case (e.g., literature, presentation)	Dose of ESL	List all TEAEs described in the narrative of the case report	List all TEAEs coded to PTs in the case report	Outcome	ESL course

Thanks,
Sulin

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/s/

SU-LIN SUN
10/22/2013

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Thursday, October 17, 2013 4:49 PM
To: Karen.Joyce@sunovion.com
Cc: Choy, Fannie (Yuet)
Subject: NDA 22416 urgent information request

Importance: High

Dear Karen:

Below are the urgent information request from our review team for NDA 22416:

In reference to NDA 22-416, please provide the following by COB 10/18/13:

1) Provide a tabular listing of all of the ongoing studies (studies not included in the ISS datasets) that included lab measurements of bicarbonate in the protocols. Include information regarding the total number of subjects (and those who had measurements of bicarbonate) in each of these studies stratified by treatment and dose group. For these studies, also provide a comprehensive list of all laboratory chemistry measurements.

Please send your response to both me and Ms. Fannie Choy, she will help me to forward it to our review team. I will be at offsite hospital tomorrow.

Thanks,
Sulin

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/s/

SU-LIN SUN
10/17/2013

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Tuesday, October 08, 2013 7:52 PM
To: Karen.Joyce@sunovion.com
Subject: FDA's information request re: dissolution acceptance criterion

Importance: High

Dear Karen:

Below are the information request from our ONDQA team regard to your proposal for a dissolution acceptance criterion:

"Your proposal for a dissolution acceptance criterion of $Q = \text{(b) (4)}$ at 15 minutes for the 200 mg tablets is not acceptable. Based on the provided data, a dissolution acceptance criterion of $Q = \text{(b) (4)}$ at 15 minutes is appropriate. Nevertheless, it must be recognized that some batches may require Stage 2 and, occasionally, Stage 3 testing. Revise you dissolution acceptance criterion for the 200 mg tablets from $Q = \text{(b) (4)}$ at 15 minutes to $Q = \text{(b) (4)}$ at 15 minutes, and submit a revised specifications table for the drug product."

Please send your response to me as soon as possible, but no later than 1pm on 10/11/13.

Thanks,
Sulin

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/s/

SU-LIN SUN
10/08/2013

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Thursday, June 27, 2013 9:32 AM
To: Senior, John R
Subject: RE: DNP's Consult request for Dr. John Senior

Thank you :-)

From: Senior, John R
Sent: Thursday, June 27, 2013 9:05 AM
To: Yasuda, Sally; Sun, Su-Lin; CDER OSE CONSULTS; Zerislassie, Ermias
Cc: Hershkowitz, Norman; Podruchny, Teresa; Dal Pan, Gerald; Iyasu, Solomon
Subject: RE: DNP's Consult request for Dr. John Senior

Thank you all for the reminder about the eslicarbazine cases. I have lost the aid of Leonard Seeff and have fallen behind in responding to the many requests for consultation that have come to me, and have had to focus on ketoconazole, tolvaptan, macitentan which have very urgent near-term deadlines and more complexity. I should estimate that I will be caught up and able to respond on eslicarbazine by the time you propose.

John Senior

From: Yasuda, Sally
Sent: Thursday, June 27, 2013 8:21 AM
To: Sun, Su-Lin; CDER OSE CONSULTS; Zerislassie, Ermias
Cc: Senior, John R; Hershkowitz, Norman; Podruchny, Teresa
Subject: RE: DNP's Consult request for Dr. John Senior

Hi Ermias and Dr. Senior,

I would like to point out that the actual text of the consult is in the "Hy's law consult.doc" and is repeated below. We request your completed consult by July 26, 2013.

The 2 questions to be addressed are 1) whether 2 specific cases can be considered to be Hy's Rule cases due to eslicarbazepine acetate, and 2) what is your advice as to what implications the cases described should have on ongoing clinical trials in terms of exclusion or inclusion criteria, monitoring, informed consent for patients in trials, and education of investigators as to possible drug-induced liver injury with this product.

Thank you very much.

Sally

The resubmission of NDA 22-416 for the anticonvulsant, eslicarbazepine acetate, was received by DNP on February 11, 2013. The ISS noted that there were 6 subjects "partially" meeting Hy's law in the development program. None of these were in epileptic subjects. None resulted in death.

We have performed a preliminary review of the cases of these six subjects. From this review, we think one subject (2093-203-337-203058) in a trial of bipolar disorder does meet criteria for a treatment-emergent Hy's law although there are some possible caveats. Please note the narrative text describes concomitant valproic acid, but on page 4 of the narrative, the stop and start dates of the valproic acid indicate she was not on this at the time of the increases in labs and that lab values normalized after restarting valproic acid. The CRF also indicates this subject stopped valproic acid on 5-5-06 and restarted on 5-18-06. The subject's ALP increased from baseline of 69 (reference range up to 159) to 252 on Study Day 6 (after likely 4 days of eslicarbazepine).

Another subject, subject 2093206-563-563010, has a dramatic increase in transaminases but has an elevated ALP at baseline and the transaminases decrease while still on eslicarbazepine. This subject also does show an increase his ALP > 2x ULN (however <2x baseline) the day after eslicarbazepine was stopped.

We think that the remaining 4 cases either do not show patterns consistent with Hy's laws or have other obvious explanations and confounders. Three of the six were subjects in a phase 1 trial evaluating patients with hepatic impairment.

Attached please find excerpted pages from the NDA and the narratives of the two subjects described. We have also attached additional responses and follow-up information from the Sponsor. Since our first consult, there is additional information to consider for these 2 cases.

Please comment on whether these 2 cases (2093-203-337-203058 and 2093206-563-563010) can be considered to be Hy's Rule cases that are due to eslicarbazepine acetate. Due to exposure of subjects in ongoing trials, please expedite your opinion of the two cases.

We are also seeking your advice as to what implications the cases described should have on ongoing clinical trials in terms of exclusion or inclusion criteria, monitoring, informed consent for patients in trials, and education of investigators as to possible drug-induced liver injury with this product.

If you would like additional information, please contact Mary Doi at 301-796-2845 or by email. Also, the ISS can be found in the EDR under NDA 22416, SDN 65, February 11, 2013, module 5.3.5.3. Evaluation of drug-induced liver injury is discussed on pages 186-201 of the ISS.

From: Sun, Su-Lin
Sent: Wednesday, June 26, 2013 9:31 PM
To: CDER OSE CONSULTS; Zerisslassie, Ermias
Cc: Senior, John R; Hershkowitz, Norman; Podruchny, Teresa; Yasuda, Sally
Subject: DNP's Consult request for Dr. John Senior

Ermias:

DNP would like to request consult for Dr. Senior to review the attached documents related to NDA 22416 eslicarbazepine--Hy's law consult.

thanks,
Sulin

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Tuesday, April 02, 2013 2:12 PM
To: CDER OSE CONSULTS; Senior, John R
Cc: Kelley, Laurie; Hershkowitz, Norman; Podruchny, Teresa
Subject: FW: Comments on HY's law consult

Attached is DNP's consult request for Dr. Senior.
Per Dr. Senior's request to resend this consult request.

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service
Senior Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
10903 New Hampshire Ave
Silver Spring, MD 20993

Office: 301-796-0036
Fax: 301-796-9842
Email: Su-Lin.Sun@fda.hhs.gov

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From: Podruchny, Teresa
Sent: Monday, November 05, 2012 3:57 PM
To: Sun, Su-Lin
Subject: FW: Comments on HY's law consult

[IND 67466/NDA 22416](#)

Please send this consult and supporting documents to whomever consults for potential serious liver injury (like Dr. Senior?). I am not sure if it is GI but would guess it might be.
Thanks.



From: [mailto:teresa@...]
To: [mailto:teresa@...]
Subject: [mailto:teresa@...]

Teresa

IND 067466
DNP consult OSE consult request
11/2012

Recently, DNP received an NDA resubmission of an anticonvulsant. The ISS noted that there were 6 subjects meeting Hy's law in the development program. The company noted that 5 had "known liver or pancreas disorders at the time the liver dysfunction appeared." None of these were in epileptic subjects. None resulted in death. Three of the six were subjects in a phase 1 trial evaluating patients with hepatic impairment.

We have performed a preliminary review of the cases of these six subjects. From this review, we think one subject (2093-203-337-203058) in a trial of bipolar disorder does meet criteria for a treatment-emergent Hy's law although there are some possible caveats. Please note the narrative text describes concomitant valproic acid, but on page 4 of the narrative, the stop and start dates of the valproic acid indicate she was not on this at the time of the increases in labs and that lab values normalized after restarting valproic acid. The CRF also indicates this subject stopped valproic acid on 5-5-06 and restarted on 5-18-06. The subject's ALP increased from baseline of 69 (reference range up to 159) to 252 on the last day of eslicarbazepine dosing.

Another subject, subject 2093206-563-563010, has a dramatic increase in transaminases but has an elevated ALP at baseline and the transaminases go down while still on eslicarbazepine. This subject also does show an increase his ALP > 2x his baseline the day after eslicarbazepine was stopped. We think this is not a Hy's case and shows cholestatic involvement. The rest we do not think show patterns consistent with Hy's laws or have other obvious explanations and confounders. Please focus on the case of subject 2093-203-337-203058.

One other phase two subject considered by the sponsor as meeting Hy's law was diagnosed with a gastric cancer involving the pancreatic head and compressing the ductus choleducus. Thus, we did not find this case contributory.

Attached please find excerpted pages from the NDA and the narratives of the two subjects described. If you would like additional information, please contact Teresa A. Podruchny at 301-796-1132 or by email. Also, the ISS can be found in the EDR under NDA 22416, SDN 56, 9-4-12, module 5.3.5.3.28. The cases noted as meeting Hy's law are discussed on pages 159-161 of the ISS.

There are ongoing clinical trials, including trials conducted under the IND for this product. We are seeking your advice as to what implications the cases described, especially the case of subject 2093-203-337-203058, should have on ongoing clinical trials in terms of exclusion or inclusion criteria, monitoring, informed consent for patients in trials, and education of investigators as to possible drug-induced liver injury with this product.

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/s/

SU-LIN SUN
10/07/2013

MEMORANDUM OF TELECONFERENCE

Teleconference Date: September 27, 2013

Application Number: NDA 022416

Product Name: eslicarbazepine (ESL) 200mg tablet

Sponsor/Applicant Name: Sunovion Pharmaceuticals Inc.

Subject: Teleconference to discuss 200mg Biowaiver Request

FDA Participants

Ellis Unger, M.D.	Office Director, ODE1
Eric Bastings, M.D.	Acting Director, DNP
Norman Hershkowitz, M.D.	Medical Team Leader
Olen Stephens, Ph.D	Acting Branch Chief, Branch I, Division of New Drug Quality Assessment I (ONDQA)
Angelica Dorantes, Ph.D	Biopharmaceutics Team Leader
Elsbeth G. Chikhale, Ph.D	Biopharmaceutics Reviewer
Martha Heimann, Ph.D	CMC Lead
Charles Jewell, Ph.D	CMC Reviewer
Blessy George	Pharmacy Rotation Student
Su-Lin Sun, PharmD	DNP Project Manager

Olen Stephens, Acting Branch Chief, Branch I, Division of New Drug Quality Assessment I

Sunovion & BIAL Participants

Amy Schacterle, PhD	Vice President, Regulatory Affairs
Karen Joyce,	Director, Regulatory Affairs
Kim Parthum, PhD	Director, Regulatory Affairs
Andrea Young	Associate Director, Regulatory Affairs
David Blum, MD	Senior Medical Director, Clinical Development and Medical Affairs
Gary Maier, PhD	Vice President, Clinical Pharmacology
Chris Ott, PhD	Director, Quality Assurance
Bradford Sippy	Vice President, CNS Marketing
Paul McGlynn	Executive Project Director
Paula Costa, PharmD	Director, Regulatory Affairs, BIAL – Portela & C ^a , S.A.
Ricardo Lima, PharmD	Head of Pharmaceutical Development

1.0 BACKGROUND:

Sunovion was informed by Teshara Bouie, Project Manager, ONDQA, on September 5, 2013 via electronic communication that Sunovion's biowaiver request provided in NDA 22416 resubmission does not support the approval of a request for a waiver of the requirement to conduct *in vivo* BA/BE study for the ELS 200mg strength.

Sunovion requested a teleconference with DNP and ONDQA to discuss the rationale for biowaiver decision.

On September 26, 2013, ONDQA requested Sunovion to provide information on tablet hardness data eslicarbazepine acetate tablet used in BA/BE studies BIA-2093-109, BIA-2093-117, and BIA-2093-133.

On September 27, 2013, Sunovion provided response to ONDQA's September 26, 2013, request for information.

2.0 DISCUSSION:

ONDQA-Biopharmaceutics decided to grant the biowaiver for the 200mg tablet dose strength based on the following reasons:

1. The results from the *in vivo* Bioavailability (BA)/Bioequivalence (BE) studies demonstrating bioequivalence between the following clinical and commercial products.
 - BIA-2093-122 (evaluated FC 800mg vs. FP 800mg), and
 - BIA-2093-109 (evaluated FC 800mg vs. FO 200mg)
2. Although the *in vitro* dissolution profile comparison data in different pH media did not support the approval of the biowaiver request for the 200mg tablet, the overall *in vivo* data from the above BA/BE studies demonstrating that the products are bioequivalent ^{(b) (4)}

In conclusion, the data from the above BE studies support an indirect bridge between the clinical FO 200mg and commercial FP 200 mg and therefore based on these *in vivo* supportive data, ONDQA-Biopharmaceutics considers that granting the biowaiver request for the 200 mg is adequate.

3.0 ACTION ITEMS:

1. ^{(b) (4)}
ONDQA-Biopharmaceutics requested Sunovion to submit a proposal for the

dissolution acceptance criterion of the 200 mg strength and to include the dissolution data supporting their proposal.

2. Sunovion will amend the proposed label to add 200mg dose strength. For the renal impairment dosing [REDACTED] ^{(b) (4)} the Division will decide and discuss with Sunovion during the labeling negotiation in October, 2013.

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/s/

SU-LIN SUN
10/03/2013

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Friday, October 04, 2013 6:29 PM
To: Karen.Joyce@sunovion.com
Cc: Amy.Schacterle@sunovion.com
Subject: NDA 22416 eslicarbazepine information request

Importance: High

Dear Karen:

Our review team is request your team to replace figure 4 with the table format below. Please insert the value in each cell. I also provided the temporarily text for section # 14 (this is not our final draft) –hoping this may help your team to understand a little bite. If it's possible , please send your counter-proposal back to me back COB on Monday 10/7/13 or no later than Tuesday 10/8/13 noon. So our review team can work on it on Tuesday afternoon labeling section. You can just email me first with this info, don't have to submit under NDA. I can copy and paste the new info to our working label.

Thanks,
Sulin

14 CLINICAL STUDIES

14.1 Clinical Studies in Adults with Partial-Onset Seizures

The efficacy of TRADENAME as adjunctive therapy in partial-onset seizures was established in three (b) (4), randomized, double-blind, placebo-controlled, multicenter trials in adult patients (Studies 1, 2, and 3). Patients enrolled had partial-onset seizures with or without secondary generalization and were not adequately controlled with 1 to 3 concomitant AEDs. During an 8-week baseline period, patients were required to have an average of ≥ 4 partial-onset seizures per 28 days with no seizure-free period exceeding 21 days. In these 3 trials, patients had a median duration of epilepsy of 19 years and a median baseline seizure frequency of 8 seizures per 28 days. Two-thirds (69%) of subjects used 2 concomitant AEDs and 28% used 1 concomitant AED. The most commonly used AEDs were carbamazepine (50%), lamotrigine (24%), valproic acid (21%), and levetiracetam (18%). Oxcarbazepine was not allowed as a concomitant AED.

Studies 1 and 2 compared dosages of TRADENAME 400, 800, and 1200 mg once daily with placebo. Study 3 compared dosages of TRADENAME 800 and 1200 mg once daily with placebo. In all three trials, following an 8-week Baseline Phase, which established a baseline seizure frequency,

subjects were randomized to a treatment arm. Patients entered a treatment period consisting of an initial treatment phase and a subsequent maintenance phase. [REDACTED] (b) (4). The specific titration schedule differed amongst the three studies. Thus, patients were started on a daily dose of 400 mg or 800 mg and subsequently increased by 400 mg/day following one or two weeks, until the final daily target dose was achieved.

The standardized seizure frequency during the Maintenance Phase over 28 days was the primary efficacy endpoint in all three trials. [REDACTED] (b) (4)

[REDACTED] The TRADENAME treatment at 400mg/day was studied in Studies 2 and 3 and did not show significant treatment effect. A statistically significant effect was observed with TRADENAME treatment at doses of [REDACTED] (b) (4)

	Placebo	ESL 800 mg	ESL 1200 mg
Study 1			
N	xxx	xxx	xxx
LS mean seizure frequency per 28 days	x.x	x.x *	x.x*
Median Percent Reduction from Baseline in Seizure Frequency (%)	xx.x	xx.x	xx.x
Study 2			
N	xxx	xxx	xxx
LS mean seizure frequency per 28 days	x.x	x.x	x.x
Median Percent Reduction from Baseline in Seizure Frequency (%)	xx.x	xx.x	xx.x
Study 3			
N	xxx	xxx	xxx
LS mean seizure frequency per 28 days	x.x	x.x	x.x
Median Percent Reduction from Baseline in Seizure Frequency (%)	xx.x	xx.x	xx.x

[REDACTED] (b) (4)

(b) (4)

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/s/

SU-LIN SUN
10/04/2013

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Tuesday, September 24, 2013 3:23 PM
To: Amy.Schacterle@sunovion.com
Cc: Karen.Joyce@sunovion.com
Subject: NDA 22416 FDA's labeling comments (DMEPA & OPDP comments)

Importance: High

Dear Amy:

Our review team is still working on section # 14 of the PI , so at this time, I am unable to send you any change request yet since they are still engaging lots of discussions internally.

If possible there are Med Guide change request, if you can send your revised Med Guide back to me by COB on Thursday 9/26/13 (by email if you prefer) as word document, then I can include the new revised document for our DMPP and OPDP team to work on it when they review our draft PI document.

For carton and container change, I guess we may have to wait till after our Friday 9/27/13 Tcon about 200mg dose strength discussion. So probably sometimes next week, please consider submit your revised carton and container , so our DMEPA and OPDP team can review the material.

Below are the comments from DMPEA and OPDP teams for your proposed labeling (PI and Carton and container):

I.DMEPA comments:

A. General Comments for Labels and Labeling

1. Revise statements that appear in all upper case letters to title case to improve readability. For example, revise the presentation of the proposed proprietary name from all upper case letters “STEDESA” to title case “Stedesa.” (or new proposed proprietary name)

2. The established name lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2). In addition, the entire established name “(Eslicarbazepine Acetate) Tablets” should have the same font size, color, and style.

3. 60-count and 90-count bottles: Although the 60-count and 90-count bottles may be a unit-of-use container, it may also be used for more than one patient. Ensure a sufficient number of medication guides are provided.

B. Retail Preferred Oblong Bottle Container Labels: All Strengths

1. Remove or minimize and move the graphic appearing to the left of the proprietary name.

2. Relocate the statement “Keep out of reach of children” to the side panel.

3. As currently presented, the “Attention Dispenser: Each time... (b) (4) (b) (4)” statement appears more prominent than the established name.

Debold and decrease the font size of the “Attention Dispenser: Each time... (b) (4) (b) (4)” statement and remove the (b) (4) (b) (4) surrounding the statement. In addition, relocate the website information and telephone number (b) (4) (b) (4)” and “(b) (4) (b) (4)” from the principal display panel to the side panel to minimize the cluttered appearance on the principal display panel.

4. Your proposed Medication Guide statement does not comply with 21 CFR 208.24(d). As currently presented, it does not state how the Medication Guide is provided (i.e. it is unclear if the Medication Guide is “enclosed,” “accompanied,” “attached,” etc.) Revise the Medication Guide statement to include how the Medication Guide is provided per 21 CFR 208.24(d).

5. Increase the font size of the strength statement for increased prominence.

6. Revise the storage statement to read as follows ‘Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)’.

7. If space permits, we recommend separating out the “Usual Dosage” statement and the storage statements to improve readability.

8. For the 600 mg and 800 mg strength labels, decrease the font size of the “Bial” statement on the side panel since it is overly prominent.

C. Retail Alternate Round Bottle Container Labels: All Strengths

1. Please see Comments B1, B3, B4, B5, and B6 above

2. Decrease the font size of the “Bial” statement on the side

panel since it is overly prominent.

D. Retail Alternate Round Bottle Carton Labeling: All Strengths

1. Please see Comments B1, B4, B5 and B6 above

2. As currently presented, the “Attention Dispenser: Each time.. (b) (4) (b) (4) statement appears more prominent than the established name. Debold and decrease the font size of the “Attention Dispenser: Each time.. (b) (4) statement and remove the (b) (4) surrounding the statement. In addition, remove (b) (4) from the principal display panel since this information is already present on the side panel.

3. Remove the (b) (4) colored area at the bottom of the carton labeling. The use of this color on all labeling adds similarity between the packaging for the different strengths. Alternatively, consider replacing the (b) (4) color with the same color used for the strength. For example, for the 200 mg strength, use the pink color in place of the (b) (4) colored area at the bottom of the carton labeling so it matches the colored font used for statement of strength.

E. Professional Sample Blister Wallet Labeling: 400 mg, 600 mg, 800 mg, and Sample Pack

1, Please see Comments B1 and B6 above.

2. Revise the larger strength presentation so that “mg” appears on the same line of text as the number. In addition, the font used for “mg” should match the font used for the number in the strength.

3, Revise the strength presentation to read “XX mg per tablet”

4. Add dosing information similar to “Take one tablet by mouth once daily” to the panels containing drug and to the “Usual Dosage” statement on the back panel.

5. Include instructions that state how the tablets should be removed from the

blister wallet. For example, “Peel the backing from the tablet blister. Push down on the pill with your thumb so that the pill releases through the back of the blister.”

6. Remove the (b) (4) that appears on the back side of the panel containing drug product. This may confuse the patient regarding which side to push through the tablet from.
7. Remove the (b) (4) located near the colored box containing the strength statement, as these graphics are distracting.
8. Remove the (b) (4) since it is redundant to the “Attention Dispenser...” statement.
9. The “Bial” statement on the bottom of the back panel is overly prominent. Decrease the font size of this statement.
10. Decrease the font size of the “Rx Only” statement since it appears more prominent than the established name.

F. Professional Sample Blister Wallet Labeling: Sample Pack

1. The Agency does not consider starter packs to be drug samples; therefore, the use of the term “starter” on drug sample labeling is inappropriate and should not be used per 21 CFR 203.38 (c) and 64 FR 67720 at 67741. Revise the statement (b) (4) to read similar to “Sample Pack.”
2. There should be sufficient drug information on all panels of the blister wallet containing drug product in the case that the blister wallet panels are separated from each other. Add the proprietary name and established name to appear above the strength on the panels containing drug product.
3. Revise presentations of “400 & 800 mg” to read “ 400 mg and 800 mg”.

G. Professional Sample Blister Carton Labeling: 400 mg, 600 mg, 800 mg, and Sample Pack

- 1, Please see Comments F1 and F3 above

2. Relocate the Stedesa indication to below the proprietary name, established name, and strength.

3. Revise the net quantity statement to read “This package contains 28 tablets on 4 sample cards. Each sample card contains 7 tablets each.”

II. OPDP comments:

General Comments:

Since the proposed proprietary name has not been approved, we will not comment on the presentation of the proprietary name at this time.

Please apply the following comments to same or similar claims and presentations in other labeling for eslicarbazepine.

Trade Round Bottle Label

We note that the established name is presented in small, (b) (4) font which is less prominent than the other text on the proposed round bottle labeling. We recommend that the established name be presented in manner consistent with 21 CFR 201.10(g)(2) which requires that the established name be at least half the size of the letters comprising the proprietary name and have a prominence consistent with the proprietary name in terms of type, size, color, and font.

Professional Sample Blister Wallet (sample wallet)

Professional Sample Blister Wallet (sample wallet)

The proposed sample wallet includes the following claims (emphasis original):

- (b) (4)
-
-
-

These claims are misleading (b) (4)

(b) (4) We note that the primary endpoint in clinical studies with eslicarbazepine was reduction in seizure frequency from baseline to the end of the maintenance period. We recommend deleting these claims.

The front and back panels of the proposed sample wallet present (b) (4)

(b) (4). These claims are misleading (b) (4)

We acknowledge that some risk information is presented on other panels of the blister wallet and reference is made to the medication guide. However, this is not adequate. Therefore, we recommend deleting these claims or providing sufficient disclosure of the most serious and most common risks associated with the drug in depth and detail to balance these claims. Please note that reminder labeling should not include indications for use and should make no representation or suggestion relating to the drug product [21 CFR 201.100(f)].

The proposed sample wallet includes the following claims:

- (b) (4)
- (b) (4)

These claims are misleading (b) (4)

We recommend deleting these claims.

The proposed sample wallet claims. (b) (4)

This claim is misleading (b) (4)

We recommend deleting this claim.

The claim. (b) (4) is misleading (b) (4)

We recommend deleting this claim or presenting adequate risk information in conjunction with this claim.

Thanks,

Sulin

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/s/

SU-LIN SUN
09/24/2013

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Monday, September 23, 2013 7:36 PM
To: 'Amy.Schacterle@sunovion.com'
Cc: Karen.Joyce@sunovion.com
Subject: RE: NDA 22-416 FDA's labeling comments for specific sections

:-)

From: Amy.Schacterle@sunovion.com [mailto:Amy.Schacterle@sunovion.com]
Sent: Monday, September 23, 2013 7:31 PM
To: Sun, Su-Lin
Cc: Karen.Joyce@sunovion.com
Subject: RE: NDA 22-416 FDA's labeling comments for specific sections

Great! We will follow your suggestion regarding the balloon comments as well. We are happy to accommodate the discussions in sections.

Thanks again,
 Amy

From: Sun, Su-Lin [mailto:Su-Lin.Sun@fda.hhs.gov]
Sent: Monday, September 23, 2013 7:28 PM
To: Schacterle, Amy
Cc: Joyce, Karen
Subject: RE: NDA 22-416 FDA's labeling comments for specific sections

Sure, it will be helpful to insert your rational as [balloon comments](#) on the track changed version of label. So our review team will understand your team's rational.

Sorry our internal working label document still contains lots of lots of reviewer's comments which we have not discussed internally, so I can't send you that version during labeling negotiation.

Usually, we will wait till we have substantially completed PI internally, then we will send sponsor first draft label by certain date (ex. this NDA will be mid Oct). During labeling negotiation, we will just email our tracked changes version via email back and forth.

We are doing this quite differently and early at the labeling stage since there are lots of comments need to be discussed and modified. This may allow more time for both sides for labeling negotiation.

I am hoping after I send you the DMEPA and OPDP preliminary comments, and the review team OK with all the figure reformat request, then we maybe able to do the labeling negotiation via email method.

thanks,
 Sulin

From: Amy.Schacterle@sunovion.com [mailto:Amy.Schacterle@sunovion.com]
Sent: Monday, September 23, 2013 6:54 PM
To: Sun, Su-Lin
Cc: Karen.Joyce@sunovion.com
Subject: RE: NDA 22-416 FDA's labeling comments for specific sections

Sorry, one more question. Would it be OK if we omit the annotated labeling during the back and forth comments on the labeling? The annotated labeling is a heavily linked document and slows down our response time.

Thanks,
 Amy

From: Sun, Su-Lin [mailto:Su-Lin.Sun@fda.hhs.gov]
Sent: Monday, September 23, 2013 5:09 PM

To: Schacterle, Amy

Cc: Joyce, Karen

Subject: RE: NDA 22-416 FDA's labeling comments for specific sections

After we went over the CSS labeling comments discussion internally, I can send the draft comments to you. It probably will be early Oct or end of Sept.

FYI—I am hoping to send you more comments (on section 14) later tomorrow afternoon or early evening, also some DMEPA carton and container comments.

thanks,

Sulin

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From: Amy.Schacterle@sunovion.com [mailto:Amy.Schacterle@sunovion.com]

Sent: Monday, September 23, 2013 2:47 PM

To: Sun, Su-Lin

Cc: Karen.Joyce@sunovion.com

Subject: RE: NDA 22-416 FDA's labeling comments for specific sections

Hi Sulin,

Confirming receipt and thank you for the explanation. Do you think Controlled Substance Staff comments will be included in the sections we address prior to the final draft?

Thanks,

Amy

From: Sun, Su-Lin [mailto:Su-Lin.Sun@fda.hhs.gov]

Sent: Monday, September 23, 2013 1:21 PM

To: Schacterle, Amy

Cc: Joyce, Karen

Subject: RE: NDA 22-416 FDA's labeling comments for specific sections

Importance: High

Dear Amy:

There are change request from our review team for the labeling changes, I also include those sections that our review team has reviewed previously here. This will help us to moving labeling negotiation quickly if we are working together section by section (please keep that in mind the final draft version, probably won't be ready till sometimes mid or late OCT. So hopefully by then, we have most of the labeling comments agreed by then).

Please send your counter-proposed PI for those section by COB on Wed 9/25/13.

Below are the labeling changes and comments from our review team for labeling:

Section 2.3--- FDA's comments---will need to be adjusted pending data analyses

Section 2.4---see revised languages by the review team

Section 2.5---FDA's comment---We cannot make recommendation without data

Section 3---see revised language by the review team

Section 7---see revised language by the review team

Figure 1---we accepted your revised figure 1, but the review team has the following comment :

Please change the title of abscissa of the below Forrest Plot of (change of eslicarbazepine relative to the reference).

Section 8---see revised language by the review team

Figure 3-- Please make the same format as figure 1.

Section 8.9---this should be moved to DDI section

Section 14---I will send you more info on Tuesday or Wed, but below are our review team's comment for requesting (b) (4)

(Note to Sponsor:

(b) (4)

2.3 Dosage Modifications with Other Antiepileptic Drugs

(b) (4)

2.4 Dosage Modifications in Patients with Renal Impairment

A dose reduction is recommended in patients with moderate and severe renal impairment (i.e., creatinine clearance less than 50 mL/min).

(b) (4)

[see *Use in Specific Populations (8.6)* and *Clinical Pharmacology (12.3)*]

2.5 Patients with Hepatic Impairment

Dose adjustments are not required in patients with mild to moderate hepatic impairment. Use of TRADENAME in patients with severe hepatic impairment has not been studied, and use in these patients is not recommended. [see *Use in Specific Populations (8.6)* and *Clinical Pharmacology (12.3)*]

3. DOSAGE FORMS AND STRENGTHS

TRADENAME tablets are available in the following shapes and color (Table 1) with respective one-sided engraving:

Table 1: TRADENAME Tablet Presentations

Tablet Strength	Tablet Color/Shape	Tablet Markings	Functional Score
400 mg	White circular bi-convex	ESL 400	No
600 mg	White oblong	ESL 600	Yes
800 mg	White oblong	ESL 800	Yes

7 DRUG INTERACTIONS

7.1 General Information

Several AEDs (e.g., carbamazepine, (b) (4); phenobarbital, (b) (4); phenytoin, (b) (4), and primidone) can induce enzymes that metabolize TRADENAME

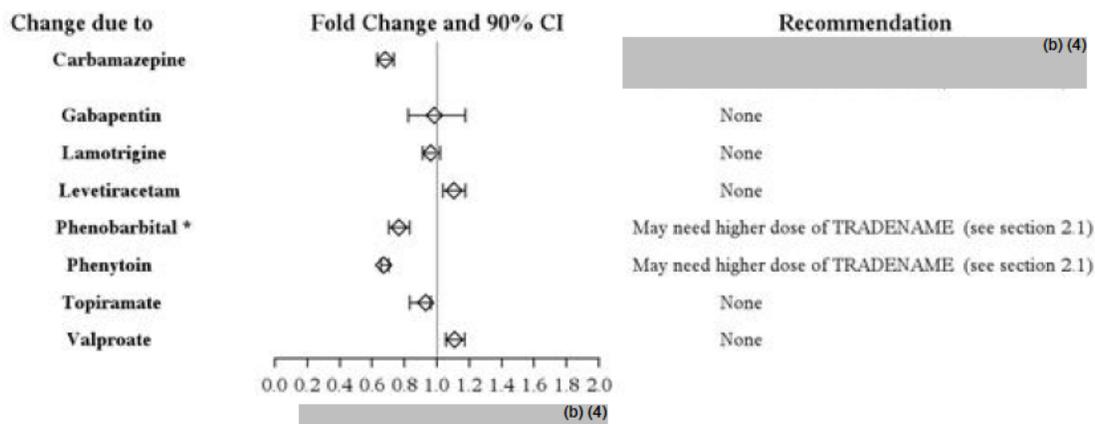
and can cause decreased plasma concentrations of eslicarbazepine (see figure 1).

TRADENAME can inhibit CYP2C19, which can cause increased plasma concentrations of drugs that are metabolized by this isoenzyme (e.g., phenytoin, clobazam, and omeprazole). In vivo studies suggest that TRADE NAME can induce CYP3A4, decreasing plasma concentrations of drugs that are metabolized by this isoenzyme (e.g., simvastatin) (see figure 2).

7.2 Potential for Other AEDs to Affect Eslicarbazepine

The potential impact of other AEDs on the systemic exposure (area under the curve, AUC) of eslicarbazepine, the active metabolite of TRADENAME, is shown in Figure 1:

Figure 1: Potential Impact of Other AEDs on AUC of eslicarbazepine



*Phenobarbital and/or phenobarbital-like AEDs (e.g., primidone)

7.3 Potential for TRADENAME to Affect Other Drugs

The potential impact of TRADENAME on the systemic exposure (AUC) of other drugs (including AEDs) is shown in Figure 2:

Figure 2: Potential Impact of TRADENAME on the AUC of (b) (4)

(b) (4)

8.1 Geriatric Use

There were insufficient numbers of elderly patients enrolled in partial-onset seizure controlled trials (N^{(b) (4)}) to determine the efficacy of TRADENAME in this patient population. The pharmacokinetics of TRADENAME were evaluated in (N=12) ^{(b) (4)} (Figure 3). Although the pharmacokinetics of eslicarbazepine are not affected by age independently, dose selection should take in consideration the greater frequency of renal impairment and other concomitant medical conditions and drug therapies in the elderly patient. Dose adjustment is necessary if CrCl is ^{(b) (4)} 50 mL/min [see *Clinical Pharmacology (12.3)*]

8.2 Patients with Renal Impairment

Clearance of eslicarbazepine is decreased in patients with impaired renal function and is correlated with creatinine clearance. Dosage adjustment is necessary in patients with CrCl^{(b) (4)} 50 mL/min (Figure 3) [see *Dosage and Administration (2.1)* and *Clinical Pharmacology (12.3)*]

8.7 Patients with Hepatic Impairment

Dose adjustments are not required in patients with mild to moderate hepatic impairment (Figure 3). Use of TRADENAME in patients with severe hepatic impairment has not been evaluated, and use in these patients is not recommended. [see ^{(b) (4)} *Clinical Pharmacology (12.3)*]

8.8 Gender

No dosage adjustment is recommended on the basis of gender (Figure 3). [see *Clinical Pharmacology (12.3)*]

Figure 3: Impact of Intrinsic Factors on ^{(b) (4)}s of TRADENAME

8.9 Females of Reproductive Potential

Because concomitant use of TRADENAME and ethinlyestradiol and levonorgestrel is associated with lower plasma levels of these hormones, females of reproductive potential should use additional or alternative non-hormonal birth control [*see Drug Interactions (7.3)*].

From: Karen.Joyce@sunovion.com [<mailto:Karen.Joyce@sunovion.com>]

Sent: Sunday, September 22, 2013 8:46 AM

To: Sun, Su-Lin

Cc: Amy.Schacterle@sunovion.com

Subject: NDA 22-416

Hi Sulin,

I will be out of the office on September 23rd and 24th. Please send all communication for NDA 22-416 to Amy Schacterle and cc me during my absence.

Thanks-

Karen

Karen Joyce

Director, Regulatory Affairs

Sunovion Pharmaceuticals Inc.

84 Waterford Drive | Marlborough, MA 01752

Office: 508-357-7856 | Fax 508-357-7491 | karen.joyce@sunovion.com

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/s/

SU-LIN SUN
09/23/2013

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Thursday, September 12, 2013 10:56 AM
To: Karen.Joyce@sunovion.com
Subject: NDA 22416 FDA's information request

Importance: High

Below is the information request from our review team for your NDA 22416:

Please send the trial number of any trials that utilized the (b) (4) 2 x 400 mg tablets for dosing. If these were phase 3 epilepsy trials, include the phase/part of the study in which this product was utilized. Please send your response as soon as possible, but no later than COB on 9/16/2013.

*Thanks,
Sulin*

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/s/

SU-LIN SUN
09/13/2013

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Friday, September 13, 2013 6:35 PM
To: Karen.Joyce@sunovion.com
Subject: FDA"s information request and FDA" proposed comments for section 7.1, 7.2, 8.1, 8.2, and 8.7--with comments--pls use this version

Importance: High

Dear Karen:

Here is the updated version, please disregard my previous 2 emails. Sorry for the confusion, it's Friday evening and my brain is toasted.

Below is the urgent request from our review team for your NDA 22416 proposed labeling :

Our review team provided comments to you and request you to modify your figure 1 and 2, Please send your revised labels back to us as soon as possible, but no later than COB on 9/18/13 Wed.

I also include our preliminary proposed comments for section 7.1, 7.2, 8.1, 8.2, and 8.7 at this time. I am hoping this will help to facilitate our labeling discussion at timely fashion.

Comments to sponsor for figure # 1:

1. Please left justified all columns

2. Delete (b) (4)

3. (b) (4)

4. (b) (4)

5. Revise Recommendation column

a. For carbamazepine—pls change recommendation to (b) (4)
Section yet to be determined.

b. please do the same for phenytoin, phenobarbital, (b) (4)

7 DRUG INTERACTIONS

7.1 General Information

7.2 Potential for Other AEDs to Affect Eslicarbazepine

The potential impact of other AEDs on the systemic exposure (area under the curve, AUC) of eslicarbazepine, the active metabolite of TRADENAME, is shown in Figure 1:



Comments to sponsor for figure # 2:

1. Please left justified all columns

2. Delete (b) (4)

3. (b) (4) e of the X-axis to the maximum number of 2, and adjust the numeric internal of X-axis to show more detail (e.g., place tics at 0.2, 0.4, 0.6, 0.8, 1, 1.2, 1.4, 1.6, 1.8, and 2).

4. Revise Recommendation column

- a. For carbamazepine—please provide an asterisk on the recommendation and add a footnote—describe this is potential pharmacodynamic interaction
- b. Phenytoin—adjustment may be needed based on clinical response and serum levels.

7.3 Potential for TRADENAME to Affect Other Drugs

The potential impact of TRADENAME on the (b) (4) of other drugs (including AEDs) is shown in Figure 2:





8.1 Geriatric Use

There were insufficient numbers of (b) (4) patients enrolled in partial-onset seizure controlled trials (N= (b) (4)) to determine the efficacy of TRADENAME in this patient population. The pharmacokinetics of TRADENAME were evaluated in (N=12) (b) (4) (Figure 3). Although the pharmacokinetics of eslicarbazepine is not affected by age (b) (4), dose selection (b) (4)

. Dose adjustment is necessary if CrCl is (b) (4) 50 mL/min. [see *Clinical Pharmacology (12.3)*]

8.2 Patients with Renal Impairment

Clearance of eslicarbazepine is decreased in patients with impaired renal function and is correlated with creatinine clearance. Dosage adjustment is necessary in patients with CrCl (b) (4) 50 mL/min (Figure 3) [see (b) (4) and *Clinical Pharmacology (12.3)*]

8.7 Patients with Hepatic Impairment

Dose adjustments are not required in patients with mild to moderate hepatic impairment (Figure 3). Use of TRADENAME in patients with severe hepatic impairment has not been evaluated, and use in these patients is not recommended. [see (b) (4) *Clinical Pharmacology (12.3)*]

P.S. Probably next week, I will send you other comments from DMEPA team regard to carton and container, currently it's still under clearance process with other teams.

Thanks,
Sulin

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/s/

SU-LIN SUN
09/13/2013

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Monday, August 26, 2013 3:39 PM
To: 'Karen.Joyce@sunovion.com'
Subject: RE: NDA 22416 information request

OK, thanks :-)

From: Karen.Joyce@sunovion.com [mailto:Karen.Joyce@sunovion.com]
Sent: Monday, August 26, 2013 2:59 PM
To: Sun, Su-Lin
Subject: RE: NDA 22416 information request

Hi Sulin,

Confirming receipt. I am back from vacation so no need to cc: Amy any more.

Thanks-
Karen

Karen Joyce
Director, Regulatory Affairs
Sunovion Pharmaceuticals Inc.
84 Waterford Drive | Marlborough, MA 01752
Office: 508-357-7856 | Fax 508-357-7491 | karen.joyce@sunovion.com

From: Sun, Su-Lin [mailto:Su-Lin.Sun@fda.hhs.gov]
Sent: Monday, August 26, 2013 2:43 PM
To: Joyce, Karen
Cc: Schacterle, Amy
Subject: NDA 22416 information request
Importance: High

Dear Karen and Amy:

Below is the information request from our review team for your NDA 22416, please send your response to us as soon as possible, but no later than COB on 9/2/13:

Please provide CRFs for all cases of overdoses, medication errors, poisoning and toxicity for period covered by NDA and all new post-marketing cases. If the CRF is already in the data base provide a link.

Thanks,
Sulin

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/s/

SU-LIN SUN
08/26/2013

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Friday, August 23, 2013 2:19 PM
To: 'Amy.Schacterle@sunovion.com'
Cc: Karen.Joyce@sunovion.com
Subject: RE: FDA's comments on [REDACTED] (b) (4)

(b) (4)

3 pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SU-LIN SUN
08/23/2013

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Friday, August 23, 2013 5:58 PM
To: 'Amy.Schacterle@sunovion.com'
Cc: Karen.Joyce@sunovion.com
Subject: NDA 22416 FDA's information request

Importance: High

Dear Amy:

Below is the information request from our review team for your NDA 22416:

The response in sequence 110 to NDA 22416 indicates that there were no instances where a patient's actual seizure data over time comes from both an EE and DE diary source. However, upon our review of diary data submitted in sequence 91 for subject 304-004-00407, it appears that baseline diary data are from an EE diary (diary D00701 in the CRF bookmark) and other maintenance data are from DE diaries (N84338). Please explain.

If you have any question, please feel free to contact me.

Thanks,
Sulin

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/s/

SU-LIN SUN
08/23/2013

MEMORANDUM of TELECONFERENCE

MEETING DATE: July 30, 2013
TIME: 11:30 AM-12:00 PM
LOCATION: WO Rm 5313, Bldg 22
APPLICATION: NDA 022416
DRUG NAME: (b) (4)
TYPE OF MEETING: Guidance, Proprietary Name

MEETING CHAIRS: Irene Z. Chan, PharmD, BCPS, Team Leader, DMEPA

FDA ATTENDEES: Irene Z. Chan, PharmD, BCPS, Team Leader, DMEPA
Julie Villanueva Neshiewat, PharmD, Safety Evaluator, DMEPA
Marcus Cato, MBA, Team Leader OSE Project Management

SPONSOR ATTENDEES: Karen Joyce, Director, Regulatory Affairs
Lisa Herman, PharmD, MS, R.Ph., Associate Director, Regulatory Affairs
Andrea Young, Associate Director, Regulatory Affairs
David Blum, M.D., Senior Medical Director, Clinical Development and
Medical Affairs

(b) (4)
(b) (4)
(b) (4)

Paula Costa, PharmD, Director, Regulatory Affairs, BIAL – Portela & Ca, S.A.

BACKGROUND:

The Division of Medication Error Prevention and Analysis (DMEPA) previously evaluated the proposed proprietary name, Stedesa, for this application (see OSE review # 2009-675 dated July 2, 2009). Due to a change in product characteristics, a subsequent review of the proposed name determined it was unacceptable due to orthographic similarities and overlapping product characteristics with the marketed product, Stalevo. The Applicant was informed by teleconference, and the Applicant subsequently withdrew the request to review the proposed proprietary name, Stedesa. On May 16, 2013, the Applicant submitted for review the proposed proprietary name, (b) (4)

MEETING OBJECTIVES:

DMEPA requested a teleconference with the Applicant to discuss the review of the proposed proprietary name, (b) (4)

DMEPA CONCERNS WITH THE PROPOSED NAME

DMEPA has safety concerns with the proposed proprietary name, (b) (4)

(b) (4)

(b) (4)



REGULATORY OPTIONS

- 1) Withdraw the proposed proprietary name, (b) (4) and submit a proposed proprietary name that is orthographically different from (b) (4)
- 2) Wait for DMEPA to complete our review of the name, (b) (4) and issue a denial letter.

DISCUSSION

When queried by the applicant, FDA stated that it could not provide any more information regarding the pending proposed proprietary name that is vulnerable to name confusion. The applicant expressed a desire to avoid ambiguity around an acceptable trade name late in the review cycle. The applicant inquired if it would be acceptable to submit 3 additional alternate names along with their request for review of their primary name when resubmitting. FDA advised that it was acceptable and advised the Applicant to clearly delineate their choices in their resubmission cover letter. However, the FDA reminded the Applicant that they review only one name at a time.

The Applicant noted that it would take the DMEPA comments under advisement but they were not ready to make a decision regarding the regulatory path forward.

POST MEETING NOTE

On August 02, 2013, the Applicant sent the below via e-mail:

Sunovion would like to thank the representatives from DMEPA for taking the time to discuss their preliminary assessment of our proposed trade name, [REDACTED]^{(b) (4)} (eslicarbazepine acetate).

As indicated during the July 30, 2013 teleconference, we understand that DMEPA has concerns of potential medication errors with the proposed trade name [REDACTED]^{(b) (4)} based on perceived similarities with [REDACTED]^{(b) (4)}, and an unnamed product currently pending review.

We have decided to maintain the current application for [REDACTED]^{(b) (4)} and we request that DMEPA take the following information into consideration when conducting the overall risk assessment and finalizing the review of the trade name [REDACTED]^{(b) (4)}



Based on the information presented above, Sunovion believes that the risk of medication error is low as there are significant and obvious differences between the product characteristics of each product identified and [REDACTED] (b) (4). With this in mind, Sunovion requests that DMEPA continue the review of the application for the evaluation of the proposed trade name [REDACTED] (b) (4).

In the event the final DMEPA assessment for [REDACTED] (b) (4) is consistent with the preliminary assessment, we would respectfully request a copy of the formal report in order to understand the methodology and rationale for DMEPA's assessment. With the NDA PDUFA date approaching, this information would help us to identify viable alternate names for submission to DMEPA.

Please do not hesitate to contact me if you have any questions regarding the above.

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/s/

IRENE Z CHAN
08/15/2013



NDA 022416

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Sunovion Pharmaceuticals Inc.
84 Waterford Drive
Marlborough, MA 01752

ATTENTION: Karen Joyce
Director, Regulatory Affairs

Dear Ms. Joyce:

Please refer to your New Drug Application (NDA) dated March 29, 2009, and received March 30, 2009, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Eslicarbazepine Acetate Tablets, 200 mg, 400 mg, 600 mg, and 800 mg.

We also refer to your correspondence, dated and received May 16, 2013, requesting review of your proposed proprietary name, (b) (4) We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:



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

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review (see the Guidance for Industry, *Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”).

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Ermiyas Zerislassie, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0097. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Su-Lin Sun, at (301) 796-0036.

Sincerely,

{See appended electronic signature page}

Kellie Taylor, PharmD, MPH
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

KELLIE A TAYLOR
08/14/2013

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Monday, August 12, 2013 2:14 PM
To: 'Karen.Joyce@sunovion.com'
Subject: NDA 22416 information request

Importance: High

Dear Karen:

Below are the information request from our review team for your NDA 022416:

In reference to NDA 22-416, please submit the following information by COB August 16, 2013:

- 1) For subject 304-051-05101, explain why the labs drawn during the discontinuation visit or the post study visits are not included in the integrated laboratory dataset or the tabulations dataset for study 304.
- 2) Provide follow up information regarding the postmarketing report (#2013SP001942), specifically including start date of ESL therapy (and dosage), complete set of laboratory values (along with the normal ranges and baseline values) that includes AST/ALT, ALP, total bilirubin, electrolytes, BUN/Creatinine, WBC, eosinophils, Hgb/Hct, platelets), any radiologic imaging, consultative evaluations, biopsy results, hospitalizations/clinic visits, prior liver disease (if any), alcohol use. Furthermore, please report any additional work up for alternative causes for the liver test abnormalities (specifically any of the viral hepatitises [hepatitis A, B, C, D, E], CMV, EBV, HSV, toxoplasmosis, varicella, parvovirus, serologic tests for autoimmune hepatitis, comprehensive list of all concomitant medications including herbal supplements).
- 3) Confirm that the analysis laboratory datasets do not contain laboratory measurements drawn outside of study visits (e.g., hospitalizations).

Thanks,
Sulin

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/s/

SU-LIN SUN
08/12/2013



NDA 022416

MEETING DENIED

Sunovion Pharmaceuticals Inc.
Attention: Karen Joyce
Director, Regulatory Affairs
84 Waterford Drive
Marlborough, MA 01752

Dear Ms. Joyce:

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

We also refer to your July 26, 2013, correspondence requesting a type B meeting to discuss

(b) (4)

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

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/s/

ERIC P BASTINGS
08/07/2013

Sun, Su-Lin

From: Karen.Joyce@sunovion.com
Sent: Thursday, August 01, 2013 2:54 PM
To: Sun, Su-Lin
Subject: RE: NDA 22416 information request

Dear Sulin,

This is confirmation of receipt of the RFI.

Kind regards,

Karen

Karen Joyce

Director, Regulatory Affairs

Sunovion Pharmaceuticals Inc.

84 Waterford Drive | Marlborough, MA 01752

Office: 508-357-7856 | Fax 508-357-7491 | karen.joyce@sunovion.com

From: Sun, Su-Lin [mailto:Su-Lin.Sun@fda.hhs.gov]
Sent: Thursday, August 01, 2013 2:43 PM
To: Joyce, Karen
Subject: NDA 22416 information request
Importance: High

Dear Karen:

Below are the information request from our review team for your NDA 22416:

“Amendment 3 dated 9-16-10 implemented the daily entry diary (DE) versus the event entry diary (EE). Table 20 of the CSR for study 304 indicates that 154 placebo, 137 of the 800 mg eslicarbazepine acetate group, and 136 of the 1200 mg eslicarbazepine acetate group provided DE dairy data in the ITT population. Table 14.2.1.2 indicates that 48 to 63 subjects from each group included in the analyses of the ITT population used EE diary. Did any subjects use both diaries? If so, identify these subjects. Please respond within one week of receipt of this request.”

Thanks,
Sulin

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/s/

SU-LIN SUN
08/02/2013

From: Sun, Su-Lin
To: ["Karen.Joyce@sunovion.com";](mailto:Karen.Joyce@sunovion.com)
Subject: NDA 22416 FDA's information request
Date: Wednesday, July 24, 2013 10:33:00 AM

Dear Karen:

Below are the information request from our review team for your NDA 22416:

Please submit the following information for NDA 22-416 by COB July 29th:

1) For the subjects listed with ECGs that were “unable to evaluate,” please enumerate and list those subjects with adverse events in the SOC cardiac disorders and other cardiac-related PTs in HLGTS Cardiac and vascular investigations, Enzyme investigations. Also enumerate and list those subjects with serious adverse events and TEAEs leading to discontinuation in the SOC cardiac disorders and other cardiac-related PTs in HLGTS Cardiac and vascular investigations, Enzyme investigations.

2) For the Nonepilepsy Controlled Pool, explain the discrepancy between the number of subjects who had WBC differentials and the number of subjects who had WBC values listed in the ISS tables. Also explain why for the majority of the subjects from Study 203, although the WBC differentials were included in the CRFs, these values were not included in the analysis laboratory datasets.

We have noted your response in the Safety Information Amendment dated 5/20/13 on page 14 that the following laboratory parameters were obtained and included in the raw datasets, but were not intended for integration and therefore are not considered as missing: “Hematology differentials in % form – the absolute values for hematology differentials were selected for integration, so the % unit results were not considered necessary.” It does appear that for these subjects in Study 203, when the WBC differentials were only recorded as % unit results (and not the absolute values) in the CRFs, these values were not included in the analysis laboratory datasets. However, when subjects only have WBC differential data recorded as % unit results (and not in both % unit and absolute values), these % unit results should be included in the analysis datasets (either as raw values or after converting into absolute values). Importantly, the analysis datasets should not be missing laboratory data because the data was collected in different units.

Confirm that all of the missing WBC differentials are limited to the bipolar studies

(or if these was not limited to the bipolar studies, identify all of the studies in which WBC differentials were not included in the analysis datasets but recorded in the CRF as a percentage). All of the WBC differentials that were collected on the subjects in all of the completed ESL studies should be included in the analysis laboratory datasets. After converting all of the WBC differentials that were recorded as % unit values into absolute values, reperform the analyses for the hematology parameters and fill in the following table shells for the nonepilepsy double-blind studies together (including Study 206) by randomized dose groups.

Table 1: Potentially Clinically Significant Changes (≥ 1 post-dose value) for Subjects Normal at Baseline

Parameter	Placebo		ESL (randomized dose groups)					
	n	#PCS (%)	<600 mg ≥ 1400 mg		600-<1000 mg Total ESL		1000-<1400 mg	
	n	#PCS (%)	n	#PCS (%)	n	#PCS (%)	n	#PCS (%)
Neutrophils $<1.5 \times 10^3/\text{mm}^3$								
Neutrophils $>13.5 \times 10^3/\text{mm}^3$								
Lymphocytes $>12 \times 10^3/\text{mm}^3$								
Monocytes $>2.5 \times 10^3/\text{mm}^3$								
Eosinophils $>1.6 \times 10^3/\text{mm}^3$								
Basophils $>1.6 \times 10^3/\text{mm}^3$								

Table 2: Consecutive Potentially Clinically Significant Changes for ≥ 2 visits for Subjects Normal at Baseline

Parameter	Placebo		ESL (randomized dose groups)					
	n	#PCS (%)	<600 mg ≥ 1400 mg		600-<1000 mg Total ESL		1000-<1400 mg	
	n	#PCS (%)	n	#PCS (%)	n	#PCS (%)	n	#PCS (%)

Neutrophils $<1.5 \times 10^3/\text{mm}^3$

Neutrophils $>13.5 \times 10^3/\text{mm}^3$

Lymphocytes $>12 \times 10^3/\text{mm}^3$

Monocytes $>2.5 \times 10^3/\text{mm}^3$

Eosinophils $>1.6 \times 10^3/\text{mm}^3$

Basophils $>1.6 \times 10^3/\text{mm}^3$

Table 3: Mean change from baseline to end of treatment

Parameter	Placebo	ESL (randomized dose groups)							
		<600 mg		600-<1000 mg		1000-<1400 mg		≥ 1400 mg	
		n	mean Δ	n	mean Δ	n	mean Δ	n	mean Δ
Neutrophils ($\times 10^3/\text{mm}^3$)									
Lymphocytes ($\times 10^3/\text{mm}^3$)									
Monocytes ($\times 10^3/\text{mm}^3$)									
Eosinophils ($\times 10^3/\text{mm}^3$)									
Basophils ($\times 10^3/\text{mm}^3$)									

Table 4: Shifts at end of study (or early termination visit) from normal at baseline

Parameter	Placebo	ESL (randomized dose groups)							
		<600 mg		600-<1000 mg		1000-<1400 mg		≥ 1400 mg	
		n	# shift (%)	n	# shift (%)	n	# shift (%)	n	# shift (%)
Neutrophils to low									

Neutrophils to high
Lymphocytes to low

Monocytes to low
Eosinophils to low
Basophils to low

If you have any question, please feel free to contact me.

Thanks,
Sulin

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/s/

SU-LIN SUN
07/24/2013

Bouie, Teshara

From: Bouie, Teshara
Sent: Thursday, July 11, 2013 4:55 PM
To: 'kimberly.parthum@sunovion.com'
Cc: Sun, Su-Lin
Subject: NDA 22416 - Information Request

Hi Kimberly,

The Biopharm reviewer has the following requests for information:

1. Provide full dissolution profile data (e.g. 10, 15, 20, 30, 45, and 60 minutes) with figures and tables containing individual data, mean, and SD for a 200 mg drug product batch with formulation FP, manufactured at (b) (4) (b) (4) and compare it to dissolution profiles of 400 mg, 600 mg, and 800 mg tablet batches with formulation FP that were used in clinical studies (include batches used in the BIA-2093-130 clinical study). Provide f2 calculations for the comparisons.
2. Provide full dissolution profile data (e.g. 10, 15, 20, 30, 45, and 60 minutes) with figures and tables containing individual data, mean, and SD for the 400, 600, and 800 mg (b) (4) tablets. Provide f2 calculations for the comparisons.
3. Provide full dissolution profile data (e.g. 10, 15, 20, 30, 45, and 60 minutes) with figure and tables containing individual data, mean, and SD for the 200 mg (b) (4) tablets used to create Figure 16. Provide f2 calculations for the comparison.

Regards,

Teshara G. Bouie, MSA, OTR/L

CDR, United States Public Health Service
Regulatory Health Project Manager
FDA/CDER/OPS/ONDQA
Division of New Drug Quality Assessment I
Phone (301) 796-1649
Fax (301) 796-9749

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/s/

TESHARA G BOUIE
07/11/2013

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Friday, June 28, 2013 2:13 PM
To: 'Karen.Joyce@sunovion.com'
Subject: NDA 22416 information request

Dear Karen:

Below is the information request from our review team for your NDA 22416:

Submission 99 to NDA 22416 (6-21-13) provides additional information for two patients. Please provide your consultant's opinion on case 203-337-203058 with consideration of the additional medical information in submission 99. Also, we acknowledge you sent the summary of (b) (4) conclusions. Please send a copy of the original reports (i.e. the first consult and the re-consult) from (b) (4) as well. Thank you.

Thanks,
Sulin

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/s/

SU-LIN SUN
06/28/2013

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Thursday, June 27, 2013 2:53 PM
To: 'Karen.Joyce@sunovion.com'
Subject: NDA 22416 FDA's information request

Importance: High

Attachments: example of vilazdone label--2013.pdf

Dear Karen:

Below are information request from our review team for your NDA 22416:

I. Clinical Team's information request:

In order to further evaluate the potential hepatotoxicity of eslicarbazepine acetate, please provide a table similar to ISS Table 7.7.1.3.1 that displays the data from study 46, the completed historical-control monotherapy study. For patients who did have ALT elevations > 3x ULN, report any signs or symptoms consistent with gastrointestinal toxicity or hepatitis. If you are aware of any IND or non-IND clinical trial cases of serious hepatic injury that were not included in the NDA submissions, provide them with this response. For any subjects who do meet Hy's criteria, send the narratives and CRF. Provide your response within 5 business days of receipt of this request. Thank you.

II. Clinical Pharmacology Team's information request:

We request you to use "forest plots" (b) (4) to present the drug PK at Sections 7 (Drug Interactions) and 8 (Use in Specific Populations) of the Stedesa label according to the attached publication. The SAS code to make the forest plot is also provided for your reference.

Using forest plots in drug labeling can more effectively communicate intrinsic and extrinsic factors effects on pharmacokinetics (b) (4). This approach has been implemented successfully in several recent new approvals and labeling revisions (e.g., VIIBRYD® (vilazodone HCl)).

Should you have any questions please contact us via the Regulatory Project Manager for this submission. Thank you.



example of vilazdone label--20..

Thanks,
Sulin

13 pages of Approved Labeling of Viibryd (Vilazodone HCl) have been Withheld in Full immediately following this page as it can be found at drugs@fda website

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2 pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

Essential Pharmacokinetic Information for Drug Dosage Decisions: A Concise Visual Presentation in the Drug Label

D Menon-Andersen¹, B Yu¹, R Madabushi¹, V Bhattaram¹, W Hao¹, RS Uppoor¹, M Mehta¹, L Lesko¹, R Temple², N Stockbridge², T Laughren² and JV Gobburu¹

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SU-LIN SUN
06/27/2013

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Thursday, June 27, 2013 4:28 PM
To: 'Karen.Joyce@sunovion.com'
Subject: NDA-22416 Information Request --additional info
Importance: High
Attachments: NDA 22146--FDA's information request-06-27-2013.pdf; SASCode_ForestPlots.doc; ForestPlotsPaper.pdf

Dear Karen:

The first attachment is the email I just sent to you about the IR.
I am including 2 more documents that our clinical pharmacology team would those to be included in our information request email.

thanks,
Sulin

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Sun, Su-Lin

From: Sun, Su-Lin
Sent: Friday, June 14, 2013 10:19 AM
To: 'Amy.Schacterle@sunovion.com'; Karen.Joyce@sunovion.com
Subject: RE: Request for Status Update Meeting - NDA 22416--FDA's response comments
Importance: High

Dear Amy and Karen:

Below are the comments from our review team ,(approved by Dr. Katz), for your NDA 22416:

We acknowledge your June 6, 2013 electronic communication requesting a status update meeting with the Division. We have determined that, at this time, such a meeting would not be productive. Our review team is focusing on reviewing your NDA application as efficiently and quickly as possible. We expect to take an action on your application by the November 2013 goal date; it is not possible at this time to commit to taking an action prior to that date. We realize that the Division has sent many information requests; we consider requests such as these a routine part of the review process.

If you have any question, please feel free to contact me.

thanks,
Sulin

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From: Sun, Su-Lin
Sent: Thursday, June 06, 2013 11:01 PM
To: 'Amy.Schacterle@sunovion.com'
Subject: RE: Request for Status Update Meeting - NDA 22416

Your request has been forward to our review team which including CSS team. As soon as I receive their recommendation, I will follow up with you.

thanks,
Sulin

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From: Amy.Schacterle@sunovion.com [mailto:Amy.Schacterle@sunovion.com]
Sent: Thursday, June 06, 2013 5:05 PM
To: Sun, Su-Lin
Subject: Request for Status Update Meeting - NDA 22416

Dear Sulin,

Having received the May 8, 2013 letter indicating a 3 month extension of the review period for NDA 22-416 and noting the number and nature of the requests regarding both the safety data as well as the abuse liability data, we would like to request a meeting to discuss the status of the NDA review. Our team is fully dedicated to supporting the review and providing responses to questions posed by the Division and CSS. However, in keeping with FDA's Transparency Initiatives, we believe a meeting might provide additional efficiency in the review process, particularly if there are potential review concerns for which we might be able to provide additional clarification. We would also like to better understand the Division's and CSS' review processes and expectations regarding timing for completion of the review. In particular, can the Division and the CSS provide status updates on their respective reviews? Further, can the Division pursue the shortest extension possible to allow the potential for completion of the review in advance of the November 2013 PDUFA date? Can the CSS identify any opportunities to complete their review within the original PDUFA timeframe of August 2013, since the basis of the review extension was unrelated to the assessment of abuse potential?

We would like to schedule the meeting as soon as possible in order to afford the greatest efficiency to the remainder of the review. We prefer to meet in person, but would accommodate a teleconference if a face-to-face meeting cannot be arranged quickly.

Best regards,
Amy

Amy L. Schacterle, Ph.D.
Vice President, Regulatory Affairs
Sunovion Pharmaceuticals Inc.
84 Waterford Drive, Marlborough, MA 01752
Tel: 508.787.4025
Email: amy.schacterle@sunovion.com

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SU-LIN SUN
06/17/2013

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Monday, June 17, 2013 1:52 PM
To: Karen.Joyce@sunovion.com
Subject: NDA 22416 information request

Importance: High

Dear Karen:

Below is the information request for your NDA 22416:

Please submit the following information for eslicarbazepine acetate by June 21st:

1) In the ISS, it is reported that the postmarketing data includes a total of “2 cases consistent with a diagnosis of Stevens-Johnson syndrome.” In the Safety Information Amendment dated June 10, 2013, there was 1 case coded to SJS. Please provide the case report for the other case of SJS (or the case report number if the case report was already provided in this recent Safety Information Amendment). For cases BIAL-01037 and BIAL-01249, provide the following additional information regarding this patient: onset date of events, hospitalization dates, any treatment information, other associated symptoms, consultative evaluations, biopsy results, start dates of the concomitant medications, and serum laboratory values (including HLA testing). Furthermore, please report any additional work up for alternative causes (specifically any infectious etiologies, comprehensive list of all concomitant medications including herbal supplements).

2) In the Safety Information Amendment dated June 10, 2013, a case report was provided for a case of “hepatorenal syndrome.” Provide the following additional information regarding this patient: start date of ESL therapy, any radiologic imaging, consultative evaluations, biopsy results, complete set of laboratory values (along with the normal ranges and baseline values) that includes AST/ALT, ALP, electrolytes, BUN/Creatinine, WBC, eosinophils, Hgb/Hct, platelets. Furthermore, please report any additional work up for alternative causes for the liver test abnormalities (specifically any of the viral hepatitis [hepatitis A, B, C, D, E], CMV, EBV, HSV, toxoplasmosis, varicella, parvovirus, serologic tests for autoimmune hepatitis, comprehensive list of all concomitant medications including herbal supplements).

3) Provide the narratives for subjects who experienced metamorphopsia and Sjogren’s syndrome.

If you have any question, please feel free to contact me.

Thanks,

Sulin

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/s/

SU-LIN SUN
06/17/2013

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Thursday, June 13, 2013 2:03 PM
To: 'Amy.Schacterle@sunovion.com'; Karen.Joyce@sunovion.com
Subject: RE: NDA 22-416, Response to June 6, 2013 RFI--FDA's comment for submission date

Dear Amy and Karen:

Per our review team, your proposed submission date June 21, 2013 is acceptable.

thanks,
Sulin

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From: Amy.Schacterle@sunovion.com [mailto:Amy.Schacterle@sunovion.com]
Sent: Wednesday, June 12, 2013 6:03 PM
To: Sun, Su-Lin
Cc: Karen.Joyce@sunovion.com
Subject: RE: NDA 22-416, Response to June 6, 2013 RFI

Dear Sulin,

Serial 96 is a response to the June 6, 2013 request to modify the IB and informed consent, affording us the opportunity to respond within 5 days if we believed there was a misinterpretation or discussion was necessary. We do believe there should be more discussion in advance of modifying the IB/consent and we provided the justification, as requested in the June 6, 2013 communication.

Serial 96, however, is not a complete response to the May 31, 2013 request for additional information concerning subject 203-337-203058. As we highlighted in an email communication dated June 6, 2013, the statement in serial 93 (submitted June 5, 2013) that no further information was available is based solely on the available records at Bial, our partner who sponsored the study. Bial has since contacted the clinical site and we are awaiting additional information, which we intend to submit by June 21, 2013.

Best regards,
Amy

From: Sun, Su-Lin [mailto:Su-Lin.Sun@fda.hhs.gov]
Sent: Wednesday, June 12, 2013 12:06 PM
To: Schacterle, Amy
Cc: Joyce, Karen
Subject: RE: NDA 22-416, Response to June 6, 2013 RFI
Importance: High

Dear Amy and Karen:

Our review team would like me to double check the following with you:

Serial 96 to NDA 22416 is a response to an IR dated June 6, 2103. Is this to be considered a complete response?

thanks,

Sulin

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From: Amy.Schacterle@sunovion.com [<mailto:Amy.Schacterle@sunovion.com>]

Sent: Tuesday, June 11, 2013 4:51 PM

To: Sun, Su-Lin

Cc: Karen.Joyce@sunovion.com

Subject: NDA 22-416, Response to June 6, 2013 RFI

Dear Sulin,

Please see attached the cover letter and response submitted today, within 5 days of the Division's June 6, 2013 request to revise the IB and informed consent forms for ongoing studies.

Best regards,

Amy

Amy L. Schacterle, Ph.D.

Vice President, Regulatory Affairs

Sunovion Pharmaceuticals Inc.

84 Waterford Drive, Marlborough, MA 01752

Tel: 508.787.4025

Email: amy.schacterle@sunovion.com

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/s/

SU-LIN SUN
06/13/2013



NDA 22416

INFORMATION REQUEST

Sunovion Pharmaceuticals Inc.
Attention: Karen Joyce, Director, Regulatory Affairs
84 Waterford Drive
Marlborough, MA 01752-7010

Dear Ms. Joyce:

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

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

CMC:

1. Update the Structured Product Labeling (SPL) section to include the 200 mg strength tablet information.
2. Bulk stability testing on 400 mg, 600 mg and 800 mg tablets was not performed at standard long term storage conditions, provide justification for this.
3. Revise your post approval commitment for stability testing so that you put your first three commercial lots of each strength / packaging configuration on stability testing. You may use an appropriate bracketing strategy for strength and headspace ratio in bottles and for strength in blisters, but the bracketing strategy should be separate for bottles and blisters (e.g., bottles and blister cannot be mixed for bracketing of stability testing). For determination of the expiration dating period for the various drug product strength/packaging configurations in the application, the agency will use the current round bottle and blister data.
4. Revise your annual stability testing strategy for the drug product so that annually, one batch of each strength in each packaging configuration is submitted to stability testing. Again, bracketing can be used, if appropriate, but bottles and blisters should not be mixed in the bracketing strategy for this annual stability testing commitment.

Biopharmaceutics:

5. In order to set the dissolution acceptance criteria, provide multi point dissolution profile data (individual, mean, SD, batch numbers) in tabulated and graphical form for the pivotal clinical

and registration batches for each strength of your proposed drug product using the proposed dissolution method

6. It appears that you do not have BA/BE data for the 200 mg drug product manufactured at (b) (4). Therefore, you may request a Biowaiver for the 200 mg drug product including a justification and supportive information such as dissolution data and comparative dissolution profiles with f2 testing between:

- The 200 mg drug product, formulation FP, made at (b) (4) and
- The 400 mg, 600 mg and 800 mg tablets with formulation FP used in the BIA-2093-122 clinical study

7. Provide a corrected Table 11 (pg 18/50 section P.2.drug product). The provided table appears to have several typographical errors (for example the entry for (b) (4) tablets for 400 mg at 15 minutes, 800 mg at 15 and 45 minutes).

If you have any questions, contact Teshara G. Bouie, Regulatory Project Manager, at (301) 796-1649.

Sincerely,

{See appended electronic signature page}

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

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/s/

RAMESH K SOOD
06/13/2013

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Friday, June 07, 2013 3:51 PM
To: 'Karen.Joyce@sunovion.com'
Subject: NDA 22416 information request

Importance: High

Dear Karen:

Below are the information request from our review team for your NDA 22416:

Please provide the following information for ESL by June 14th:

- 1) For subject 2093114-000-0008 laboratory values after the April 11, 2005 visit are not included in the ADLAB dataset. Provide a new narrative that includes the adverse events (in the ADEVENTX dataset) that began on or after April 19, 2005 and the corresponding laboratory values and vital signs. Please also specify the name of the single dose of DDI drug that the subject received.
- 2) Provide the unique subject ID for the subject reported on page 186 of the ISS with a SAE of DRESS syndrome in Study 305. Provide the narrative (if not already provided).

Please provide the following information for ESL by June 21st:

- 1) We have noted in the June 5th response to our information request that “there is no additional follow-up information” for subject 206-563-563010. However, we request additional attempts to collect follow up information (repeat laboratory values, procedures/surgeries, medical conditions, hospitalizations, radiology reports, pathology reports after study discontinuation) by contacting the clinical site, subject, site investigator, hospital, etc.

Thanks,
Sulin

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/s/

SU-LIN SUN
06/07/2013

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Thursday, June 06, 2013 11:24 AM
To: 'Karen.Joyce@sunovion.com'
Subject: NDA 22416 information request

Importance: High

Dear Karen:

Below are the information request from our review team for your NDA 22416:

Subject 203-337-203058 in the bipolar disorder study appears to meet Hy's rule for drug-induced liver injury. Though the narrative is medically insufficient, we do not find the valproate or pancreatitis convincing to rule out eslicarbazepine. Based on information in the narrative (Prior and Concomitant Medications) and in the CRF, the valproic acid was stopped on 5-5-06 and restarted on 5-18-06. Transaminases and bilirubin normalize in the face of restarting valproic acid. No pancreatic enzyme results were provided.

Given the potential consequences of drug-induced-liver-injury, the Investigator's Brochure should be revised upon receipt to include a description of this case. The case summary should be written by an appropriately trained medical professional who can adequately and succinctly describe the pertinent details. The discussion of the case should include

- That this case is a potential Hy's case ($ALT \geq 3x$ ULN plus serum bilirubin $\geq 2x$ ULN)
- That preliminary review indicates it is probably related to eslicarbazepine acetate though there is imperfect medical information
- That full review of the potential of eslicarbazepine to induce liver injury is ongoing.

Finally, Investigators should be advised and subjects should be consented/re-consented accordingly.

If you believe there is misinterpretation or requires discussion, make the argument within the next 5 days after receipt of this email.

Otherwise, the time line to initiate the processes described is 2 weeks.

Thanks,

Sulin

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/s/

SU-LIN SUN
06/06/2013

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Friday, May 31, 2013 2:45 PM
To: 'Karen.Joyce@sunovion.com'
Subject: NDA 22416 information request

Importance: High

Dear Karen:

Below are the information request from our review team for your NDA 22416:

In reference to NDA 22-416, please submit Items 1 and 2 by June 5th, 2013, Items 4-10 by June 7th, and Item 3 by June 14th :

1) For Subject 2093203-337-203058, it is reported in the ISS (page 195) that this subject was “taking valproic acid as a concomitant medication” and “[w]hile on a titration dose of 600 mg (randomized to 1200 mg), the subject developed elevated liver test values, which on Day 5 were: AST 1447, ALT 1154 (ULN for both 38), total bilirubin 2.56 (ULN 1.2).” Please explain the discrepancy between this information in the ISS and the following information provided in the narrative: the valproic acid was stopped 5 days prior to the first dose of ESL and while on the ESL dose of 1200 mg/day, on Day 6 the labs were AST 1447 ALT 1154 total bilirubin 2.56. Furthermore, please report any additional work up for alternative causes for the liver test abnormalities (specifically any of the viral hepatitis [hepatitis A, B, C, D, E], CMV, EBV, HSV, toxoplasmosis, varicella, parvovirus, serologic tests for autoimmune hepatitis, radiologic imaging, biopsy results, comprehensive list of all concomitant medications including herbal supplements).

2) For subject 206-563-563010, INR values were not included in the ISS datasets. Report all INR, PT, or PTT laboratory parameters that were collected for this subject (or confirm that these coagulation parameters were not obtained). Furthermore, please report any additional work up for alternative causes for the liver test abnormalities (specifically any of the viral hepatitis [hepatitis A, B, C, D, E], CMV, EBV, HSV, toxoplasmosis, varicella, parvovirus, serologic tests for autoimmune hepatitis, radiologic imaging, biopsy results, comprehensive list of all concomitant medications including herbal supplements). Provide any additional follow up information on this subject (repeat laboratory values, medical conditions, procedures, pathology reports, hospitalizations, radiology reports, etc after study discontinuation).

3) In your listing of all uninterpretable ECGs (for Studies 301, 302, 304), for Study 301 subject 2093-301-101-90186 is listed as have ECGs “unable to evaluate.” However in the CRF for this subject, the 6 ECGs (dated from 2/23/05 to 10/25/06) were adequate enough to evaluate the ECG parameters. Please explain why this subjects’ ECGs were reported as “unable to evaluate.” Furthermore, the CRFs for subjects 304-801-80101 and 304-353-35301 (among others) did not contain the actual copies of the ECGs. Please explain – were these missing?. Please reevaluate all of the ECGs reported a “uninterpretable” and obtain all of the ECG parameters (potentially clinically significant values, mean changes, ECG abnormalities). Reperform the analyses for ECG parameters – specifically provide revised ISS Tables 10.1.1, 10.1.2, and 10.1.4 that includes this additional ECG data.

4) Explain the discrepancy between the number of subjects in the Phase 3 Epilepsy Controlled Pool with potentially clinically significant values for free T4 <0.75 ng/dL reported in the ISS and Safety Information Amendment dated 5/20/13 Table 9.1.12.9.r1.

5) In ISS Table 7.7.4.16.1, it is reported that no subjects had “any TEAEs of the SMQ Drug-Related Hepatic Disorder that were serious.” However, the following subject reported PTs in the SMQ Drug-related hepatic disorder (comprehensive search): 207-222-222011 jaundice and cholestasis. Please explain this discrepancy.

Identify all of the subjects that reported in the ISS with any TEAEs of the SMQ Drug-Related Hepatic Disorder (comprehensive search) that were serious.

6) In Section 6.4.2.3, postmarketing cases are reported that could suggest hepatic disorders or hepatotoxicity. For all of the serious adverse events reported in the SOC Hepatobiliary Disorders or in the SMQ Hepatic disorders, provide the case reports.

7) In Section 6.4.2.2, postmarketing cases are reported that could suggest hypersensitivity reactions. For all of the serious adverse events reported as DRESS, or in the SOC Skin/Subcutaneous disorders or in the SMQs Anaphylactic reaction, Angioedema, or Severe cutaneous adverse reactions, provide the case reports.

8) Provide the case reports for the postmarketing cases of all deaths.

9) Provide the case reports for the postmarketing cases of all cases of pancytopenia, agranulocytosis, aplastic anemia, and acute pancreatitis.

10) Fill in the table shell below and provide the unique subject IDs for any subject (in the entire ESL database) who fits the last 3 categories: ALT or AST >3x baseline and total bilirubin > baseline, ALT or AST >3x baseline and total bilirubin >2x baseline, ALT or AST >3x baseline and total bilirubin >2x baseline and ALP <2x baseline.

Liver Test Result Outliers (using baseline values), Controlled Pools

Test/Cutoff threshold	Phase 3 DB Epilepsy		Nonepilepsy DB Pool (including Study 206)	
	Placebo n=426	ESL n=1021	Placebo n=507	ESL n=1755
ALT				
ALT >3x baseline				
ALT >5x baseline				
ALT >10x baseline				
ALT >20x baseline				
AST				
AST >3x baseline				
AST >5x baseline				
AST >10x baseline				
AST >20x baseline				
Total bilirubin				
Total bilirubin > baseline				
Total bilirubin >1.5x baseline				
Total bilirubin >2x baseline				

ALP				
ALP >1.5x baseline				
ALT or AST >3x baseline and total bilirubin > baseline				
ALT or AST >3x baseline and total bilirubin >2x baseline				
ALT or AST >3x baseline and total bilirubin >2x baseline and ALP <2x baseline				

Thanks,
Sulin

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/s/

SU-LIN SUN
05/31/2013

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Tuesday, May 21, 2013 3:32 PM
To: Karen.Joyce@sunovion.com
Subject: NDA 22416 information request

Importance: High

Attachments: Picture (Enhanced Metafile); Picture (Enhanced Metafile)

Dear Karen:

Below are information request from our review team, please send your response to us as soon as possible, but no later than COB on June 4, 2013.

Information Request for NDA 22416

If any of the information requested below was already submitted in the NDA, provide the information regarding its location.

Human Physical Dependence Data

1. You should provide updated tables for the Physical Dependency Population regarding withdrawal AEs at 7 and 30 days, separated by disease. In the current tables (A.1.2.3.1 and A.1.2.3.2), there is a discrepancy between the total number of subjects (N=1269, based on 30 healthy volunteers + 98 epilepsy patients + 1141 non-epilepsy patients) compared to those listed in the summary tables (N = 1725, A.1.1.1.1 and A.1.1.1.2). Provide an explanation regarding the 584 subjects that were not accounted for in the current tables, and provide data for these subjects in the form of updated tables.
2. Page 414 of the ISS states that 187 epilepsy patients who completed the study were included in the Physical Dependency Population. However, Table A.1.2.3.1 (7 day withdrawal data) and Table A.1.2.3.2 (30 day withdrawal data) show only a total N=98. Similarly, the ISS states that there were 50 healthy volunteers, but the withdrawal tables show a total of 30 subjects. You should provide an explanation regarding the missing subjects that were not accounted for in the current tables, and provide data for these subjects in the form of updated tables.
3. Withdrawal data for non-epilepsy patients (N=1141) were provided in the Physical Dependency Population. However, there is a discrepancy between the number of subjects in that population compared to the number of subjects who completed at least Phase I studies for diabetic and herpetic neuropathy, fibromyalgia and migraine (an approximate N= 1908). You should provide an explanation regarding the missing subjects that were not accounted for in the current tables, and provide data for these subjects in the form of updated tables.
4. You should provide withdrawal data for all healthy volunteers (at 7 and 30 days) based on the criteria provided on page 387 of the ISS. Tables A.1.2.3.1 and A.1.2.3.2 provide data for only 30 healthy volunteers. However, there appears to be at least 160 volunteers who completed more than 7 days of eslicarbazepine treatment and who were without concomitant use of other drugs, which should be accounted for in the submitted data.
5. You should provide withdrawal data at 7 and 30 days for epilepsy patients that are not currently included in the total epilepsy population. The data submitted to date only include Study #301, 302, 303 and 304, but there are additional placebo-controlled studies in epilepsy patients that have not been

included (such as Study #201).

6. Include data from all epilepsy patients who completed the studies or had at least 7 days of treatment in the withdrawal data for the epilepsy population. The present withdrawal data show that for Study #301, 302 and 304, the total number of patients who underwent a drug tapering period was N=269 and the number of patients who underwent abrupt withdrawal was N= 98, for a total patient number of N=367. Based on adverse events data in ISS Table 7.1.4.1.s5 and Table 7.2.3.1, the number of Phase 3 eslicarbazepine patients in the Controlled pool was N=1021 and the number in the Uncontrolled pool was N=639, for a total patient population of N=1660. You should provide an explanation regarding the 1293 subjects that were not accounted for in the current tables, as well as data for these subjects in form of updated tables.
7. You should provide an explanation regarding the inclusion of patients from epilepsy Study # 301 and 304 (ISS: Table 90, page 387, see below) in the Physical Dependency Population. These patients were described as having a drug tapering period in the submission, which would have excluded them from the abrupt population pool. If these patients were abruptly discontinued, provide recalculated tables for the pool of patients who underwent a drug tapering period.

Table 90: Studies for Evaluation of Physical Dependence following Abrupt Discontinuation

Study #	Patient Population	Study Type	ESL Dose Range	Duration on ESL	Duration off Drug
Epilepsy Studies					
2093-301	Epilepsy	Phase III, Part 1	400 to 1200 mg	16 weeks	2-6 weeks
2093-302	Epilepsy	Phase III, Part 1	400 to 1200 mg	14 weeks	4 weeks
2093-303	Epilepsy	Phase III, Part 1	800 to 1200 mg	14 weeks	4 weeks
2093-304	Epilepsy	Phase III, Part 1	400 to 1600 mg	16 weeks	4 weeks

8. You should provide information regarding all patients from Study #301 and 304 who were abruptly discontinued, including the reason for the drug discontinuation.
9. ISS Table 88, page 386 (below) shows drug tapering periods of 4 and 2 weeks (respectively) for Study # 301 and 304. However, Table 88 shows that for Study #301, patients underwent a drug tapering period of 2 weeks, followed by placebo administration for an additional 2 weeks. You should provide clarification regarding whether the total drug tapering period was only 2 weeks before drug discontinuation was completed. Provide information regarding the follow-up for all patients who had a drug tapering period as well as information regarding the duration of time that these patients were followed after the drug tapering periods. Provide clarification regarding whether the collection of withdrawal adverse events started on the first day of the drug tapering period.

Study	Randomized Treatment Group (mg)	Titration Dose (mg), Week 1 / Week 2	Maintenance Dose (mg), Weeks 1-12	Tapering-off Dose ^a (mg), Week 1 / Week 2 / Weeks 3-4
2093-301 Part 1	400	400 / 400	400	400 / 400 / Placebo
	800	400 / 800	800	800 / 400 / Placebo
	1200	400 / 800	1200	800 / 400 / Placebo
2093-302 Part 1	400	400 / 400	400	No Taper
	800	800 / 800	800	No Taper
	1200	800 / 800	1200	No Taper
2093-304 Part 1	800	400 / 400	800	400 / 400 / No Dose
	1200	600 / 600	1200	600 / 600 / No Dose
		800 / 800 ^b	1200	800 / 800 / No Dose ^c 800 / 400 / No Dose ^d

10. You should provide information regarding the number and timing of follow-up visits that each patient or healthy volunteer had following abrupt drug discontinuation.
11. You should provide CRFs for all cases of seizures and convulsions that occurred during drug tapering and abrupt discontinuation withdrawal periods.
12. You should provide CRFs for all incidents of the AE of drug toxicity (ISS: Table A.1.2.3.2) during the withdrawal period.
13. You should provide available withdrawal data from pediatric epilepsy studies.

Physical dependence study in mice following oral administration of eslicarbazepine Study #093-890

- 1 You should provide a statistical analysis to validate the study by showing that the diazepam-treated group produced withdrawal behaviors that a) differentiate from placebo statistically and b) are sufficiently similar to known withdrawal behaviors produced in animals following chronic administration of diazepam in other studies. A non-statistical observation of the data suggests that there is only a single behavior (startle response) that may differentiate from placebo during the drug discontinuation period. However, diazepam withdrawal is known to produce many more behaviors in animals, such as piloerection, tremor, pelvic elevation, tail elevation, changes in body tone, abdominal tone and pupil size, seizures, anxiety, hypersalivation, writhing, and muscle rigidity.
- 2 You should provide a statistical analysis for the eslicarbazepine data. One comparison should evaluate the behaviors observed in each eslicarbazepine treatment group to both placebo and to the two diazepam groups, during the drug discontinuation period. A second comparison should evaluate the behaviors observed in each eslicarbazepine treatment group during the drug discontinuation period to the behaviors observed in the same groups during drug administration.
- 3 You should summarize the behaviors observed during the drug discontinuation period on the basis of the time of occurrence (e.g., which day or hour). If possible, these data should be correlated to pharmacokinetic data on the plasma levels of eslicarbazepine in animals at those timepoints.
- 4 You should provide an explanation of the term "intubation error", given that you attribute 4 of 8 animal deaths to this cause. Specifically, explain if intubation refers to a tube placed into the trachea for life-saving purposes, or to a tube placed into the stomach for oral drug or food administration.

Su-Lin Sun, PharmD
LCDR, United States Public Health Service
Senior Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4200
10903 New Hampshire Ave
Silver Spring, MD 20993

Office: 301-796-0036
Fax: 301-796-9842
Email: Su-Lin.Sun@fda.hhs.gov

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/s/

SU-LIN SUN
05/21/2013

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Wednesday, May 15, 2013 12:56 PM
To: 'Amy.Schacterle@sunovion.com'
Cc: Karen.Joyce@sunovion.com
Subject: NDA 22416 information request clarification

Importance: High

Dear Amy:

Below is information request clarification from our review team for your NDA 22416:

In reference to NDA 22416, please submit the following information ([clarification in blue to previous request Item #3](#)) by May 17th:

3) To follow up on item #7 in our request on April 17th that is due to us on May 17th, please confirm that the bilirubin (total, indirect, and direct), glucose, and total cholesterol values from Study 304 are missing from the ISS analysis datasets. Identify and list (by study) any other laboratory, vital, or ECG values that are missing from the ISS analysis datasets. Submit new updated analysis datasets [and analyses](#) that include these missing values. [Please name these new datasets with new names \(e.g., ADLAB1, ADLAB2, ADLAB3, ADLAB4\) that are different from the ADLB datasets \(ADLB1, ADLB2, ADLB3, ADLB4\) that were submitted in February 2013.](#)

Thanks,
Sulin

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/s/

SU-LIN SUN
05/15/2013



NDA 022416

**PROPRIETARY NAME REQUEST
WITHDRAWN**

Sunovion Pharmaceuticals Inc.
84 Waterford Drive
Marlborough, MA 01752

ATTENTION: Karen Joyce
Director, Regulatory Affairs

Dear Ms. Joyce:

Please refer to your New Drug Application (NDA) dated and received February 10, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Eslicarbazepine Acetate Tablets, 200 mg, 400 mg, 600 mg, and 800 mg.

We acknowledge receipt of your correspondence, dated and received on May 9, 2013, notifying us that you are withdrawing your request for a review of the proposed proprietary name Stedesa. This proposed proprietary name request is considered withdrawn as of May 9, 2013.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Ermias Zerislassie, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0097. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager Su-Lin Sun, at (301) 796-0036.

Sincerely,

{See appended electronic signature page}

Carol Holquist, 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

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/s/

FRANKLIN T STEPHENSON
05/15/2013

CAROL A HOLQUIST
05/15/2013

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Monday, May 13, 2013 12:50 PM
To: 'Karen.Joyce@sunovion.com'
Subject: NDA 22416 information request

Importance: High

Dear Karen:

Below is information request from our review team for your NDA 22416:

In reference to NDA 22416, please submit the following information by May 17, 2013:

1) Provide potentially clinically significant ECG values for Study 201, 206, and 207 in tabular format stratified by PCS criteria and by treatment group.

2) Provide the unique subject IDs for the subjects in studies 301, 302, and 304 whose ECGs were "uninterpretable."

3) To follow up on item #7 in our request on April 17th that is due to us on May 17th, please confirm that the bilirubin (total, indirect, and direct), glucose, and total cholesterol values from Study 304 are missing from the ISS analysis datasets. Identify and list (by study) any other laboratory, vital, or ECG values that are missing from the ISS analysis datasets. Submit new updated analysis datasets that include these missing values.

If you have any question, please feel free to contact me.

Thanks,

Sulin

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/s/

SU-LIN SUN
05/14/2013

MEMORANDUM of TELECONFERENCE

MEETING DATE: May 1, 2013
TIME: 11:00 AM EST
LOCATION: Teleconference
APPLICATION: NDA 022416
DRUG NAME: Stedesa (Eslicarbazepine Acetate) Tablets
TYPE OF MEETING:

MEETING CHAIRS: Irene Z. Chan, PharmD, BCPS *DMEPA TL*
Laurie Kelley, PA-C, MPAS, MPH *OSE SRPM*

FDA ATTENDEES:

Office of Surveillance and Epidemiology

Laurie Kelley, PA-C, MPAS, MPH, Safety Regulator Project Manager

Division of Medication Error Prevention and Analysis

Irene Z. Chan, Pharm.D., BCPS, Team Leader

Julie Neshiewat, Pharm.D., Safety Evaluator

SPONSOR ATTENDEES:

Sunovion Attendees:

Amy Schacterle, Vice President, Regulatory Affairs

Karen Joyce, Director, Regulatory Affairs

David Blum, Senior Medical Director, CDMA

Brad Sippy, Vice President, Marketing

Chris Fanale, Director, Marketing

Paul McGlynn, Executive Project Director, Product Development

(b) (4)

Attended for Training Purposes from Sunovion:

Lisa Herman, Associate Director, Regulatory Affairs

Andrea Young, Associate Director, Regulatory Affairs

Bial – Portela Attendee:

Paula Costa, Director, Regulatory Affairs.

BACKGROUND: On April 15, 2009, the Applicant submitted for review to the Division of Medication Error Prevention and Analysis (DMEPA) the proposed proprietary name, Stedesa, for NDA 022416, Eslicarbazepine Acetate Tablets. The Applicant received a conditional approval for the proposed proprietary name, Stedesa, on July 10, 2009. The Applicant received a Complete Response Letter on April 30, 2010. During the resubmission of the NDA, the Applicant resubmitted a request for proprietary name review for Stedesa on February 26, 2013.

MEETING OBJECTIVES:

The purpose of the teleconference is to inform the Applicant that based on DMEPA's preliminary review of the proposed proprietary name, Stedesa, we have concern with the currently marketed name, Stalevo.

DMEPA CONCERNS WITH THE PROPOSED NAME:

The proposed proprietary name, Stedesa, has orthographic similarity and overlapping product characteristics with the currently marketed product, Stalevo (Carbidopa, Levodopa, and Entacapone). The orthographic similarity can be attributed to the fact that both names begin with 'St,' contain an upstroke letter at the fourth position, which is followed by the letter 'e,' and the last letter 'o' in Stalevo and the last letter 'a' in Stedesa look similar when scripted. Both names also have a similar shape and contain seven letters, giving the names a similar length when scripted.

We consulted the USP Quality Review Use Caution—Avoid Confusion¹ and the ISMP List of Confused Drug Names² and identified name confusion between drug names that have the letter 'l' and 'd' in the infix: Avelox vs. Avandia, Eulexin vs. Edocrin, and Ritalin vs. Ritodrine. Confusion between these drug names supports our concerns regarding the potential for orthographic confusion between Stalevo and Stedesa. In addition to orthographic similarity, these products have overlapping product characteristics such as dosage form (tablets) and route of administration (oral). Although Stalevo is a combination product involving three ingredients, the levodopa strength of Stalevo is reflected in the proprietary name as a modifier. Therefore, there is numerical overlap between Stalevo 200 and Stedesa 200 mg. In addition, the frequencies 'QID' and 'QD' can look similar when scripted (i.e. if Stalevo 200 is prescribed QID and Stedesa is prescribed QD). Given the totality of this information, we are concerned that the name pair Stalevo and Stedesa is vulnerable to name confusion, which may lead to medication errors.

Stalevo 200 1 tab po QID
Stedesa 200mg 1 tab po QD

We acknowledge that our conclusion on the acceptability of the name differs from our previous review of the proposed proprietary name and differs from the conclusions reached by the [REDACTED] (b) (4). However, since the original review of the proposed proprietary name, the product characteristics have changed: a 200 mg strength and dosage was added for patients with renal impairment. Although Stalevo was identified in the external name study from [REDACTED] (b) (4) did not re-evaluate the list of names that are orthographically and/or phonetically similar to the name Stedesa when the new strength and dosage of 200 mg was added. During our re-evaluation of the proposed proprietary name, Stedesa, we determined that the additional 200 mg strength and dosage increases the risk for name confusion with Stalevo 200.

REGULATORY OPTIONS:

1. Wait for DMEPA to complete our review of the name, Stedesa, and issue a denial letter.
2. Withdraw the proposed proprietary name, Stedesa, and submit a proposed proprietary name that is orthographically different from Stedesa.

¹ United States Pharmacopeia Quality Review Use Caution—Avoid Confusion. No. 79. April 2004.

² Institute for Safe Medication Practices' List of Confused Drug Names. 2011.

DISCUSSION:

1. Question from Applicant – If the 200 mg dose was removed from the proprietary name request would this change DMEPA’s decision with regards to acceptability of the name?
 - a. DMEPA can only review a proprietary name based on the product characteristics submitted by the Applicant, which should match the product characteristics they intend to seek approval for. If changes in strength or dosing are to be made to the application, this would need to be discussed with the review division. DMEPA therefore suggests that any such discussion be vetted through the Division of Neurology Products.
2. Question from Applicant – If the product characteristics are identical to those reviewed during the first cycle, would DMEPA find the proposed proprietary name, Stedesa, acceptable?
 - a. DMEPA response – If there are no additional changes in product characteristics or new information that needs to be considered, then DMEPA would likely maintain our original decision regarding the proposed proprietary name.

ACTION ITEMS

- Sponsor to discuss and provide decision with regards to regulatory options.

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/s/

LAURIE A KELLEY
05/08/2013

IRENE Z CHAN
05/08/2013



NDA 022416

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Sunovion Inc.
Attention: Karen Joyce
Director, Regulatory Affairs
84 Waterford Drive
Marlborough, MA 01752

Dear Ms. Joyce:

Please refer to your March 29, 2009 New Drug Application (NDA), received March 30, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for eslicarbazepine acetate tablets

We also refer to your February 10, 2013 amendment, received on February 11, 2013, which in combination with your September 4, 2012 amendment, constituted a complete, class 2 response to our Complete Response (CR) letter dated April 30, 2010, and our Acknowledge Incomplete Response (AIR) letter dated November 2, 2012.

On March 27, 2013, we received your March 27, 2013, solicited major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is November 11, 2013.

Finally, we remind you of your April 26, 2013, agreement to send your responses to questions 5-9 from our April 17, 2013, Information Request prior to May 17, 2013.

If you have any questions, call Su-Lin Sun, Pharm.D, Regulatory Project Manager, at (301) 796-0036 or email su-lin.sun@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

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/s/

RUSSELL G KATZ
05/08/2013

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Friday, May 03, 2013 11:49 AM
To: 'Karen.Joyce@sunovion.com'
Subject: NDA 22416 SAS dataset request for eDISH

Importance: High

Dear Karen:

Below are the urgent request from our review team for NDA 22416:

Your April 23, 2013 submitted liver enzyme data for eDISH (evaluation of drug-induced serious hepatotoxicity) as xlsx files rather than SAS data. Those xlsx files cannot be converted to SAS data sets. We request you to redo the data so that all the data that we receive are SAS data. Please send us SAS data for Studies 301, 302, and 304.

Please send 2 desk copies of CD to my office as soon as possible.

Note: my office room number has changed to room # 4200 (not 4209).

Thanks,
Sulin

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/s/

SU-LIN SUN
05/03/2013

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Thursday, May 02, 2013 12:32 PM
To: Karen.Joyce@sunovion.com
Subject: NDA 22416 information request

Importance: High

Dear Karen:

Below is the information request from our review team for your NDA 22416:

Please clarify the possible data discrepancy for subject 30505 between the diary transcription information and the dataset information. Though we are unable to locate the seizure diary itself, the "Transcription of Patient's Seizures" in the CRF indicates that not all seizures were documented between visits 3 and 4 (p.66/184) and between visits 4 and 5 (p 81/184). The dataset seizure.xpt and Listing 16.2.6.1.1 of the CSR indicate that there were no seizures on 2-4-10 (Visit 3 date) and none for the remainder of the maintenance phase. Also, send the diary for this subject or reference the CRF page numbers for the diary if the diary is already present. Please respond within 5 days of receipt of this request. Thank you

Thanks,

Sulin

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/s/

SU-LIN SUN
05/02/2013

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Thursday, April 25, 2013 3:04 PM
To: 'Amy.Schacterle@sunovion.com'
Cc: Karen.Joyce@sunovion.com
Subject: NDA 22416 information request

Importance: High

Dear Amy:

Below are the information request from our CSS team for your NDA 22416, please send your response to me as soon as possible, no later than COB on 4/30/13:

1. Please provide explanation what was the reason for missing such a large number of sessions in 18 subjects for alprazolam 3 mg, if it was due to AEs, please provide description of AE, subject # and treatment session ID, or indicate where this information can be found within NDA.
2. Please provide explanation why on the Drug Liking VAS both doses of alprazolam 1.5 and 3 mg have 2 and 3 Emax peaks, respectively; we were not able to find drug concentrations data for alprazolam to correlate with PD data..
3. Please provide explanation why there were so many subjects who had high placebo responses for Good Drug Effects VAS and High VAS in this study.

If you have any question, please feel free to contact me.

Thanks,

Sulin

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/s/

SU-LIN SUN
04/25/2013

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Wednesday, April 24, 2013 5:58 PM
To: Amy.Schacterle@sunovion.com
Cc: 'Karen.Joyce@sunovion.com'
Subject: NDA 224416 efficacy diary audits--

Importance: High

Attachments: CRF audit request for study 304.jmp

Dear Amy:

Below are information request from our review team for your NDA 22416:

1) We are conducting an audit of diary data. In order to complete this audit, please send the CRFs for the subjects from study 304 that are included in the JMP table under the column "subjid". Please send these CRFs within 1 week of receipt of this email. Also, perform a comparison of the seizure diary data to the dataset data for each subject in the JMP table. Fill out the JMP dataset that is attached and send this back to us. Please submit the completed JMP table results within 3 weeks.



CRF audit request
for study 30...

2) Please confirm that all studies conducted in humans, all phases of development, IND or non-IND, epilepsy or other indications, have included informed consent and have had IRB approval, or the local equivalent of IRB approval. If this information is already in the NDA submissions, please advise where we may find it.

If you can't open the JMP table attachment, please let me know as soon as possible.
If you have any question, please feel free to contact.

Thanks,

Sulin

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/s/

SU-LIN SUN
04/24/2013

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Wednesday, April 17, 2013 10:35 AM
To: 'Karen.Joyce@sunovion.com'
Cc: Kelley, Laurie
Subject: NDA 22416 Sample request clarification

Importance: High

Dear Karen:

Below are the comments from our review team:

On April 5, 2013, you submitted samples of the actual (b) (4) blisters containing drug. However, we are interested in receiving samples of the blisters contained within the wallets. At this time, we request that samples of the blisters be sent inside the wallets with artwork (i.e. the packaging configuration that a patient would receive - wallet labeling that contains the blisters of drug) for the all of the strengths and in particular, the starter pack containing the 400 mg and 800 mg tablets. We request a response by COB Tuesday, April 23, 2013. Thank you.

Once again, please ship the sample to Ms. Laurie Kelley.

Thanks,
Sulin

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/s/

SU-LIN SUN
04/17/2013

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Wednesday, April 17, 2013 1:21 PM
To: 'Karen.Joyce@sunovion.com'
Subject: NDA 22416 FDA's information request

Importance: High

Attachments: Table shells 3--04-17-13.doc

Dear Karen:

Below are the information request from our review team:

In reference to NDA 22-416, please submit the following information by COB April 24, 2013.

- 1) Explain why only 76% of ESL subjects and 78% of placebo subjects had at least one post-dose ECG assessment. Explain why in ISS Table 10.1.2, the number of subjects with a maximum change from baseline for QTcB/QTcF intervals for the 3 categories (<30 ms, >=30-<60 ms, >=60 ms) does not add up to the total number of subjects with measured ECG parameters (334 placebo subjects and 771 ESL subjects).
- 2) For ISS Table 10.1.4 (ECG abnormalities), please list the specific examples of abnormalities under each ECG category (rhythm, conduction, morphology abnormalities) (similar to Table 10.5.4 for the Phase 1 Study Pool). Please confirm that these are all treatment emergent ECG abnormalities.
- 3) For the nonepilepsy studies, please list all of the studies in which ECGs were collected and the number of subjects per study with ECG data. Explain the discrepancy between the number of subjects with ECGs listed in ISS Tables 10.4.1/10.4.2.1 (59 ESL subjects and 17 placebo subjects) and ISS Table 10.4.4.1 (1124 ESL subjects and 354 placebo subjects). Reperform the analyses for Tables 10.4.1 and 10.4.2.1 with the ECG data from all of the subjects.
- 4) Provide potentially clinically significant ECG values for Study 201, 206, and 207.
- 5) For the urinalysis parameters, provide mean changes from baseline for pH and specific gravity and shift results to abnormal from baseline to end of study/early termination visit for urine parameters (RBC, WBC, bacteria, casts, crystals, epithelial cells, and yeast/fungi).
- 6) There are no bicarbonate values reported in the ISS. Provide potentially clinically significant values, measures of central tendency, shift changes for bicarbonate values. Provide also potentially clinically significant values, measures of central tendency, shift changes for magnesium values (if available). Reperform the PCS analyses (for all pooled groups) for creatinine using >1.5 xULN instead of >=2 mg/dL.
- 7) Explain why for the Phase 3 Epilepsy Controlled Pool, only 201 placebo subjects and 577 ESL subjects had glucose values (both baseline and end of study values) and 201 placebo and 580 ESL subjects had bilirubin values and 202 placebo and 582 ESL subjects had total cholesterol values, even though >400 placebo and >990 ESL subjects had other electrolyte values, hepatic values, and LDL values.
- 8) For hyponatremia, perform analyses (similar to ISS Tables 7.7.1.1.2 and 7.7.1.1.3) for time to and duration of hyponatremia determined by sodium values (<130 meq/L).

9) Fill in the table shells in the attached file.



Table shells
3--04-17-13.doc (...)

If you have any question, please feel free to contact me.

Thanks,
Sulin

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List all of the studies that measured orthostatic changes in vital signs. For each controlled study that measured orthostatic changes, fill out the following table:

Table 1. Concurrent Orthostatic SBP Decrement and Pulse Increment

	Study 1	
	Placebo	ESL
# Subjects	n=	n=
SBP decrement ≥ 20 mmHg and HR increase		
HR increase ≥ 15		
HR increase ≥ 30		
SBP decrement ≥ 40 mmHg and HR increase		
HR increase ≥ 15		
HR increase ≥ 30		

Table 2. Increase from Baseline in SBP and DBP by Study Period, Epilepsy Phase 3 DB Pool

	Systolic BP		Diastolic BP	
	Placebo n (%)	Total ESL n (%)	Placebo n (%)	Total ESL n (%)
End of Titration Period				
	n=	n=	n=	n=
Increase 5 - 10 mm Hg				
Increase 11 - 15 mm Hg				
Increase 16 - 20 mm Hg				
Increase > 20 mm Hg				
Maintenance Period				
	n=	n=	n=	n=
Increase 5 - 10 mm Hg				
Increase 11 - 15 mm Hg				
Increase 16 - 20 mm Hg				
Increase > 20 mm Hg				
End of Treatment				
	n=	n=	n=	n=
Increase 5 - 10 mm Hg				
Increase 11 - 15 mm Hg				
Increase 16 - 20 mm Hg				
Increase > 20 mm Hg				

Table 3. Decrease from Baseline in SBP and DBP by Study Period, Phase 3 Epilepsy Controlled Pool

	Systolic BP		Diastolic BP	
	Placebo n (%)	Total ESL n (%)	Placebo n (%)	Total ESL n (%)
End of Titration Period				
	n=	n=	n=	n=
Decrease 5 - 10 mm Hg				
Decrease 11 - 15 mm Hg				
Decrease 16 - 20 mm Hg				
Decrease > 20 mm Hg				
Maintenance Period				
	n=	n=	n=	n=
Decrease 5 - 10 mm Hg				
Decrease 11 - 15 mm Hg				
Decrease 16 - 20 mm Hg				
Decrease > 20 mm Hg				
End of Treatment				
	n=	n=	n=	n=
Decrease 5 - 10 mm Hg				
Decrease 11 - 15 mm Hg				
Decrease 16 - 20 mm Hg				
Decrease > 20 mm Hg				

Table 4. Weight Change Categories, Phase 3 Epilepsy Controlled Pool

Amount Change (kg) from baseline	Placebo n (%)	ESL n (%)			
		400 mg	800 mg	1200 mg	Total
Total subjects	n=	n=	n=	n=	n=
-10 to ≤-5					
-5 to ≤0					
0 to ≤5					
>5 to ≤10					
>10 to ≤15					
>15 to ≤20					

Table 5. Concurrent low chloride and low sodium levels, Phase 3 Epilepsy Controlled Pool (*please perform same analyses for every pooled group)

Category	Placebo n (%)	ESL n (%)			
		400 mg	800 mg	1200 mg	Total
	n=	n=	n=	n=	n=
Chloride \leq 90 meq/L and					
sodium $>$ 135 meq/L					
sodium $>$ 130- \leq 135					
sodium $>$ 125- \leq 130					
sodium \leq 125 meq/L					
Chloride \leq LLN and					
sodium $>$ 135 meq/L					
sodium $>$ 130- \leq 135					
sodium $>$ 125- \leq 130					
sodium \leq 125 meq/L					

*concurrent values at the same lab visit

LLN= lower limit of normal

Table 6. Increases and Shifts in Lipids, Phase 3 Epilepsy Controlled Pool (*please perform same analyses for every pooled group)

Laboratory Evaluation	Placebo n (%)	ESL n (%)			
		400 mg	800 mg	1200 mg	Total
	n=	n=	n=	n=	n=
Total cholesterol					
Increase \geq 50 mg/dL*					
Increase \geq 100 mg/dL*					
Shift from Normal to borderline (<200 to \geq 200 and <240)					
Shift from Normal to High (<200 to \geq 240)					
Shift from Borderline to High (\geq 200 and <240 to \geq 240)					
Triglycerides					
Increase \geq 50 mg/dL*					
Increase \geq 100 mg/dL*					
Shift from Normal to borderline (<150 to \geq 150 and <200)					
Shift from Normal to High (<150 to \geq 200)					
Shift from Borderline to High (\geq 150 and <200 to \geq 200)					
Shift from Normal to Very High (<150 to \geq 500)					
Shift from Borderline to Very High (\geq 150 and <200 to \geq 500)					

*Number (%) of Subjects with at least one post-baseline measurement that crossed the specified thresholds of abnormalities

Table 7. Creatine phosphokinase Outliers, Phase 3 Epilepsy Controlled Pool

Test/Cutoff threshold	Placebo n (%)	ESL n (%)			
		400 mg	800 mg	1200 mg	Total
	n=	n=	n=	n=	n=
CPK ≤3x ULN					
CPK >3x and ≤5x ULN					
CPK >5x ULN					

ULN= upper limit of normal

Table 8. Consecutive potentially clinically significant values for at least 2 visits (for subjects with normal values at baseline, Phase 3 Epilepsy Controlled Pool

Category	Placebo n (%)	ESL n (%)			
		400 mg	800 mg	1200 mg	Total
	n=	n=	n=	n=	n=
RBC ≤3.5 x10 ⁶ /mm ³					
Hematocrit ≤37% (male) or ≤32% (females)					
Hemoglobin ≤11.5 g/dL (M) or ≤9.5 g/dL (female)					
WBC ≤2.8 x10 ³ /mm ³					
Neutrophils <1.5x10 ³ /mm ³					
Platelets ≤75 x10 ³ /mm ³					
Sodium ≤130 meq/L					
Potassium ≥5.5 meq/L					
Chloride ≤90 meq/L					
Phosphate >5.0 mg/dL					
CPK >2.5xULN					
Cholesterol >300 mg/dL					
LDL >160 mg/dL					
HDL <30 mg/dL					
Triglycerides >300 mg/dL					

Table 9. Concurrent Thyroid Function Tests, Phase 3 Epilepsy Controlled Pool (*please perform same analyses for every pooled group)

Category	Placebo n (%)	ESL n (%)			
		400 mg	800 mg	1200 mg	Total
	n=	n=	n=	n=	n=
Thyrotropin >ULN and Free T3 <LLN					
Free T4 <LLN					
Total T3 <LLN					
Total T4 <LLN					
Thyrotropin <LLN and Free T3 >ULN					
Free T4 >ULN					
Total T3 >ULN					
Total T4 >ULN					

*concurrent values do not have to be at the same lab visit

ULN= upper limit of normal

LLN= lower limit of normal

Table 10. TEAEs overall for subjects with Low Free T4 levels (<LLN) for Phase 3 Epilepsy Controlled Pool

(*please perform same analyses for every pooled group)

MedDRA SOC PT	Placebo n (%)	ESL n (%)			
		400 mg	800 mg	1200 mg	Total
	n=	n=	n=	n=	n=

Table 11. TEAEs overall for subjects with Normal Free T4 levels for Phase 3 Epilepsy Controlled Pool

(*please perform same analyses for every pooled group)

MedDRA SOC PT	Placebo n (%)	ESL n (%)			
		400 mg	800 mg	1200 mg	Total
	n=	n=	n=	n=	n=

Table 12. Concurrent PCS values, Phase 3 Epilepsy Controlled Pool (*please perform same analyses for every pooled group)

Category	Placebo n (%)	ESL n (%)			
		400 mg	800 mg	1200 mg	Total
	n=	n=	n=	n=	n=
Free T4<0.75 ng/dL and Sodium ≤130 meq/L					
Chloride ≤90 meq/L					
CPK >2.5xULN					
Cholesterol >300 mg/dL					
LDL >160 mg/dL					
HDL <30 mg/dL					
Triglycerides >300 mg/dL					

*concurrent values at the same lab visit

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/s/

SU-LIN SUN
04/17/2013

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Tuesday, April 16, 2013 3:34 PM
To: 'Karen.Joyce@sunovion.com'
Subject: NDA 22416 information request

Dear Karen:

Below are information request from our review team:

The bioanalysis report, Study SBA_S_07157, for Study 2093-130 is not provided in the current submission. The link for analysis report for Study 2093-130 listed in Table 19 in Module 2.7.1 is the bioanalysis report for Study 2093-117. Please provide the right analysis report for Study 2093-130 within 3 business days. If you have submitted it, please provide the location.

Thanks,

Sulin

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/s/

SU-LIN SUN
04/16/2013

Sun, Su-Lin

From: Karen.Joyce@sunovion.com
Sent: Thursday, April 04, 2013 2:27 PM
To: Sun, Su-Lin
Subject: RE: Follow-UP: Information request for NDA 22416-FDA's comments

Thank you Sulin

From: Sun, Su-Lin [mailto:Su-Lin.Sun@fda.hhs.gov]
Sent: Thursday, April 04, 2013 2:26 PM
To: Joyce, Karen
Subject: RE: Follow-UP: Information request for NDA 22416-FDA's comments
Importance: High

Dear Karen:

Below are the clarification comments from our review team, they would like your response within 3 weeks from Stephanie's original information request on March 28, 2013:

Question # 1. It is requested that we submit the eDISH data by study. Does this mean that you would like individual data files for each study or all studies combined in one data file?

FDA's response : Yes. Please submit eDISH data by study. This means that for each study, you will submit a liver data set, a demography data set, and a narrative data set (or narratives in PDF as detailed in the eDISH-Data Request). Those data will be organized in separate data folders bearing proper study numbers as part of the folder names.

Question #2. For the requested narratives, we intend to submit native SAS datasets on CD/DVD and not transport files. Is this acceptable?

FDA's response: Yes. It is actually preferable to put SAS datasets on the CD/DVD. Please also send me 4 desk copies of CD/DVD to my office as soon as you can.

If you have any question, please feel free to contact me.

thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service
Senior Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
10903 New Hampshire Ave
Silver Spring, MD 20993

Office: 301-796-0036

Fax: 301-796-9842

Email: Su-Lin.Sun@fda.hhs.gov

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From: Karen.Joyce@sunovion.com [<mailto:Karen.Joyce@sunovion.com>]
Sent: Wednesday, April 03, 2013 12:18 PM
To: Sun, Su-Lin
Subject: FW: Follow-UP: Information request for NDA 22416

Dear Sulin,

We are requesting clarification on the March 28, 2013 RFI regarding hepatotoxicity and eDISH data as below:

1. It is requested that we submit the eDISH data by study. Does this mean that you would like individual data files for each study or all studies combined in one data file?
2. For the requested narratives, we intend to submit native SAS datasets on CD/DVD and not transport files. Is this acceptable?

Kind regards,

Karen

From: Parncutt, Stephanie [<mailto:Stephanie.Parncutt@fda.hhs.gov>]
Sent: Thursday, March 28, 2013 2:33 PM
To: Joyce, Karen
Cc: Choy, Fannie (Yuet); Sun, Su-Lin
Subject: Follow-UP: Information request for NDA 22416
Importance: High

[Karen,](#)

[Please also see the following amendment to the IR below:](#)

We want to clarify the request you just received regarding possible hepatotoxicity. We are requesting eDISH data for all studies, not limited to epilepsy. Please submit within 3 weeks of the date of this request.

[Thank you,](#)

[Stephanie](#)

tephanie
arch 28, 2013 1:50 PM
@sunovion.com'
(Yuet); Sun, Su-Lin
nation request for NDA 22416
jh

Karen,

Please see the Clinical Information Request below, for NDA 22416, and please confirm receipt of the email and it's attachment:

We are evaluating IND 67466/NDA 22416 for possible hepatotoxicity. For this evaluation, we request that you prepare data as specified in the following Excel file that describes requirement for eDISH data. Please note eDISH data should be submitted by study. Please contact us if you need additional assistance regarding the data standards after you have read the instructions in the attached Excel file. Thank you.

<< File: (SULIN)eDISHdataRequirement.xls >>

I am covering in Su-Lin's absence, for today, so please cc Su-Lin on your receipt confirmation. Please also let me know if you have any questions.

Thank you,

Stephanie N. Parncutt, MHA
Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research, FDA
10903 New Hampshire Avenue; WO22 Rm. 4355
Silver Spring, MD 20993-0002

phone: 301-796-4098
email: stephanie.parncutt@fda.hhs.gov

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/s/

SU-LIN SUN
04/04/2013

From: Karen.Joyce@sunovion.com
To: [Parncutt, Stephanie](#)
Subject: RE: Follow-UP: Information request for NDA 22416
Date: Thursday, March 28, 2013 2:39:12 PM

Dear Stephanie,

I am confirming receipt of the request for information.

Kind regards,

Karen

From: Parncutt, Stephanie [mailto:Stephanie.Parncutt@fda.hhs.gov]
Sent: Thursday, March 28, 2013 2:33 PM
To: Joyce, Karen
Cc: Choy, Fannie (Yuet); Sun, Su-Lin
Subject: Follow-UP: Information request for NDA 22416
Importance: High

Karen,

Please also see the following amendment to the IR below:

We want to clarify the request you just received regarding possible hepatotoxicity. We are requesting eDISH data for all studies, not limited to epilepsy. Please submit within 3 weeks of the date of this request.

Thank you,

Stephanie

Stephanie
March 28, 2013 1:50 PM
e@sunovion.com'
ie (Yuet); Sun, Su-Lin
ormation request for NDA 22416
high

Karen,

Please see the Clinical Information Request below, for NDA 22416, and please confirm receipt of the email and it's attachment:

We are evaluating IND 67466/NDA 22416 for possible hepatotoxicity. For this evaluation, we request that you prepare data as specified in the following Excel file that describes requirement for eDISH data. Please note eDISH data should be submitted by study. Please contact us if you need additional assistance regarding the data standards after you have read the instructions in the attached Excel file. Thank you.

<< File: (SULIN)eDISHdataRequirement.xls >>

I am covering in Su-Lin's absence, for today, so please cc Su-Lin on your receipt confirmation. Please also let me know if you have any questions.

Thank you,

Stephanie N. Parncutt, MHA
Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research, FDA
10903 New Hampshire Avenue; WO22 Rm. 4355
Silver Spring, MD 20993-0002

phone: 301-796-4098
email: stephanie.parncutt@fda.hhs.gov

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/s/

STEPHANIE N PARNCUTT
03/29/2013

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Tuesday, March 26, 2013 11:32 PM
To: 'Karen.Joyce@sunovion.com'
Cc: Choy, Fannie (Yuet)
Subject: NDA 22416 urgent information request

Importance: High

Attachments: Picture (Metafile); Picture (Metafile); Picture (Metafile)

Dear Karen:

Below are urgent information request from our review team, please send your response to us as soon as possible :

Please clarify how you determine if seizure data is missing (SEIZURE.DAYMISS=1) for patients using EE (event entry) diary. For example, the transcription of the seizures for patient '20101' at Visit 2 (Baseline) had 32 seizures recorded on 28 days between 2/19/2009 and 4/14/2009 (about 8 weeks in the baseline period). The days without a seizure recorded were assigned 'Missing diary' in your dataset, hence excluded from calculating the seizure frequency. The resulting standardized seizure frequency was 32 (per 28 days) for the baseline.

However, the reviewer could not find anything in the CRF (attached below) that indicates missing diary for the days without recorded seizures. It seems that the patient did not experience any seizure on the days for which no seizure was recorded in the diary and the baseline seizure frequency should be 16 if all 8 weeks of baseline are counted in the calculation.

If you decide that it is an error in deriving this key variable, please submit updated analysis datasets, results and SAS codes (including all SAS macro code so that the programs could be run to generate the analysis datasets and tables).

FYI: I will be on leave till 4/2/13, please send via email first to Ms. Fannie Choy and cc me, then officially submit your response.

2 pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

Su-Lin Sun, PharmD
LCDR, United States Public Health Service
Senior Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
10903 New Hampshire Ave
Silver Spring, MD 20993

Office: 301-796-0036
Fax: 301-796-9842
Email: Su-Lin.Sun@fda.hhs.gov

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/s/

SU-LIN SUN
03/27/2013

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Thursday, March 21, 2013 3:04 PM
To: 'Karen.Joyce@sunovion.com'
Cc: Choy, Fannie (Yuet)
Subject: NDA 22416 FDA's information requests

Importance: High

Attachments: NDA 22416--FDA's Table requests--022113.doc

Dear Karen:

Below are urgent information request for your NDA 22416 from our review team:

In reference to NDA 022416, please submit the following by COB March 26th, 2013:

1) It is stated that for Study 302 and 303, "Patients completing Part 1 may enter a 1- year open-label extension; patients completing Part 2 could participate in a further study extension by continuing until marketing authorization was obtained or clinical development was discontinued." Please specify which extension study # this data was obtained under. Please confirm that the information from this extension study is included in the ISS.

2) Confirm that for the data from the following ongoing studies (deaths, SAEs, and DCs due to adverse events) have been included in the ISS as of the data cut-off of January 31, 2012: Study 304 Part 3 and 302 Part 3.

3) Explain the following discrepancy in Table 1.1 of the ISS: the overall #unique subjects for eslicarbazepine reported = 3993. However, after adding the totals for the eslicarbazepine group for each study phase (Phase 3 epilepsy studies 1195 + Phase 2 epilepsy studies 127+ Bipolar studies 148+9 Neuropathic pain 87+ Migraine/Fibromyalgia 671+ Phase 1 studies 847), the total #unique subjects = 3975.

4) We have noted that the person-years exposure information was provided for the placebo group. However, for all of the extent of exposure tables for the controlled pooled groups, the other rows were not included for the placebo group (e.g., duration of exposure mean, median, etc and also 1-7 days, >1-2 weeks, etc.). Please provide these rows for the placebo group for all of the extent of exposure tables for the controlled pooled groups. Additionally please stratify the extent of exposure tables for the Phase 3 Epilepsy Controlled Pool by 2 weeks increments from 2 weeks to 26 weeks (please fill in table 1 shell).

5) Provide the person-years exposure for the following studies/study groups: for the total ESL group in the Phase II Neuropathic Pain Studies (206 Parts 1+2, 207 Parts 1+2) , for the placebo group and total ESL group in Study 206 Part 1.

6) Please provide the narrative for Subject 401-46402 and the CRF for Subject 304-010-01010.

7) Please fill in the table shells that are attached.



NDA 22416--FDA's
Table request...

8) Please reconcile the discrepancies between the number of subjects listed in the tables in the Section 1.2.2 of the ISS who discontinued due to adverse events with the corresponding number of subjects listed in Section 2.1.4 who discontinued due to treatment emergent adverse events for each pooled group.

In addition, below are the information request from our DMEPA team:

The container and carton labels and labeling that we received on February 11, 2013 for Eslicarbazepine Acetate are in a jpg format. The text on the labels and labeling appear faint and difficult to read in the jpg format. Could you please send

an IR to the Applicant requesting that all container labels and carton labeling be submitted in a pdf format by COB Thursday, March 28, 2013.

Also I will be on annual leave next week (3/25 to 3/30/13). Please send your correspondence to Ms. Fannie Choy.

Thanks,

Sulin

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Table 1 Extent of Exposure by Randomized Dose, Phase 3 Epilepsy Controlled Pool

Extent of Exposure	Placebo n (%)	ESL n (%)			
		400 mg	800 mg	1200 mg	Total
Any exposure, n (%)	426	196	415	410	1021
1-7 days		1 (0.5%)	18 (4.3%)	24 (5.9%)	43 (4.2%)
> 1 to 2 weeks		2 (1.0%)	10 (2.4%)	16 (3.9%)	28 (2.7%)
> 2 to 4 weeks		0	8 (1.9%)	26 (6.3%)	34 (3.3%)
> 4 to 6 weeks					
> 6 to 8 weeks					
> 8 to 10 weeks					
> 10 to 12 weeks					
> 12 to 14 weeks					
> 14 to 16 weeks					
> 16 to 18 weeks					
> 18 to 20 weeks					
> 20 to <26 weeks					
≥ 26 to <52 weeks		0	1 (0.2%)	0	1 (<0.1%)
Missing		1 (0.5%)	3 (0.7%)	6 (1.5%)	10 (1.0%)
Duration of exposure (wks)					
n		195	412	404	1011
Mean		14.4	13.0	11.6	12.7
Median		14.9	14.0	14.0	14.0
Number of subject-years	116.2	53.9	102.3	90.1	246.3

Table 2 Disposition and Primary Reason for Discontinuation, Phase 3 Epilepsy Uncontrolled and Controlled Pool (excluding Study 303)

Category	ESL n (%), modal dose groups				Total
	<600 mg	600-<1000	1000-<1400	≥1400 mg	
n					
Completed					
Discontinued					
Primary reason for discontinuation from therapy:					
Adverse event					
Withdrew Consent					
Administrative reasons					
Protocol related					
Disallowed Concomitant Med					
Lack of Compliance					
Pregnancy					
Protocol violation					
Subject Ineligible					
Inadequate therapy					
Exacerbation of Seizures					
Lack of Efficacy					
Other					
Lost to follow-up					

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/s/

SU-LIN SUN
03/21/2013

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Tuesday, March 19, 2013 1:08 PM
To: Karen.Joyce@sunovion.com
Subject: FDA's requested information

Importance: High

Dear Karen:

Below are information request from our review team:

We received the samples of Eslicarbazepine Acetate that you sent on September 19, 2012. However, we only received samples of the bottles and not samples of the blister packs. At this time, we would like to request physical samples of all of the blister packs including the starter pack configuration containing both the 400 mg and 800 mg tablets. The blister packs should contain either placebo tablets or active drug. We request a response by COB Wednesday, March 27, 2013.

Thanks,
Sulin

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/s/

SU-LIN SUN
03/19/2013

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Wednesday, March 13, 2013 5:26 PM
To: Karen.Joyce@sunovion.com
Subject: NDA 22416 FDA's information request

Importance: High

Dear Karen:

Below are information request from our review team for your NDA 22416:

We note that Eslicarbazepine Acetate is currently approved in other countries. Please clarify if the starter pack configuration containing both the 400 mg and 800 mg tablets are marketed in any of the other countries. If so, please submit any complaints or cases of medication errors reported with the starter pack configuration. We request a response by COB Tuesday, March 19, 2013. Thank you.

Thanks,

Sulin

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/s/

SU-LIN SUN
03/13/2013

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Friday, March 01, 2013 6:14 PM
To: 'Amy.Schacterle@sunovion.com'
Cc: Karen.Joyce@sunovion.com
Subject: RE: NDA 22416

I forward your email to our review team, as soon as I receive their comments, I will follow up with you.

thanks,
Sulin

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From: Amy.Schacterle@sunovion.com [mailto:Amy.Schacterle@sunovion.com]
Sent: Friday, March 01, 2013 6:00 PM
To: Sun, Su-Lin
Cc: Karen.Joyce@sunovion.com
Subject: RE: NDA 22416

Dear Sulin,

The response to the modal doses question includes 250+ tables. We will require additional time to allow for programming and validation for this number of tables. To facilitate the review, we initially will provide 36 tables describing SAEs, deaths, all AEs and discontinuation due to AEs for all study pools including OLE studies which we anticipate to submit by March 8, 2013. We will then provide the remaining tables describing adverse events of special interest and subgroup analyses, etc. by the end of March, 2013.

During final preparation of one of the other responses, we recognized that a revision to Table 2.6.1.s1 and the requested summary table is required. Therefore, we will also submit these by March 8, 2013.

This is also explained in the response we are sending in today.
Best regards,
Amy

From: Sun, Su-Lin [mailto:Su-Lin.Sun@fda.hhs.gov]
Sent: Thursday, February 28, 2013 10:29 AM
To: Schacterle, Amy
Cc: Joyce, Karen
Subject: RE: NDA 22416

Do you have estimate time for modal doses for uncontrolled study pool?
I will forward your clarification email to my review team.

From: Amy.Schacterle@sunovion.com [<mailto:Amy.Schacterle@sunovion.com>]
Sent: Thursday, February 28, 2013 10:16 AM
To: Sun, Su-Lin
Cc: Karen.Joyce@sunovion.com
Subject: RE: NDA 22416

Hi Sulin,

Just to be clear, we will submit all responses on Friday, with the exception of the one regarding the modal doses for uncontrolled study pools which will require additional time.

Thanks,
Amy

From: Sun, Su-Lin [<mailto:Su-Lin.Sun@fda.hhs.gov>]
Sent: Thursday, February 28, 2013 9:35 AM
To: Schacterle, Amy
Cc: Joyce, Karen
Subject: RE: NDA 22416

I forward your email to our review team, as soon as I receive their recommendation, I will follow up with you.

thanks,
Sulin

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From: Amy.Schacterle@sunovion.com [<mailto:Amy.Schacterle@sunovion.com>]
Sent: Wednesday, February 27, 2013 8:02 PM
To: Sun, Su-Lin
Cc: Karen.Joyce@sunovion.com
Subject: NDA 22416

Dear Su-Lin,

I'd like to give you a quick update on our progress.

- We formally submitted the response to the February 22, 2013 requests for information on Monday, February 25, 2013.
- We also submitted the tradename request on Monday, February 25, 2013.
- We have submitted the additional 2% tables including the 400 mg dose group today (see attached copy).
- We intend to submit responses to the February 25, 2013 requests for information on Friday, March 1, 2013. However, we note that we can provide responses to two of the requests now to facilitate the team's review. Please see below. These will be included in our formal submission on Friday with hyperlinks, as well. We also note that the request for tables of uncontrolled data by modal dose group will require additional time to program the analyses requested. We will provide these as soon as they

are available.

FDA Request (February 25, 2013): Provide individual tabulations datasets (nonanalysis) for the following studies: 202 and 204.

SUNOVION RESPONSE:

The individual tabulations datasets for the requested epilepsy study (2093-202) and bipolar study (2093-204) have been previously submitted to NDA 22-416. Please refer to Table 1 for the sequence number and submission date for each respective study, along with hyperlinks to the define documents describing the tabulations datasets for each study. The study datasets that were submitted are consistent with the individual Clinical Study Reports and have not been updated to include modifications derived from the "2012 data review" in the ADEVENTS dataset.

Table 1: NDA 22-416 Locations to Individual Tabulations Datasets for Study 2093-202 and Study 2093-204

Study Number	NDA Sequence/Date Submitted
Study 2093-202	Module 5.3.3.2 in Sequence 0000/March 29, 2009 (define.pdf) Updates to some datasets due to request in NDA Filing Review Letter dated June 12, 2009: Module 5.3.3.2 in Sequence 0007/August 28, 2009 (define.pdf)
Study 2093-204	Module 5.3.5.4 in Sequence 0000/March 29, 2009 (define.pdf)

FDA Request (February 25, 2013): Confirm that the datasets, ADLB1, ADLB2, ADLB3, ADLB4, and XRGSCAR1, are to replace the previously submitted datasets (with the same labels) in the August 2012 submission. We have noted the information in Table 1 (of the Reviewer Guide for Tables, February 3, 2103) regarding the corresponding adverse event datasets in the 2013 submission. Please confirm that for all other datasets that were previously submitted in the 2012 submission (but not included in the 2013 submission) are to still be used for the 2013 submission (e.g., ADSL, ADTRT, ADVS, etc).

SUNOVION RESPONSE:

It is confirmed that ADLB1, ADLB2, ADLB3, ADLB4, XRGSCAR1 are to replace the datasets with the same name and labels submitted in the August 2012 submission (NDA Sq. 0053).

It is also confirmed that all other datasets submitted in the August 2012 submission (but not included in the 2013 submission) are still to be used for the 2013 submission (NDA Sq. 0062) (e.g. ADSL, ADTRT, ADVS, etc.).

Please refer to the information in the Reviewer Guide for Tables (February 3, 2013) for information about the particular datasets to be used for the tables in the August 2012 submission and the 2013 submission.

For the Adverse Event summaries, in particular, a new set of Adverse Event datasets (with new names) was created to incorporate events from the 2012 data review. These were used to generate all the Adverse Event summaries submitted in the 2013 submission.

As noted, Table 1 in the Reviewer Guide for Tables documents the correlation of the new 2013 AE datasets to the August 2012 AE datasets.

The new AE datasets can be used to generate the August 2012 AE summaries, as well as the 2013 AE tables, however it may be easier to use the older AE datasets when working with the August 2012 AE tables. Please refer to the Reviewer Guide for Tables document for details.

Please let me know if you have any questions.

Best regards,

Amy

Amy L. Schacterle, Ph.D.

Vice President, Regulatory Affairs

Sunovion Pharmaceuticals Inc.

84 Waterford Drive, Marlborough, MA 01752

Tel: 508.787.4025

Email: amy.schacterle@sunovion.com

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/s/

SU-LIN SUN
03/08/2013

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Friday, March 08, 2013 12:33 PM
To: Karen.Joyce@sunovion.com
Cc: 'Amy.Schacterle@sunovion.com'
Subject: NDA 22416 information request

Importance: High

Dear Karen:

Below are information request from our review team for your NDA 22416:

In reference to the NDA 022416 resubmission, please provide the following by COB March 13th:

- 1) For subject 302-388-80468, please confirm that the last seizure diary obtained from the subject is #15385 (collected during Visit 9 on June 1, 2006) and that there are no seizure diary records collected from June 1st to the subject's death on July 15, 2006.
- 2) Provide the narrative for subject 303-702-70196
- 3) Provide the tabulations dataset (nonanalysis) for Study 204. It is not located in Module 5.3.5.4 from the March 29, 2009 submission (only the study report is included in that folder).
- 4) It is noted in the study protocol that HLA typing would be offered to patients who develop serious allergic reactions. Provide all of the HLA typing results that were obtained.
- 5) In the Safety Amendment dated March 1st, Item #9 refers to the discrepancies between Table 2.6.1.s1 and the corresponding tables in the ISS and CSRs. We understand that Table 2.6.1.s1 differs from ISS Table 4 by including subjects from non-Phase 3 epilepsy controlled studies. However, the sum of the number of subjects who discontinued due to "withdrew consent" and "other" listed in Table 2.6.1.s1 for each study do not match up with the corresponding number reported for each study in the individual CSRs and the corresponding study pools. For example, the number of subjects in Table 2.6.1.s1 for Studies 301, 302, and 304 in the placebo group who withdrew consent (12) and other (9) do not equal the number of placebo subjects in Table 4 of the ISS who withdrew consent (17) and other (11). Another example: for Study 153, in Table 2.6.1.s1 for the placebo group, 3 patients withdrew consent and 2 discontinued due to administrative reasons versus the information in the CSR for Study 153 (Table 5) which reports 0 patients who withdrew consent or discontinued due to administrative reasons. Explain these discrepancies (which are also present for the ESL groups and for other studies). Please provide a summary table for Table 2.6.1.s1 for the number of subjects stratified by reason for discontinuation and study numbers - along with the corresponding numbers from the individual Clinical Study Reports for each study. Explain all of the discrepancies.

If you have any question, please feel free to contact me,

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service
Senior Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
10903 New Hampshire Ave
Silver Spring, MD 20993

Office: 301-796-0036
Fax: 301-796-9842
Email: Su-Lin.Sun@fda.hhs.gov

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/s/

SU-LIN SUN
03/08/2013

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Monday, February 25, 2013 12:04 PM
To: Amy.Schacterle@sunovion.com
Cc: 'Karen.Joyce@sunovion.com'
Subject: FDA's information request

Importance: High

Dear Amy:

Below are the information request from our review team, please send us your response by March 1, 2013:

In reference to the NDA 022416 resubmission, please provide the following by March 1st:

- Provide narratives for the following subjects who died in the ongoing studies (listed in Table 31 of the ISS): 046-3028-S0005 and 308-1201-811.
- Provide the narratives and case report forms to the following subjects who discontinued due to “other” reason in the epilepsy Phase 3 studies: 301-151-90516, 301-213-90305, 302-342-80333.
- Provide individual tabulations datasets (nonanalysis) for the following studies: 202 and 204.
- Provide the case report form for subject #30308 who died in Study 304 P2/P3 (the hyperlink to the case report form is not working). We note that this death occurred after the cutoff date of January 31, 2012.
- Provide the case report form for 2 subjects who discontinued due to adverse event: 301-112-90393 and 301-211-90059 (detailed in meeting minutes from July 30, 2010 meeting)
- Confirm that the datasets, ADLB1, ADLB2, ADLB3, ADLB4, and XRGSCAR1, are to replace the previously submitted datasets (with the same labels) in the August 2012 submission. We have noted the information in Table 1 (of the Reviewer Guide for Tables, February 3, 2103) regarding the corresponding adverse event datasets in the 2013 submission. Please confirm that for all other datasets that were previously submitted in the 2012 submission (but not included in the 2013 submission) are to still be used for the 2013 submission (e.g., ADSL, ADTRT, ADVS, etc).
- Provide patient-time values for the placebo group in all of the extent of exposure tables. We note that patient-time values were provided for the eslicarbazepine treatment groups.
- Provide the following tables:
 - For all of the tables for the pooled groups that include OLE studies (such as Table 7.3.2.1 for the Combined Phase III Epilepsy Controlled and Uncontrolled Study Pool and Table 7.4.1.7 for the Bipolar Controlled and Uncontrolled Pool and Table 7.6.1.3 for the All Studies pool), please report results for all of the eslicarbazepine dose groups (as modal dose groups) in addition to the total eslicarbazepine group. Please also report the variables (dose groups in the datasets) that were used to populate these tables.
- Provide explanations for the following discrepancies:
 - The number of subjects in Table 2.6.1.s1 listed as having a primary reason for discontinuation as “other” or “withdrew consent” do not equal the number of subjects in the corresponding disposition tables (e.g., Table 4 in the ISS or the individual CSR for each study) with the primary reason for withdrawal as “other” or “withdrew consent.” Please provide summary tables for Table 2.6.1.s1 for the number of subjects stratified by reason for discontinuation and study numbers.

Thanks,

Su-Lin Sun, PharmD

LCDR, United States Public Health Service
Senior Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
10903 New Hampshire Ave
Silver Spring, MD 20993

Office: 301-796-0036
Fax: 301-796-9842
Email: Su-Lin.Sun@fda.hhs.gov

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/s/

SU-LIN SUN
02/25/2013



NDA 022416

**ACKNOWLEDGE –
CLASS 2 RESPONSE**

Sunovion Pharmaceuticals Inc.
Attention: Karen Joyce
Director, Regulatory Affairs
84 Waterford Drive
Marlborough, MA 01752

Dear Ms. Joyce:

We acknowledge receipt on February 11, 2013, of your February 10, 2013, resubmission of your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Eslicarbazepine Acetate 200mg, 400 mg, 600 mg, and 800 mg Tablets.

We also refer to your September 4, 2012 resubmission and our November 2, 2012 Acknowledge Incomplete Response letter.

We consider the September 4, 2012 and the February 10, 2013 resubmissions, in combination, to be a complete, class 2 response to our April 30, 2010 action letter. Therefore, the user fee goal date is August 11, 2013.

If you have any questions, call me at (301) 796-0036 or email su-lin.sun@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Su-Lin Sun, PharmD
Senior Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

SU-LIN SUN
02/22/2013

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Friday, February 15, 2013 9:40 PM
To: 'Karen.Joyce@sunovion.com'
Cc: Amy.Schacterle@sunovion.com
Subject: NDA 22416 urgent Information request

Importance: High

Dear Karen:

Below are urgent information request for NDA 22416, please response by 2/20/13.

- 1) The individual tabulations datasets (nonanalysis) for each of the following epilepsy studies: 301 (parts 1-4), 302 (parts 1 and 2), 303 (parts 1 and 2), 304 (part 1), and 201.
- 2) The ISS Programs Table of Contents (programs.pdf).

Thanks,
Sulin

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/s/

SU-LIN SUN
02/15/2013

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Monday, December 17, 2012 12:53 PM
To: 'Karen.Joyce@sunovion.com'
Subject: RE: NDA 22-416 - List of 100 random subjects
Importance: High
Attachments: NDA 22416 esli--FDA's list for 100 random subject--121712.xls

Dear Karen:

Attached is your requested-- list of the 100 randomly selections subjects for your NDA 22416 from our review team.

If you have any question, please feel free to contact me.

thanks,

Sulin

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From: Karen.Joyce@sunovion.com [<mailto:Karen.Joyce@sunovion.com>]
Sent: Saturday, December 15, 2012 9:03 AM
To: Sun, Su-Lin
Subject: NDA 22-416 - List of 100 random subjects

Dear Sulin,

This is in follow-up to our communication of December 4, 2012, in which we sent the Division a dataset to aid in the selection of 100 random subjects for a QC review. As requested by the Division in the email message of November 27, 2012, we are notifying the Division that the review of all CRFs, narratives and CIOMS reports (where applicable) is finished, coding is complete and the clinical safety database was locked on December 3, 2012.

We are now ready to receive the list of 100 random subjects from the Division to initiate the QC review. Please note that the review will be conducted by a third party under a protocol and to maintain the work schedule established it would be greatly helpful if the Division could provide this listing to us during the upcoming week.

Kind Regards,

Karen

Karen Joyce
Director, Regulatory Affairs

Sunovion Pharmaceuticals Inc.

84 Waterford Drive | Marlborough, MA 01752

Office: 508-357-7856 | Fax 508-357-7491 | karen.joyce@sunovion.com

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ESLI

STUDYID	USUBJID	SAFETY	REGION	TRT	DOSE	RTRT	RDOSE	NARRAT
2093105	2093105-000-00008	Y	WESTERN EUROPE	ESL	600 mg - < 1000 mg			N
2093105	2093105-000-00027	Y	WESTERN EUROPE	ESL	600 mg - < 1000 mg			N
2093107	2093107-000-00005	Y	WESTERN EUROPE	ESL	1000 mg - < 1400 mg			N
2093107	2093107-000-00008	Y	WESTERN EUROPE	ESL	1000 mg - < 1400 mg			N
2093108	2093108-000-00004	Y	WESTERN EUROPE	ESL	1000 mg - < 1400 mg			N
2093108	2093108-000-00009	Y	WESTERN EUROPE	ESL	1000 mg - < 1400 mg			N
2093109	2093109-000-00001	Y	WESTERN EUROPE	ESL	600 mg - < 1000 mg			N
2093110	2093110-000-00002	Y	WESTERN EUROPE	ESL	600 mg - < 1000 mg			N
2093112	2093112-001-00023	Y	REST OF WORLD	ESL	600 mg - < 1000 mg			N
2093114	2093114-000-00019	Y	WESTERN EUROPE	ESL	1000 mg - < 1400 mg			N
2093116	2093116-001-00031	Y	NORTH AMERICA	ESL	>= 1400 mg			N
2093119	2093119-000-00012	Y	NORTH AMERICA	ESL	1000 mg - < 1400 mg			N
2093120	2093120-000-00021	Y	NORTH AMERICA	ESL	1000 mg - < 1400 mg			N
2093121	2093121-000-00002	Y	NORTH AMERICA	ESL	1000 mg - < 1400 mg			N
2093122	2093122-000-00003	Y	NORTH AMERICA	ESL	< 600 mg			N
2093122	2093122-000-00043	Y	NORTH AMERICA	ESL	600 mg - < 1000 mg			N
2093122	2093122-000-00061	Y	NORTH AMERICA	ESL	600 mg - < 1000 mg			N
2093124	2093124-001-S019	Y	WESTERN EUROPE	ESL	600 mg - < 1000 mg			N
2093129	2093129-001-S044	Y	WESTERN EUROPE	ESL	600 mg - < 1000 mg			N
2093150	2093150-001-S005	Y	NORTH AMERICA	ESL	600 mg - < 1000 mg			N
2093150	2093150-001-S048	Y	NORTH AMERICA	ESL	600 mg - < 1000 mg			N
2093153	2093153-001-09009	Y	NORTH AMERICA	PBO				N
2093153	2093153-001-09012	Y	NORTH AMERICA	ESL	>= 1400 mg			N
2093153	2093153-001-09013	Y	NORTH AMERICA	ESL	>= 1400 mg			N
2093201	2093201-003-09015	Y	EASTERN EUROPE	PBO		PBO		N
2093201	2093201-005-09038	Y	EASTERN EUROPE	PBO		PBO		N
2093201	2093201-005-09041	Y	EASTERN EUROPE	ESL	600 mg - < 1000 mg	ESL	400 mg - 8	N
2093202	2093202-000-00206	Y	EASTERN EUROPE	ESL	600 mg - < 1000 mg			N
2093203	2093203-309-203005	Y	EASTERN EUROPE	ESL	>= 1400 mg	ESL	600 mg	N
2093203	2093203-339-203160	Y	EASTERN EUROPE	ESL	600 mg - < 1000 mg	ESL	600 mg	N
2093203	2093203-343-203155	Y	EASTERN EUROPE	ESL	600 mg - < 1000 mg	ESL	600 mg	N
2093204	2093204-453-204173	Y	LATIN AMERICA	ESL	>= 1400 mg	ESL	1800 mg	N
2093204	2093204-453-204184	Y	LATIN AMERICA	ESL	600 mg - < 1000 mg	ESL	600 mg	N
2093204	2093204-459-204162	Y	LATIN AMERICA	ESL	1000 mg - < 1400 mg	ESL	1200 mg	N
2093205	2093205-531-203075	Y	EASTERN EUROPE	ESL	< 600 mg	ESL	300 mg	N
2093206	2093206-563-563008	Y	EASTERN EUROPE	ESL	1000 mg - < 1400 mg	ESL	1200 mg	N
2093206	2093206-563-563009	Y	EASTERN EUROPE	ESL	< 600 mg	ESL	800 mg	N
2093206	2093206-565-565007	Y	EASTERN EUROPE	ESL	600 mg - < 1000 mg	ESL	800 mg	N
2093206	2093206-569-569002	Y	EASTERN EUROPE	PBO		PBO		N
2093206	2093206-569-569004	Y	EASTERN EUROPE	ESL	1000 mg - < 1400 mg	ESL	1200 mg	N
2093206	2093206-569-569011	Y	EASTERN EUROPE	ESL	600 mg - < 1000 mg	ESL	800 mg	N
2093206	2093206-569-569015	Y	EASTERN EUROPE	ESL	600 mg - < 1000 mg	ESL	1200 mg	N
2093206	2093206-649-649012	Y	EASTERN EUROPE	ESL	1000 mg - < 1400 mg	ESL	800 mg	N
2093206	2093206-682-682001	Y	EASTERN EUROPE	ESL	600 mg - < 1000 mg	PBO		N
2093206	2093206-683-683009	Y	EASTERN EUROPE	ESL	< 600 mg	ESL	1200 mg	N
2093206	2093206-685-685005	Y	EASTERN EUROPE	ESL	600 mg - < 1000 mg	ESL	800 mg	N
2093206	2093206-701-701018	Y	EASTERN EUROPE	ESL	1000 mg - < 1400 mg	ESL	1200 mg	N
2093207	2093207-164-164023	Y	EASTERN EUROPE	ESL	600 mg - < 1000 mg	ESL	800 mg	N

ESLI

STUDYID	USUBJID	SAFETY	REGION	TRT	DOSE	RTRT	RDOSE	NARRAT
2093207	2093207-201-201001	Y	WESTERN EUROPE	ESL	< 600 mg	ESL	800 mg	N
2093207	2093207-287-287002	Y	EASTERN EUROPE	ESL	600 mg - < 1000 mg	ESL	1200 mg	N
2093207	2093207-326-326006	Y	EASTERN EUROPE	ESL	1000 mg - < 1400 mg	ESL	1200 mg	N
2093207	2093207-387-387006	Y	EASTERN EUROPE	PBO		PBO		N
2093207	2093207-424-424002	Y	EASTERN EUROPE	PBO		PBO		N
2093207	2093207-428-428019	Y	EASTERN EUROPE	ESL	< 600 mg	ESL	800 mg	N
2093209	2093209-103-90299	Y	WESTERN EUROPE	PBO		PBO		N
2093209	2093209-105-90656	Y	WESTERN EUROPE	ESL	1000 mg - < 1400 mg	ESL	1200 mg	N
2093209	2093209-111-90495	Y	EASTERN EUROPE	ESL	1000 mg - < 1400 mg	ESL	1200 mg	N
2093209	2093209-112-90380	Y	EASTERN EUROPE	ESL	600 mg - < 1000 mg	ESL	800 mg	N
2093209	2093209-114-90389	Y	EASTERN EUROPE	ESL	1000 mg - < 1400 mg	ESL	1200 mg	N
2093209	2093209-114-90623	Y	EASTERN EUROPE	ESL	600 mg - < 1000 mg	ESL	800 mg	N
2093209	2093209-125-90341	Y	EASTERN EUROPE	ESL	600 mg - < 1000 mg	ESL	800 mg	N
2093209	2093209-133-90097	Y	WESTERN EUROPE	ESL	1000 mg - < 1400 mg	ESL	1200 mg	N
2093209	2093209-162-90688	Y	EASTERN EUROPE	ESL	600 mg - < 1000 mg	ESL	1200 mg	N
2093209	2093209-185-90516	Y	EASTERN EUROPE	ESL	600 mg - < 1000 mg	ESL	800 mg	N
2093210	2093210-501-501014	Y	WESTERN EUROPE	ESL	< 600 mg	ESL	400 mg	N
2093210	2093210-583-583007	Y	WESTERN EUROPE	ESL	600 mg - < 1000 mg	ESL	800 mg	N
2093210	2093210-585-585008	Y	WESTERN EUROPE	ESL	< 600 mg	ESL	400 mg	N
2093210	2093210-586-586010	Y	WESTERN EUROPE	ESL	600 mg - < 1000 mg	ESL	800 mg	N
2093210	2093210-612-612047	Y	WESTERN EUROPE	ESL	< 600 mg	ESL	400 mg	N
2093210	2093210-613-613002	Y	WESTERN EUROPE	PBO		PBO		N
2093210	2093210-641-641006	Y	WESTERN EUROPE	PBO		PBO		N
2093210	2093210-703-703006	Y	EASTERN EUROPE	ESL	600 mg - < 1000 mg	ESL	1200 mg	N
2093210	2093210-764-764005	Y	WESTERN EUROPE	ESL	600 mg - < 1000 mg	ESL	800 mg	N
2093210	2093210-764-764018	Y	WESTERN EUROPE	ESL	600 mg - < 1000 mg	ESL	800 mg	N
2093210	2093210-765-765002	Y	WESTERN EUROPE	PBO		PBO		N
2093210	2093210-766-766005	Y	WESTERN EUROPE	ESL	< 600 mg	ESL	400 mg	N
2093210	2093210-766-766007	Y	WESTERN EUROPE	ESL	1000 mg - < 1400 mg	ESL	1200 mg	N
2093210	2093210-766-766010	Y	WESTERN EUROPE	ESL	600 mg - < 1000 mg	ESL	800 mg	N
2093210	2093210-766-766013	Y	WESTERN EUROPE	PBO		PBO		N
2093210	2093210-822-822006	Y	WESTERN EUROPE	PBO		PBO		N
2093301	2093301-121-90368	Y	EASTERN EUROPE	PBO		PBO		N
2093301	2093301-122-90372	Y	EASTERN EUROPE	ESL	600 mg - < 1000 mg	ESL	1200 mg	N
2093301	2093301-122-90386	Y	EASTERN EUROPE	ESL	600 mg - < 1000 mg	PBO		N
2093301	2093301-213-90033	Y	EASTERN EUROPE	ESL	600 mg - < 1000 mg	ESL	400 mg	N
2093301	2093301-213-90297	Y	EASTERN EUROPE	ESL	600 mg - < 1000 mg	ESL	800 mg	N
2093302	2093302-312-80293	Y	REST OF WORLD	ESL	1000 mg - < 1400 mg	PBO		N
2093303	2093303-606-70162	Y	WESTERN EUROPE	ESL	1000 mg - < 1400 mg	ESL	1200 mg	N
2093303	2093303-712-70143	Y	LATIN AMERICA	ESL	< 600 mg	ESL	800 mg	N
2093303	2093303-712-70148	Y	LATIN AMERICA	ESL	600 mg - < 1000 mg	PBO		N
2093304	2093304-021-02108	Y	NORTH AMERICA	ESL	1000 mg - < 1400 mg	ESL	1200 mg	N
2093304	2093304-042-04208	Y	NORTH AMERICA	PBO		PBO		N
2093304	2093304-102-10207	Y	LATIN AMERICA	PBO		PBO		N
2093304	2093304-303-30318	Y	LATIN AMERICA	PBO		PBO		N
2093304	2093304-307-30714	Y	LATIN AMERICA	PBO		PBO		N
2093304	2093304-307-30715	Y	LATIN AMERICA	ESL	1000 mg - < 1400 mg	ESL	1200 mg	N
2093304	2093304-351-35103	Y	REST OF WORLD	PBO		PBO		N

ESLI

STUDYID	USUBJID	SAFETY	REGION	TRT	DOSE	RTRT	RDOSE	NARRAT
2093304	2093304-650-65001	Y	EASTERN EUROPE	ESL	1000 mg - < 1400 mg	ESL	1200 mg	N
2093304	2093304-701-70103	Y	WESTERN EUROPE	PBO		PBO		N
2093304	2093304-801-80105	Y	WESTERN EUROPE	ESL	600 mg - < 1000 mg	ESL	800 mg	N
2093304	2093304-903-90310	Y	EASTERN EUROPE	ESL	1000 mg - < 1400 mg	ESL	1200 mg	N

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/s/

SU-LIN SUN
12/18/2012

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Thursday, December 13, 2012 7:39 PM
To: 'Karen.Joyce@sunovion.com'
Subject: RE: NDA 22416 Information request

Thanks :-)

From: Karen.Joyce@sunovion.com [mailto:Karen.Joyce@sunovion.com]
Sent: Thursday, December 13, 2012 5:32 PM
To: Sun, Su-Lin
Subject: RE: NDA 22416 Information request

Dear Sulin,

This is confirmation of receipt of the information request.

Thanks-

Karen

Karen Joyce
Director, Regulatory Affairs
Sunovion Pharmaceuticals Inc.
84 Waterford Drive | Marlborough, MA 01752
Office: 508-357-7856 | Fax 508-357-7491 | karen.joyce@sunovion.com

From: Sun, Su-Lin [mailto:Su-Lin.Sun@fda.hhs.gov]
Sent: Thursday, December 13, 2012 5:01 PM
To: Joyce, Karen
Subject: NDA 22416 Information request
Importance: High

Dear Karen:

Below are the information requests from our Clinical Pharmacology, CMC, and ONDQA review team for your NDA 22416:

1. Please clarify which API sources (new or current) of your drug products were used in Phase 1 and Phase 3 clinical studies in this application. It will be more helpful for you to provide us with a complete tabular listing of the new or current API source with the corresponding study.
2. Please provide the bioanalytical report for assay performance for Study 2093-129 as part of the NDA submission. You should provide adequate hyperlinks to the report and supporting data to facilitate the review process.

I don't remember I have send this previously or not.

Thanks,

Sulin

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/s/

SU-LIN SUN
12/14/2012

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Wednesday, December 12, 2012 3:31 PM
To: 'Karen.Joyce@sunovion.com'
Subject: RE: NDA 22-416 -FDA's comments for Sample Table
Importance: High

Dear Karen:

[Below are the comments from our Safety Team for your proposed sample table format:](#)

We note that this is only a partial table listing AEs up to the MedDRA SOC Ear and Labyrinth Disorder. It appears that there were no AEs in the SOC Congenital familial and genetic disorders. Assuming that is the case and assuming that the rest of the table is formatted similarly, the format of this sample partial table is acceptable.

If you have any question, please feel free to contact me.

thanks,

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From: Karen.Joyce@sunovion.com [<mailto:Karen.Joyce@sunovion.com>]
Sent: Wednesday, December 12, 2012 1:57 PM
To: Sun, Su-Lin
Subject: RE: NDA 22-416 - Safety Reviewer Request - Sample Table?
Importance: High

Dear Sulin,

We are anxious to receive feedback from the safety team on the sample table provided on Friday. Do you think we will have comments by end of day today?

Kind regards,

Karen

Karen Joyce
Director, Regulatory Affairs
Sunovion Pharmaceuticals Inc.
84 Waterford Drive | Marlborough, MA 01752
Office: 508-357-7856 | Fax 508-357-7491 | karen.joyce@sunovion.com

From: Sun, Su-Lin [<mailto:Su-Lin.Sun@fda.hhs.gov>]
Sent: Friday, December 07, 2012 11:45 AM
To: Joyce, Karen
Subject: RE: NDA 22-416 - Safety Reviewer Request - Sample Table?

Dear Karen:

Per our safety team, please send us your sample ISS tablets, they will try to provide you comments early next week.

thanks,

Sulin

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From: Karen.Joyce@sunovion.com [<mailto:Karen.Joyce@sunovion.com>]
Sent: Friday, December 07, 2012 11:04 AM
To: Sun, Su-Lin
Subject: RE: NDA 22-416 - Safety Reviewer Request - Sample Table?

Thank you Sulin

Karen Joyce
Director, Regulatory Affairs
Sunovion Pharmaceuticals Inc.
84 Waterford Drive | Marlborough, MA 01752
Office: 508-357-7856 | Fax 508-357-7491 | karen.joyce@sunovion.com

From: Sun, Su-Lin [<mailto:Su-Lin.Sun@fda.hhs.gov>]
Sent: Friday, December 07, 2012 11:02 AM
To: Joyce, Karen
Subject: RE: NDA 22-416 - Safety Reviewer Request - Sample Table?

I forward your email to our safety team, as soon as I receive their comment, I will follow up with you.

From: Karen.Joyce@sunovion.com [<mailto:Karen.Joyce@sunovion.com>]
Sent: Friday, December 07, 2012 10:01 AM
To: Sun, Su-Lin
Subject: NDA 22-416 - Safety Reviewer Request - Sample Table?
Importance: High

Dear Sulin,

With reference to the minutes of the November 6 teleconference and FDA's clarification to their original request:

“The Division requests that all of the adverse event incidence tables in the ISS be sorted by MedDRA system organ class (SOC) grouped in alphabetical order and then by MedDRA preferred term in alphabetical order grouped by incidence. (Please present preferred terms with the same incidence in alphabetical order).”

We are finalizing the ISS tables and were wondering if the safety reviewer would like to take a quick look at a sample table and confirm that it is in the format requested? We would request a 1-2 day turn around period on the review to accommodate our timeline to resubmit at the end of January.

Kind regards,

Karen

Karen Joyce

Director, Regulatory Affairs

Sunovion Pharmaceuticals Inc.

84 Waterford Drive | Marlborough, MA 01752

Office: 508-357-7856 | Fax 508-357-7491 | karen.joyce@sunovion.com

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/s/

SU-LIN SUN
12/12/2012

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Tuesday, December 11, 2012 11:33 AM
To: 'Amy.Schacterle@sunovion.com'
Cc: 'Karen.Joyce@sunovion.com'
Subject: RE: NDA 22-416 - Confirmation of cut-off for ongoing studies--FDA's IR
Importance: High

Dear Amy:

Per our review team that your plan seems reasonable, but before we provide a final agreement, we would like to have an estimate know--how many new patients exposures and patient-year exposure we would be missing, and how does this compare (as a percent) of the total epilepsy safety database.

thanks,
Sulin

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From: Sun, Su-Lin
Sent: Monday, December 10, 2012 11:59 AM
To: 'Amy.Schacterle@sunovion.com'
Cc: Karen.Joyce@sunovion.com
Subject: RE: NDA 22-416 - Confirmation of cut-off for ongoing studies

Your email has been forward to our review team (including Dr. Katz). As soon as I receive their comments, I will follow up with you.

thanks,
Sulin

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From: Amy.Schacterle@sunovion.com [mailto:Amy.Schacterle@sunovion.com]
Sent: Monday, December 10, 2012 9:57 AM
To: Sun, Su-Lin
Cc: Karen.Joyce@sunovion.com
Subject: NDA 22-416 - Confirmation of cut-off for ongoing studies

Dear Sulin,
Could you please forward the following email to Dr. Katz for his consideration?
Thank you,
Amy

Dear Dr. Katz,

In the Division's November 6, 2012 meeting minutes, it was noted that the cut-off date for ongoing studies should be 6 months prior to the resubmission date. However, in the June 2011 Meeting minutes, the "Division noted that the request to have a cut-off date within 6 months of NDA resubmission was a recommendation and not obligatory." We also note that under similar circumstances in the case of a Refusal to File of the original Fycompa NDA, the most recently approved new anti-epileptic drug, it was agreeable to FDA for the Sponsor to keep the original cut-off date that was more than one year prior to resubmission (i.e. December 1, 2010 cut-off ; submitted December 22, 2011), with the provision that a listing of deaths and SAEs within 6 months (July 2011) of resubmission was included (PDF pg 189, Administrative Documents and Correspondence, Fycompa Drug Approval Package)

We note that we will be producing listings for inclusion in the upcoming IND annual report based on a December 19, 2012 data cut-off date for ongoing studies. We propose to include a listing of discontinuations due to adverse events, deaths and SAEs from the same date for inclusion in the NDA. This is expected to be well within 3 months of our resubmission target (January 2013). We will continue to produce the CRFs and narratives for submission based on the cut-off date of January 31, 2012. Based on the inclusion of data that is more comprehensive than that accepted for the Fycompa NDA and based on the prior correspondence for the eslicarbazepine acetate NDA indicating that 6 months is not obligatory, we believe this is sufficient to conduct a substantive review of the data from ongoing studies.

We would appreciate very much your confirmation that the one-year cut-off date for ongoing studies along with a more recent data listing is acceptable for review of the resubmission.

Best regards,

Amy L. Schacterle, Ph.D.
Vice President, Regulatory Affairs
Sunovion Pharmaceuticals Inc.
84 Waterford Drive, Marlborough, MA 01752
Tel: 508.787.4025
Email: amy.schacterle@sunovion.com

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/s/

SU-LIN SUN
12/11/2012

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Tuesday, December 04, 2012 2:51 PM
To: 'Karen.Joyce@sunovion.com'
Subject: NDA 022416 Tcon meeting minutes

Importance: High

Attachments: NDA 022416--Incomplete Response Tcon--12042012.pdf

Dear Karen:

Attached is Tcon meeting minutes, approved by Dr. Katz, for your NDA 22416.



NDA
.6--Incomplete Resp

If you have any question, please feel free to contact me.

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service
Senior Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
10903 New Hampshire Ave
Silver Spring, MD 20993

Office: 301-796-0036
Fax: 301-796-9842
Email: Su-Lin.Sun@fda.hhs.gov

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Teleconference Date: November 6, 2012

Time: 12:45-1:30 PM EST

Sponsor: Sunovion Inc.

Product: Stedesa (eslicarbazepine acetate) 400, 600, and 800mg tablets

Proposed Use: Adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy.

Question 1:

Does the Division agree that additional information from the old narratives and potential adverse events from the review CIOMS and case report forms will provide additional context to the previously reviewed narrative format to address the reviewer's concerns?

Meeting Discussion:

All of the narratives should be comprehensive enough for the reader to come to a reasonable conclusion regarding the subject and the adverse event. The new additional information for these narratives should be well integrated with the previous information in order to make a cohesive narrative. The Division recommended that the Sponsor arrange for an independent review of the narratives prior to submission to assure that this goal has been met.

Additionally, the Sponsor confirmed that the previous audits held before this resubmission did not include CIOMS forms as source documents. The company stated that the previous audit did include hospitalization records. The Division noted that there are multiple types of source documents and it is expected that all sources are checked for adverse events and that all adverse events end up in the datasets.

The Sponsor noted that the adverse event dataset now included events that were crossed out by investigators on the CRFs. The Division requested an additional dataset that did not include these cross-outs but that did include all adverse events from all sources.

Question 2:

Can the Division clarify how many cases will be requested and is the Division prepared to provide the list within two weeks?

Meeting Discussion:

The Division requests 100 randomly selected cases. The Division is prepared to provide this list upon notification by the Sponsor that the review is complete.

Question 3:

Can the Division confirm that we are being requested to provide the data management plans only for the three studies listed?

Meeting Discussion:

The Division requests that the “epilepsy data management plans” for the following 4 Phase III epilepsy studies, 301, 302, 303, and 304.

Post-Meeting Note:

The study report of study 302 references a data management plan. The Division is seeking the document or documents that were used to detail how adverse events were to be captured, documented, and transferred to CRFs and eventually into datasets. If these documents contain the processes just described, send them for all studies. If not, please send them only for studies 301, 302, 303, and 304.

Question 4a:

Regarding case report forms, would the Division agree to our proposal to provide 1) case report forms for all deaths from ongoing studies; 2) case report forms for serious adverse events and discontinuations due to an adverse event from Bial’s and Sunovion’s monotherapy epilepsy studies; and 3) case report forms that are currently available to the Sponsor (i.e. already collected) for discontinuations due to an AE for the ongoing adjunctive epilepsy studies (which utilize paper)?

Meeting Discussion:

The Sponsor confirmed that all of the narratives for the ongoing studies for deaths, serious adverse events, and discontinuations due to adverse events will be provided at the time of the resubmission. It is acceptable that the case report forms for the serious adverse events for subjects who did not have an outcome of death and did not drop out of the study at clinical sites which utilize paper case report forms will be provided by the Sponsor within 45 days of the resubmission. For studies that do not utilize paper CRFs, the CRFs and narratives for deaths, serious adverse events, and discontinuations secondary to adverse events are to come with the initial re-submission, not in the 45 day period. The Sponsor stated that the group with paper CRFs refers to about 25% of the case report forms from the ongoing studies, primarily pediatric and elderly epilepsy studies¹. The data cut-off date for these events (deaths,

¹ As a post-meeting note, an email of November 16, 2012 from the Sponsor indicated that this accounts for less than 10% of the total CRFs for the ongoing studies.

serious adverse events, discontinuations due to adverse events) in these ongoing studies should be 6 months prior to the resubmission date.

Question 4b:

Would the Division agree to the proposed timing to submit the case report forms and narratives for subjects from ongoing studies as described in Question 4a within 45 days following submission of our response to address the other items in the Division's letter?

Meeting Discussion:

See response to 4a.

Question 5a:

Would the Division agree to our proposal to provide narratives and CRFs for these subjects from Part 1 (double-blind period) of the phase III epilepsy studies 2093-301, 2093-302 and 2093-304? This is expected to constitute approximately 90 subjects.

Meeting Discussion:

It is acceptable for the resubmission to provide narratives and case report forms for discontinuations due to subject choice and 'other' reasons for only subjects from Part 1 of the Phase III epilepsy studies 2093-301, 2093-302, and 2093-304. However, for all of the other studies in the ISS, the Division requests a tabular listing of all subjects with discontinuations due to subject choice and 'other' reasons. The table should include columns for study number, treatment group, unique subject ID, primary reason for discontinuation, and more specific information regarding the discontinuation. All of the information described above (i.e. case report forms, narratives and tables) should be provided in the resubmission (rather than within 45 days following the resubmission).

Question 5b:

Would the Division agree to the proposed timing to submit the case report forms and narratives for subjects described in Question 5a within 45 days following submission of our response to address the other items in the Division's letter?

Meeting Discussion:

No, we do not agree. See response to question 5a.

Question 6:

Would the Division agree to our proposal to provide any new or revised tables in the requested format as a consequence of responding to other items in the Division's letter? Can the Division identify a small selection of key tables (e.g. adverse event incidence tables for the phase III controlled epilepsy study pool) that could be provided in alphabetical format to aid the reviewer?

Meeting Discussion:

No we do not agree to that proposal. The Division requests that all of the adverse event incidence tables in the ISS be sorted by MedDRA system organ class (SOC) grouped in alphabetical order and then by MedDRA preferred term in alphabetical order grouped by incidence. (Please present preferred terms with the same incidence in alphabetical order). Please note that this is a clarification of our original request #4 on page 4.

Question 7:

We believe we did provide these measures. Could the Division clarify which measures are missing?

Meeting Discussion:

We have noted that the measures of central tendency and shift changes for all of the thyroid function laboratory values are located in the Adverse Events section of the ISS.

Question 8:

Could the Division identify a small group of key tables for a selected study pool for which we can re-run tables in the desired format? This could be done following the acceptance of the resubmission as a complete response, once the Division has determined their preference for the study pool(s) appropriate for inclusion in their review report.

Meeting Discussion:

The Division requests that the Sponsor format all of the tables in the ISS according to examples in the FDA's Reviewer Guidance as stated in Item 15.

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/s/

SU-LIN SUN
12/04/2012

Sun, Su-Lin

From: Karen.Joyce@sunovion.com
Sent: Thursday, November 29, 2012 4:15 PM
To: Sun, Su-Lin
Subject: RE: NDA 22416 FDA's information request

Dear Sulin,

We are working on the request.

Thanks-

Karen Joyce

Director, Regulatory Affairs

Sunovion Pharmaceuticals Inc.

84 Waterford Drive | Marlborough, MA 01752

Office: 508-357-7856 | Fax 508-357-7491 | karen.joyce@sunovion.com

From: Sun, Su-Lin [mailto:Su-Lin.Sun@fda.hhs.gov]
Sent: Thursday, November 29, 2012 4:05 PM
To: Joyce, Karen
Subject: NDA 22416 FDA's information request
Importance: High

Dear Karen:

Below are the comment from our review team regard to the 100 random patient selection:

"As a follow-up to our communication on 11/27/2012, in order for us to provide you with 100 randomly selected subjects, please compile a comprehensive list of all of the subjects in one dataset with the following 7 variables: USUBJID (with each unique subject ID listed once), STUDYID, REGION, TRT (treatment group: placebo or eslicarbazepine), DOSE (randomized eslicarbazepine dose group), SAFETY (safety population Y or N), and NARRAT (with narrative Y or N). Please submit this dataset as an xpt file."

If you have any question, please feel free to contact me

Thanks,
Sulin

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/s/

SU-LIN SUN
11/29/2012

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Tuesday, November 27, 2012 12:51 PM
To: 'Karen.Joyce@sunovion.com'
Subject: NDA 22416

Importance: High

Dear Karen:

Attached is the updated comment from our review team for your NDA 22416:

Before we provide you with 100 randomly selected subjects, please confirm by email that all AE datasets, narratives, ISS tables, and reconciled CRFs are completed and locked.

If you have any question, please feel free to contact me.

Please disregard the comment from my yesterday's email. The above comment is approved by Dr. Katz.

Thanks,

Sulin

Sun, Su-Lin

From: Karen.Joyce@sunovion.com
Sent: Wednesday, November 21, 2012 1:00 PM
To: Sun, Su-Lin
Subject: NDA 22-416 - Follow-up to your e-mail

Dear Sulin,

Thank you for your recent message from the Review Team. We have made significant progress in addressing the concerns noted by the Division in the Acknowledge Incomplete Response letter and recent teleconferences. Since the September teleconferences, we engaged a large number of contractors to conduct data review of CRFs and CIOMS, and many medical writers and external physician consultants to address the Division's request for new and revised narratives. Recognizing the time and resource constraints under which the Division must operate, we would appreciate any effort the Division can make to provide their comments on Sunovion's 11/5 and 11/16 e-mails (telecon discussion points and follow-up e-mail) as soon as possible, to facilitate completion of the work. In addition, next week we will be ready to receive the list of 100 randomly selected patients without narratives to conduct the QC review requested by the Division as discussed during the November 6th teleconference.

Kind regards,

Karen

Karen Joyce
Director, Regulatory Affairs
Sunovion Pharmaceuticals Inc.
84 Waterford Drive | Marlborough, MA 01752
Office: 508-357-7856 | Fax 508-357-7491 | karen.joyce@sunovion.com

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/s/

SU-LIN SUN
11/27/2012



NDA 022416

ACKNOWLEDGE INCOMPLETE RESPONSE

Sunovion Inc.
Attention: Karen Joyce
Director, Regulatory Affairs
84 Waterford Drive
Marlborough, MA 01752

Dear Ms. Joyce:

Please refer to your March 29, 2009 New Drug Application (NDA), received March 30, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for eslicarbazepine acetate 400 mg, 600 mg, and 800 mg Tablets.

We also refer to your August 31, 2012 amendment, which was received on September 4, 2012, and was submitted in response to our Complete Response (CR) letter dated April 30, 2010.

As discussed with you during our teleconferences on September 24 and September 28, 2012, we do not consider your submission to constitute a complete response to our CR letter. Therefore, we will not start the review clock at this time.

Our CR letter cited deficiencies regarding the conduct and documentation of the studies, as well as deficiencies related to the accuracy, reliability, and presentation of the data. During the first review cycle, we communicated our concern that some adverse events, noted in audit reports and discovered in source documents, were not reported in the case report forms (CRFs). Such adverse events would not be included in the adverse events datasets, and would not contribute to your analyses of adverse events. Based on a preliminary review of your submission, we continue to note significant deficiencies along these lines.

The following identified deficiencies provide the rationale for our determination of an incomplete response. The list is based on a preliminary review, and may not be all-inclusive.

1. An important deficiency is our identification of adverse events that are not included in the primary or analysis datasets. For review purposes, we chose to focus on the dataset that included audit findings. There are adverse events missing from this dataset, although some are found in various other documents in the submission. All verbatim adverse event terms in the CRFs, narratives, or other reports, including CIOMS reports, must be included in the adverse event datasets, and there should be consistency across the application. Examples of omissions and inconsistencies include:

- a. Some specific adverse events were subsumed under “umbrella” terms in the adverse event dataset. This practice is not acceptable. Examples of this practice were included in our email to you on September, 25, 2012,¹ and discussed with you in the teleconference of September 28, 2012. Furthermore, discussion about the use of “diagnoses” instead of signs and symptoms occurred between your representatives and the Agency on June 7, 2011. For additional information on this discussion, please refer to pages 29 and 30 of our minutes from the June 7, 2011 Type C meeting.
 - b. We note that several patients had fractures listed in the adverse event dataset, but no adverse events suggestive of causality (e.g. fall, seizure, accident) are recorded in the dataset for those patients. If the patient had a fall or accident leading to a fracture, then these terms should also be recorded separately in the dataset. If this information is missing from source documents, simply state this.
 - c. Similarly, there are verbatim terms in the adverse event dataset that include falls but are not coded to falls (e.g. subject 103006 in study 207 who had an AETERM of “Fall, (Hematoma on Forehead)” that was coded only to “Traumatic Haematoma”); fall should have been coded as well and included in the adverse event datasets and analyses.
 - d. Subject 119-004 provides an example of lack of consistency between narrative information and dataset information (ADAE_AU.xpt). In the last cycle, we noted this narrative as an example of a potentially missed serious adverse event. The new narrative indicates that the event meets criteria for a serious adverse event and your comment in the narrative indicates it is a case of either Stevens-Johnson syndrome (SJS) or toxic epidermal necrosis. The resubmission dataset, ADAE_AU.xpt, does not appear to designate this as a serious event (variable AESER). Furthermore, the terms describing the type of hypersensitivity event are not in the dataset (i.e., SJS is not listed).
 - e. Subject 207-223-223001 experienced a treatment-emergent serious adverse event of cervical fracture. The narrative describes a fall, and notes the circumstances (the patient felt dizzy, lost her balance, and fell in a hole 1.8 meters deep, hitting her neck). The CRF adverse event pages only capture the fracture itself (not the fall or dizziness).² The dataset ADAE_AU.xpt includes three adverse events, the fracture itself and two occurrences of the word “eruptions,” but not “dizziness” or “fall.”
2. On preliminary review, we find other types of inaccuracies in your submission with respect to the presentation of important safety information that undermine the credibility of the application. For example, as discussed in our September 24, 2012, teleconference, on page 107 of the ISS (Table 30: Listing of Deaths for the Entire Eslicarbazepine Acetate Drug Development Program Including Study 2093-303), the preferred term for subject 305-30505 is “tooth ache.” We understand that this subject did not die from a toothache. Although ensuing paragraphs and legend information explains this, the term

¹ For example in that communication the narrative for subject 90333 in Study 301 reported that the patient experienced “vertigo (nausea and gait disturbance).” In this case, gait disturbance and nausea should be reported separately, in addition to vertigo.

² The CRF should constitute the definitive source, and therefore include all such events.

“toothache” was not re-coded. Although we understand and agree that primary trial data cannot be altered, there can be data reconciliation that would include re-coded datasets and table presentations accurately displaying the re-coded events. Similarly, in the case of the pancytopenia (303-701-70290), aside from the implication that there was inadequate follow-up, the Division pointed out this specific case at the End of Review Meeting, yet this narrative (see Module 5.3.5.3.28 – ISS Narratives; page 5956/6507) provides a hemoglobin value that cannot be correct. Given the multiple quality issues noted in the first review cycle, these lapses in “high-profile” safety issues are a significant concern.³

3. The narratives should allow the reviewer to come to a conclusion regarding the cause of the death or adverse event, and the relatedness to study drug, independent of your interpretation. For this reason, the narratives must include all supportive data, even if negative. We note that the narratives from the original NDA and the resubmission do not provide the same supportive information.

We provide the following advice about narratives:

For narratives, please use a common template that is easy to review. Narrative summaries should provide a common synthesis of all available clinical data and an informed discussion of the case. Narrative summaries should allow a better understanding of what the patient experienced. The following items should be included:

- Patient age and gender
- Signs and symptoms related to the adverse event being discussed
- An assessment of the relationship of exposure duration to the development of the adverse event
- Pertinent medical history
- Concomitant medications with start dates relative to the adverse event
- Pertinent physical exam findings
- Pertinent test results (e.g., lab data, ECG data, biopsy data, autopsy results)
- Discussion of the diagnosis as supported by the available clinical data
- For events without a definitive diagnosis, a list of differential diagnoses
- Treatment provided
- Re-challenge results (if performed)
- Outcomes and follow-up information

In the narratives, we noted that dates (including adverse event onset and stop dates) were included. Please include relative study day number for all of the narratives for serious adverse events and deaths.

³ Even more concerning in terms of undermining confidence is that, in your response of September 27, 2012, you note that the pancytopenia was “considered a continued symptom of the overall diagnosis of lymphoma;” however, “lymphoma” is not in the resubmission narrative. Thus, with your response of September 27, 2012, a new deficiency was identified (the lymphoma still missing from the narrative). This is similar to the first review cycle, when it seemed that in some cases new issues would be identified in responses to inquiries (see page 6 of 34 of the meeting minutes of the End of Review Meeting).

You must correct the above deficiencies. In doing so, we recommend the following:

1. Enhance the quality control procedures of data presentations based on the concepts described above and in previous communications.
2. The examples of lapses in consistency and missing dataset events that were given above or in previous communications in this cycle are representative examples. There are likely additional inconsistencies, and you should address these issues throughout the entire database.
3. Please confirm that CRFs are complete and reconciled with all source documents and datasets. We ask that you notify us after you have completed this process. We will then provide you with a list of randomly selected patients without narratives. In your next resubmission, you must provide evidence that the CRFs, source documentation, and datasets (verbatim and preferred terms) for such patients have been adequately reconciled.
4. Compare narrative events to dataset events. Create (reconcile) new datasets to capture all events and provide a listing or dataset of the subjects for whom events in the narrative did not reconcile with the existing dataset ADAE_AU.xpt. Explain, both in general terms and per subject, why there was a discrepancy.
5. Make sure epilepsy data management plans (e.g. for each of the studies 301, 302, and 304) are included in your resubmission.
6. Include narratives and case report forms for deaths, serious adverse events, and dropouts associated with adverse events for the ongoing studies.

In addition, we have the following specific requests and recommendations regarding the presentation and analyses of safety data. These are not considered reasons for our incomplete response determination, but would facilitate review of your next resubmission.

1. Please provide narratives and CRFs for discontinuations in all studies due to subject choice and “other” reasons.
2. In reference to the Division’s CR letter dated April 30, 2010, item #6 of the Section, Safety Update, please provide the person-time values in all of the extent of exposure tables.
3. Please make sure that you provide all of the reference ranges for normal laboratory values used in data analyses.
4. We request you sort all of the adverse event incidence tables in the ISS with MedDRA preferred terms by system organ class (SOC) (in alphabetical order), and then by MedDRA Preferred Term (in alphabetical order).

5. We suggest you modify the overview tables in the ISS (Tables 29 and 30) to include deaths in ongoing trials (see page 12 of our minutes from the June 7, 2011 Type C meeting). Use the same format for the ongoing trial information as used for other trials in the referenced tables (by trial and part, if applicable). It is understood that for controlled trials, the treatment assignment may be blinded. If this is the case, simply note this.
6. We request a table of treatment-emergent adverse events and a table of treatment-emergent serious adverse events reported in $\geq 2\%$ of subjects after rounding in any eslicarbazepine-treated dose group (and greater than placebo) sorted by SOC (in alphabetical order) and then MedDRA Preferred Term.
7. Please include only treatment-emergent adverse events in your analyses of serious adverse events for each study pool.
8. Table 50 of the ISS, "Listing of all subjects with ALT or AST $> 3x$ ULN and total bilirubin $> 2x$ ULN for all studies," includes subject numbers and hyperlinks to the narratives. For four of six of these subjects, there do not appear to be CRFs. Provide the CRFs for these subjects. In addition, update the table as needed for the next submission. Similar to Table 52 of the ISS, include a table of subjects who had laboratory values of AST or ALT $> 3x$ ULN, total bilirubin $> 2x$ ULN, and ALP $< 2x$ ULN during the entire study (not necessarily at the same visit).
9. Please provide measures of central tendency and shift changes for all of the thyroid function laboratory values.
10. Please identify and report all subjects with falls (by unique subject ID and study day number). Please also categorize all subjects with falls on the basis of whether they occurred with or without concurrent seizures. In addition, identify and report all injuries (in the SOC injuries and the SMQ Accidents and Injury) in the same manner.
11. The current ISS pdf file contains bookmark links to sections, subsections, and tables. We agree with the bookmark links to sections and subsections. However, please remove the bookmark links that currently go to tables and add new bookmark links that go to the appropriate pooled study groups (e.g., epilepsy studies [controlled and uncontrolled studies], non-epilepsy studies, pediatric studies, Phase 1 studies, and ongoing studies). These new bookmark links to the pooled study groups should be numbered as a new sub-subsection. For example, under the Subsection 2.1.1.1, you should remove the current bookmarks that go to Tables 14-20 and add new bookmarks that go to the corresponding pooled study groups (e.g., Epilepsy Controlled Studies in Adults, numbered as 2.1.1.1.1).
12. For ease of review, please include all narratives in the iss-narratives.pdf file, even those included in other file locations, and include bookmarks for all subjects.

13. In reference to your ISS Changes in the Planned Analysis (May 23, 2012) document, we request the following changes:
- In Section 1.1.2, Allergic Reactions, SI category Rash, we do not agree with the new search criteria. Please change the criteria back to the original search criteria.
 - In Section 1.1.2, Allergic Reactions, SI category Hypersensitivity Reactions, please perform an analysis of subjects who fit the search criteria for DRESS using the search criteria provided in the Appendix of this letter.
 - In Section 1.1.3, Evaluation of Drug-Induced Liver Injury, SI source Lab Values and Adverse Event, we do not agree with the addition of the “anorexia and bulimia syndrome” or the change to “anorexia nervosa.” Please delete “anorexia and bulimia syndrome” and “nervosa.”
14. SAS programs were provided for the tables. Provide the step-by-step algorithms (including the variables and values) that were used for the ISS ADaM datasets to populate all of the tables in the ISS. For example, for ISS Table 7.1.11.1, SAEs for Phase III Epilepsy Controlled Study Pool Safety Population:
- a) To get the Phase III Epilepsy Controlled Study Pool Safety Population, use the ADSL dataset with Safety=Y and StudyID in (‘2093301’, ‘2093302’, ‘2093304’)
 - b) Use the ADAE dataset with AESER=Y and PART=‘Part 1’
 - c) For the rows, use the ADAE dataset variables “Body System or Organ Class” and “Dictionary-Derived Term.”
 - d) For the columns, use the ADAE variable “Dose Category (Controlled Pools)”
15. Format the tables of the ISS according to examples in FDA’s “Reviewer Guidance – Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review”:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072275.pdf>
16. The coding rules for MedDRA, the ICH-endorsed “MedDRA Term Selection: Points to Consider” should be followed for the coding of all adverse events. The entire NDA safety database needs to be reevaluated to ensure that these coding rules are followed. The “MedDRA Term Selection: Points to Consider” can be accessed at the following ICH webpage: <http://www.ich.org/products/meddra/meddraptc.html>
17. Ensure that all adverse events are presented, and not only events deemed “drug-related.” Please refer to FDA’s “Guidance for Industry – Premarketing Risk Assessment” for additional information regarding coding.
<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126958.pdf>
18. If there are parts of the submission, such as within clinical study reports or within the ISS, that are not searchable, list these in one section of the ISS or in the Reviewer’s Guide.
19. Provide a reviewer’s guide in the resubmission.

20. With regard to financial disclosure, Table 2, “Financial Disclosure Information Not Available” in the document financial-cert.pdf, lists 13 sub-investigators and his/her respective study number for whom financial disclosure was not obtainable; please add a column to this table with the number of subjects in the trial who were under the named sub-investigator.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

In our letter dated November 04, 2009, we notified you that a risk evaluation and mitigation strategy (REMS) was required for eslicarbazepine acetate to ensure that the benefits of the drug outweigh the risk of suicidality. We indicated that your REMS must include a Medication Guide and timetable for submission of assessments of the REMS.

We acknowledge receipt of your proposed REMS as described in your March 29, 2009, December 4, 2009, January 8, 2010, January 29, 2010, and August 31, 2012 submissions. The proposed REMS, as amended, contains a Medication Guide and a timetable for submission of assessments of the REMS.

We have determined that a REMS is not necessary to ensure the benefits of the drug outweigh the risks described above because we have determined that maintaining the Medication Guide as part of the approved labeling is adequate to address the serious and significant public health concern and meets the standard in 21 CFR 208.1. Therefore, it is no longer necessary to include the Medication Guide as an element of the REMS to ensure that the benefits of eslicarbazepine acetate outweigh its risks. We remind you that if eslicarbazepine acetate is approved, the Medication Guide will be part of the approved labeling in accordance with 21 CFR 208.

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}

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

Appendix: Updated List of MedDRA. Search terms for identification of DRESS⁴

Modified RegiSCAR criteria for DRESS⁵

- | |
|---|
| Reaction suspected to be drug related with <ol style="list-style-type: none">1. Acute skin rash2. Involvement of at least one internal organ3. Enlarged lymph nodes of at least two sites4. One of the following blood count abnormalities (as reference you should use the limits provided by the lab that has done the analysis)<ul style="list-style-type: none">- lymphocytes above or below the lab limits- eosinophils above the lab limits (in % or absolute count)- platelets below the lab limits5. Fever above 38°C |
|---|

(At least 3 of these criteria should be present for HSS/DRESS)
Please include events that occurred within 30 days of each other.

Source: <http://regiscar.uni-freiburg.de/diseases/dress/index.html>

1. ACUTE SKIN RASH

Skin and subcutaneous tissue disorders SOC

Dermatitis (any Preferred Term that includes the word dermatitis)
Drug eruption
Eczema
Erythema multiforme
Erythema nodosum
Rash (any PT that includes the word rash)
Skin lesion
Skin reaction
Skin exfoliation
Stevens-Johnson Syndrome
Toxic epidermal necrolysis
Toxic skin eruption
Urticaria

2. INVOLVEMENT OF AT LEAST ONE INTERNAL ORGAN

Blood and lymphatic disorders SOC:

Agranulocytosis
Aplastic anaemia
Aplasia pure red cell
Autoimmune lymphoproliferative syndrome
Autoimmune neutropenia
Autoimmune pancytopenia
Blood disorder
Bone marrow disorder
Bone marrow failure
Bone marrow toxicity
Coagulopathy
Disseminated intravascular coagulation
Drug rash with eosinophilia and systemic symptoms
Eosinophilia
Febrile neutropenia

⁴ MedDRA version 13.1. Some PT may be mentioned in more than one SOC.

⁵ There should be certain temporal proximity for the onset of these AE (within 1 month of each other).

Granulocytopenia
Hemolytic anemia
Hemolysis
Hypereosinophilic syndrome
Leukemoid reaction
Leukopenia
Lymphocytosis
Lymphopenia
Leukocytoclastic vasculitis
Lymphadenitis
Lymphadenopathy
Lymphoma
Monocytosis
Mononucleosis
Neutropenia
Pancytopenia
Platelet disorder
Platelet toxicity
Splinitis
Splenomegaly
Splenosis
Thrombocytopenia

Cardiac disorders SOC

Autoimmune myocarditis
Cardiomyopathy
Endocarditis
Eosinophilic myocarditis
Myocarditis
Pericarditis
Pericardial effusion
Pericardial disease
Pleuropericarditis

Endocrine disorders SOC

Adrenalitis
Autoimmune thyroiditis
Thyroiditis

Eye disorders SOC

Eye allergy
Eye swelling
Iritis
Iridocyclitis
Optic neuritis
Retinitis
Uveitis
Vitritis
Scleritis

Gastrointestinal disorders SOC

Allergic colitis
Colitis
Eosinophilic colitis

Eosinophilic esophagitis
Gastritis
Gingival edema
Gingival swelling
Gingivitis
Glossitis
Ileitis
Mouth ulceration
Mesenteritis
Oedema mouth
Oropharyngeal swelling
Parotitis
Pancreatitis
Periodontitis
Sialoadenitis
Stomatitis
Swollen tongue
Tongue oedema
Vasculitis gastrointestinal

[Hepatobiliary disorders SOC](#)

Autoimmune hepatitis
Blood amylase increased
Blood trypsin increased
Cholangitis
Cholecystitis
Hepatic failure
Hepatic functional abnormal
Hepatic encephalopathy
Hepatic infiltration eosinophilic
Hepatitis
Hepatitis acute
Hepatitis toxic
Hepatocellular injury
Hepatomegaly
Hepatosplenomegaly
Hepatorenal failure
Hepatorenal syndrome
Hepatotoxicity
Hyperbilirubinaemia
Hyperlipasaemia
Jaundice
Liver disorder
Lipase abnormal
Lipase increased
Oedema due to hepatic disease
Oedematous pancreatitis
Pancreatic enzymes increased
Pancreatic haemorrhage
Pancreatic necrosis
Pancreatitis (any PT that includes the word pancreatitis)
Pancreatorenal syndrome
Peripancreatic fluid collection
Swollen tongue

General disorders SOC

Influenza like illness
Malaise
Multiorgan failure

Immune system disorders SOC

Allergic bronchitis
Allergic cough
Allergic cystitis
Allergic keratitis
Allergic oedema
Allergic sinusitis
Alveolitis allergic
Anaphylactic reaction
Anaphylactic shock
Anaphylactoid reaction
Asthma
Angioedema
Antiphospholipid syndrome
Autoimmune disorder
Autoimmune hepatitis
Biliary cirrhosis primary
Bronchospasm
Circumoral oedema
Cholangitis sclerosing
Dermatomyositis
Drug hypersensitivity
Drug induced hypersensitivity
Encephalitis
Encephalopathy allergic
Eyelid oedema
Eosinophilic fasciitis
Face oedema
Hypersensitivity
Idiopathic thrombocytopenic purpura
Glomerulonephritis
Laryngeal oedema
Lip oedema
Lip swelling
Myasthenia Gravis
Myositis
Nephrogenic systemic fibrosis
Oedema mouth
Panniculitis
Pemphigus
Pemphigoid
Periorbital oedema
Pruritus allergic
Polymyositis
Reaction to drug excipients
Sarcoidosis
Serum sickness
Systemic lupus erythematosus
Systemic sclerosis
Type IV hypersensitivity reaction

Vasculitis (including organ vasculitis: cerebral, GI, renal, retinal, ocular pulmonary, etc)
Vitiligo

Investigations SOC

Hematologic

Any preferred term (PT) that reflects increased, decreased or abnormal MedDRA Haematologic investigations High Level Group Term (HLGT)

Hepatobiliary

Blood tests increased or abnormal

Alanine aminotransferase

Amylase

Aspartate aminotransferase

Bilirubin conjugated

Blood amylase

Blood bilirubin

Blood bilirubin unconjugated

Gamma-glutamyltransferase increased

Lipase

Liver function test

Transaminases

Biopsy liver abnormal

Immunologic

Any PT that reflects a positive or abnormal result under MedDRA Immunology and allergy investigations HLGT, and Investigations, imaging and histopathology procedures NEC, HLGT

Lung Biopsy lung abnormal

Renal

Blood creatine increased or abnormal

Blood urea increased or abnormal

Creatinine renal clearance decreased

Glomerular filtration rate decreased

Blood urine

Cells in urine

Eosinophils urine

Protein urine

Red blood cells urine

Urinary casts

Urinary casts present

Biopsy kidney abnormal

Skin Biopsy skin abnormal

Musculoskeletal and connective tissue disorders

Arthralgia

Arthritis

Arthropathy

Joint swelling

Joint warmth

Lupus-like syndrome

Myopathy

Myositis

Polyarthritits

Tendonitis
Tenosynovitis
Synovitis
Any PT under the MedDRA Connective tissue disorder HLGT.

[Neoplasms benign, malignant and unspecified \(including cysts and polyps\) SOC](#)

Lymphoma (any kind of lymphoma)
Pseudolymphoma

[Nervous system disorders SOC](#)

Acoustic neuritis
Arachnoiditis
Central nervous system inflammation
CNS ventriculitis
Epiduritis
Encephalitis (all PTs under Encephalitis NEC, High level term [HLT])
Encephalopathy
Leukoencephalitis
Leukoencephalomyelitis
Meningitis (all PTs under Meningitis NEC, HLT)
Myelitis
Neuritis cranial
Neuropathy
Polyneuropathy
Reye's syndrome
Toxic optic neuropathy
Vasculitis cerebral

[Renal and urinary disorders SOC](#)

Anuria
Cardiorenal syndrome
Dialysis
Eosinophilic cystitis
Haematuria
Haemodialysis
Haemolytic uraemic syndrome
Hepatorenal failure
Hepatorenal syndrome
Pancreatorenal syndrome
Peritoneal dialysis
Oedema due to renal disease
Renal disorder
Renal failure
Renal impairment
Renal toxicity
Any PT under MedDRA Nephropathies HLGT

[Respiratory, thoracic and mediastinal disorders SOC](#)

Allergic bronchitis
Acute interstitial pneumonitis
Asthma
Allergic granulomatous angiitis
Alveolitis
Alveolitis allergic
Angiolymphoid hyperplasia with Eosinophilia

Eosinophilic bronchitis
Eosinophilia myalgia syndrome
Eosinophilic pneumonia
Interstitial lung disease
Pleural effusion
Pleurisy
Pleurisy viral
Pleuropericarditis
Pneumonitis
Pulmonary eosinophilia
Pulmonary vasculitis
Pulmonary toxicity

Vascular disorders SOC

Arteritis (any PT that includes the word arteritis)
Capillaritis
Vasculitis (any Pt that includes the word vasculitis)

3. ENLARGED LYMPH NODES IN AT LEAST TWO SITES

Search term: Lymphadenopathy

It may be alone or as part of other PTs: Lymphadenopathy Mediastinal
Paratracheal
Generalised
Retroperitoneal
Vaccination site

Include other PT that could reflect lymphadenopathy:

- Benign lymph node neoplasm
- Lymph node palpable
- Lymph node scan abnormal

4. ONE OF THE FOLLOWING BLOOD COUNT ABNORMALITIES

- LYMPHOCYTES ABOVE OR BELOW LAB LIMITS**
- EOSINOPHILS ABOVE THE LAB LIMITS**
- PLATELETS BELOW LAB LIMITS**

In addition to these, there are multiple potential hematologic manifestations of DRESS that were included under Internal Organ involvement

5. FEVER ABOVE 38° C

- Hyperthermia
- Hyperpyrexia
- Pyrexia
- Febrile bone marrow aplasia (and all PTs that include the word “febrile”)

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/s/

RUSSELL G KATZ
11/02/2012

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Tuesday, September 25, 2012 3:08 PM
To: 'Amy.Schacterle@sunovion.com'; Karen.Joyce@sunovion.com
Subject: RE: NDA 22416 FDA's urgent info request
Importance: High

Dear Amy and Karen:

Below are additional information request from our review team:

Please find below examples of two of the issues of concern we have found in your submission.

We mentioned that in some cases, the narratives are insufficient. For subject 80670 in Study 301, the new narrative contains less information than in the 2009 submission. For example, the 2009 narrative describes more clinical details about the condition of the patient and also provides a description of test results that are not provided in the new narrative.

The following are examples of incomplete coding (based on terms found in the narratives but not in the ADAE_AU file) :

In the audited ADAE_AU file, for subject 301-194-90132 that had death coded to "death" , hypothermia is not coded.

In the ADAE_AU file, subject 301-90341 has AEs coded to fever and exanthema (possible DRESS syndrome). The narrative says laboratory tests revealed thrombocytopenia, for example, but thrombocytopenia is not coded as an AE.

Subject 90333 in , Study 301, has dysuria, insomnia, otitis media, vertigo now coded in the ADAE_AU dataset. Gait disturbance is still missing. We note that we have not been able to find gait disturbance in the CRF.

Study 301 Subject 90387 in Study 301, has headache, nausea, and vertigo in the ADAE-AU file. The dataset is still missing others including loss of memory, loss of vision, loss of appetite that are in the narrative.

Subject 90485 in Study 301 is still missing vertigo, dyspnea, chest pressure, a tendency to fall to the right side.

Subject 35705 in study 304 slipped in her room and had a fall and had a mandibular fracture. Not coded to fall.

Subject 00104 in study 304 had a motor vehicle accident (restrained passenger), not coded.

Subject 30505 in Study 304 had death noted due to toothache. The patient died from wounds from stabbing, and the ADAE_AU file does not have a stabbing/physical assault-related term.

Please let us know where we can find these events in the AE dataset, and please also let us know how the terms in the dataset were generated. Please respond by COB on Thursday, September 27.

thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
10903 New Hampshire Ave
Silver Spring, MD 20993

Office: 301-796-0036
Fax: 301-796-9842
Email: Su-Lin.Sun@fda.hhs.gov

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From: Amy.Schacterle@sunovion.com [mailto: Amy.Schacterle@sunovion.com]
Sent: Tuesday, September 25, 2012 9:55 AM
To: Sun, Su-Lin; Karen.Joyce@sunovion.com
Subject: RE: NDA 22416

Sulin,
Thank you. I am planning on sending written correspondence today which will outline our position.
Best regards,
Amy

From: Sun, Su-Lin [mailto: Su-Lin.Sun@fda.hhs.gov]

Sent: Monday, September 24, 2012 10:53 PM
To: Joyce, Karen; Schacterle, Amy
Subject: NDA 22416

Dear Amy and Karen:

I forwarded your voice mail to our review team (including Dr. Katz and Dr. Unger). As soon as I receive their recommendation, I will follow up with you.

Thanks,

Sulin

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/s/

SU-LIN SUN
09/25/2012

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Wednesday, September 19, 2012 11:18 AM
To: 'Karen.Joyce@sunovion.com'
Subject: RE: IND 67466 information request - further clarification

Dear Karen:

Below are the comments from our review team:

In response to the request for clarification regarding death reporting, report all deaths in the historically-controlled monotherapy studies and any ongoing monotherapy trials (IND or non-IND) as expedited reports. For other trials, report as per applicable U.S. regulatory requirements.

thanks,

Sulin

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From: Karen.Joyce@sunovion.com [mailto:Karen.Joyce@sunovion.com]
Sent: Friday, September 07, 2012 6:27 PM
To: Sun, Su-Lin
Subject: IND 67466 information request - further clarification

Dear Sulin,

Please be advised that responses to the August 17th and August 31st queries regarding the historically controlled monotherapy studies were submitted to the IND today.

We would like further clarification regarding the August 31, 2012 correspondence which requested that Sunovion report all deaths to the IND with special attention to the historic controlled monotherapy trials. Would you please clarify whether all deaths received from our partner Bial from Bial sponsored studies (not conducted under the IND), postmarketing and literature reports be submitted as 15-Day reports as well?

Kind regards ,

Karen

Karen Joyce

Director, Regulatory Affairs

Sunovion Pharmaceuticals Inc.

84 Waterford Drive | Marlborough, MA 01752

Office: 508-357-7856 | Fax 508-357-7491 | karen.joyce@sunovion.com

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/s/

SU-LIN SUN
09/19/2012

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Tuesday, September 18, 2012 11:46 AM
To: 'Karen.Joyce@sunovion.com'
Cc: Kelley, Laurie
Subject: NDA 22416 urgent FDA information request

Importance: High

Dear Karen:

Below are urgent information request for your NDA 22416:

The draft Package Insert (dated 9/4/12), proposing a 30 count container for the 200 mg strength without specifying the shape of the bottle. However, submitted a label for the 200 mg 60 count round bottle and a 200 mg 30 count oblong bottle was submitted for review. Can you please clarify this discrepancy?

Also please provide samples of the following:

Blisters packs of all proposed strengths including art work and drug product (placebo would be acceptable if actual drug product is not yet available)
Any/all carton/containers being proposed

Please provide by COB Monday 9/24/2012

Samples can be forwarded to Ms. Laurie Kelley at the address below.

Laurie Kelley, PA-C
Safety Regulatory Project Manager
FDA, CDER
Office of Surveillance and Epidemiology
Bldg. 22, Room 2437
10903 New Hampshire Ave.
Silver Spring, Maryland 20993-0002
tel: 301.796.5068

If you have any question, please feel free to contact me.

Thanks,

Sulin

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/s/

SU-LIN SUN
09/18/2012

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Saturday, June 02, 2012 2:45 AM
To: 'Karen.Joyce@sunovion.com'
Subject: RE: NDA 22-416 Resubmission Question--CSS responses
Importance: High

Dear Karen:

Below are the CSS responses for your NDA 22416 resubmission questions:

The following questions submitted by Sunovion and CSS responses are provided below:

Question 1.

It is our preference to provide a detailed discussion of all available preclinical data related to abuse potential in Module 4.2.3.7.4 (Nonclinical Abuse Potential Summary) with a high level summary of the preclinical data in the Abuse Potential Section provided in Module 1.11.4. Is this approach acceptable or would the CSS prefer that the nonclinical summary provided in Module 4.2.3.7.4 be a full duplication in Module 1.11.4?

CSS response:

Yes. The organization of the Module 4.2.3.7.4 is acceptable. However, you must also include complete study reports of all nonclinical abuse potential studies in this section.

As previously stated (CSS communication to the sponsor from Jan 12 2012), the recommended details of the submission of the abuse potential section are provided in the draft Guidance for Industry - Assessment of Abuse Potential of Drugs, January 2010:

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

To facilitate the Agency's review of NDA 022416, you should provide hyperlinks in the text whenever any study is cited, and specifically, every individual study must contain primary data.

From the draft *Guidance*, for NMEs, the NDA should include an abuse potential section with the

following:

1. A summary, interpretation, and discussion of abuse potential data provided in the NDA.

2. A proposal and rationale for placing (or not placing) a drug into a particular schedule of the Controlled Substances Act (CSA).

3. All primary data related to the abuse potential characterization of the drug, organized under the following subheadings:

a. Chemistry

b. Preclinical Pharmacology

c. Animal Behavioral and Dependence Pharmacology

d. Pharmacokinetics/Pharmacodynamics

e. Human Abuse Potential Laboratory Studies

f. Clinical Trial Data Relative to Abuse and Dependence Potential

g. Integrated Summaries of Safety and Efficacy

h. Foreign Experience with the Drug (Adverse Events, Abuse Potential, Marketing and Labeling)

For an NDA submitted in electronic format, you should address points 1, 2, and 3a-h (above) under the appropriate Modules 1, 2, 3, 4 and 5 of the common technical document (CTD).

These sections should contain links to the summary of abuse data in Module 2 and the proposal for scheduling and product labeling in Module 1.

The data and studies supporting sections 3 a-g (above) should be placed in the appropriate sections of the CTD: Chemistry (Module 3), preclinical and animal pharmacology (Module 4), pharmacokinetics/pharmacodynamics (Modules 4 and 5), human abuse and clinical studies (Module 5), and integrated summaries of safety and efficacy (Module 5). Foreign experience has no specific designated location, but would fit most appropriately under Module 5, postmarketing experience.

Question 2.

We prefer to keep all narratives and end of text tables related to abuse potential in Module 5 with the Integrated Summary of Safety and hyperlink from the Abuse Potential Summary in Module 1 to the narratives and end of text tables in Module 5. There will be a discussion in both Module 1 (Abuse Potential Summary) and Module 5 (Integrated Summary of Safety) but the narratives and EOT tables will only reside in Module 5. Is that acceptable?

CSS response:

Yes, this is acceptable.

Question 3.

Do CSS have access to the entire electronic submission?

CSS response:

Yes, CSS has access to the entire electronic submission. However, the abuse related data you will provide must have functioning hyperlinks to appropriate sections in the NDA, as required for NDA filing.

If you have any question, please feel free to contact me.

thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
10903 New Hampshire Ave
Silver Spring, MD 20993

Office: 301-796-0036

Fax: 301-796-9842

Email: Su-Lin.Sun@fda.hhs.gov

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From: Karen.Joyce@sunovion.com [mailto:Karen.Joyce@sunovion.com]

Sent: Thursday, May 17, 2012 2:35 PM

To: Sun, Su-Lin

Subject: NDA 22-416 Resubmission Question

Dear Sulin,

I wanted to let you know that our Phase III Study BIA-2093-304 has read out and we are targeting resubmission of the NDA for end of August 2012.

We have a few questions for the Controlled Substance Staff regarding the presentation and location of clinical and nonclinical data related to abuse potential. We are requesting CSS response to the bullet points below:

- It is our preference to provide a detailed discussion of all available preclinical data related to abuse potential in Module 4.2.3.7.4 (Nonclinical Abuse Potential Summary) with a high level summary of the preclinical data in the Abuse Potential Section provided in Module 1.11.4. Is this approach acceptable or would the CSS prefer that the nonclinical summary provided in Module 4.2.3.7.4 be a full duplication in Module 1.11.4?
- We prefer to keep all narratives and end of text tables related to abuse potential in Module 5 with the Integrated Summary of Safety and hyperlink from the Abuse Potential Summary in Module 1 to the narratives and end of text tables in Module 5. There will be a discussion in both Module 1 (Abuse Potential Summary) and Module 5 (Integrated Summary of Safety) but the narratives and EOT tables will only reside in Module 5. Is that acceptable?
- Do CSS have access to the entire electronic submission?

We are currently generating the abuse potential documents and it would be helpful if CSS would respond within the next 2 weeks, if possible.

Please do not hesitate to contact me if you have any questions.

Kind regards,

Karen

Karen Joyce

Director, Regulatory Affairs

Sunovion Pharmaceuticals Inc.

84 Waterford Drive | Marlborough, MA 01752

Office: 508-357-7856 | Fax 508-357-7491 | karen.joyce@sunovion.com

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/s/

SU-LIN SUN
06/02/2012



NDA 022416

MEETING MINUTES

Sunovion Inc.
Attention: Karen Joyce
Director Regulatory Affairs
84 Waterford Drive
Marlborough, MA 01752

Dear Ms. Joyce:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (eslicarbazepine acetate) [REDACTED] (b) (4)

We also refer to the meeting between representatives of your firm and the FDA on December 14, 2011. [REDACTED] (b) (4)

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, Pharm D, Regulatory Project Manager at (301) 796-0036.

Sincerely,

{See appended electronic signature page}

Russell G. 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
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: Guidance
Meeting Date and Time: December 14, 2011 3:00-4:00PM (EST)
Meeting Location: CDER White Oak Bldg # 22, Room 1417
Application Number: NDA 22416
Product Name: Stedesa (eslicarbazepine acetate)

Indication:

Sponsor/Applicant Name: Sunovion Inc.
Meeting Chair: Russell G. Katz, MD
DNP Division Director
Meeting Recorder: Su-Lin Sun, PharmD

FDA ATTENDEES

Russell Katz, MD, Division Director
Norman Hershkowitz, MD, Ph.D., Clinical Team Leader
Teresa Podruchny, MD, Clinical Reviewer
Angela Men, MD, Ph.D., Clinical Pharmacology Team Leader
Xiang Ling, Ph.D., Biostatistics Reviewer
Hari Cheryl Sachs, MD, Medical Team Leader, (PMHS)
Virginia Elgin, MD, Medical Officer (PMHS)
Denise Pica-Branco, Ph.D., Senior Regulatory Health Project Manager (PMHS)
Su-Lin Sun, PharmD, Regulatory Project Manager

SPONSOR ATTENDEES

Attendees from Sunovion

Fred Grossman, D.O., Senior Vice President, Clinical Development and Medical Affairs
Amy LaForte, PhD, Vice President, Regulatory Affairs
Karen Joyce, Director, Regulatory Affairs
Mark Versavel, MD, PhD Vice President, Clinical Research and Medical Affairs
David Blum, MD Senior Medical Director, Clinical Research and Medical Affairs
Hailong Cheng, Director, Biostatistics

Jahnvi Kharidia, Ph.D., Director, Clinical Pharmacology
Lisa Organisak, RPh, Senior Program Director, Product Development

BIAL - Portela & C^a, S.A. Attendees

Paula Costa, PharmD, Director, Regulatory Affairs
Teresa Nunes, MD, Head of Clinical Development
Patricio Soares da Silva, MD, PhD, Director, R&D

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/s/

RUSSELL G KATZ
01/13/2012

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Thursday, January 12, 2012 2:34 PM
To: Karen.Joyce@sunovion.com; Amy.LaForte@sunovion.com
Subject: NDA 22416---FDA's comments

Attachments: NDA 22416--FDA's comments for Dec 2, 2011 meeting request questions--011212.pdf

Dear Karen and Amy:

Attached document contains FDA's comments for the questions listed on your December 2, 2011 meeting request submission for NDA 22416. As promised previously, CSS division has provide their comments within 30 days from our December 20, 2011 meeting request deny letter.



NDA 22416--FDA's
comments for ...

If you have any question, please feel free to contact me.

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
10903 New Hampshire Ave
Silver Spring, MD 20993

Office: 301-796-0036
Fax: 301-796-9842
Email: Su-Lin.Sun@fda.hhs.gov

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CSS' comments for NDA 22416 December 2, 2011 meeting request questions

Subject: IND 67,466 (NDA 022416) Stedesa (Eslicarbazepine acetate)

Indication: Adjunctive therapy for the treatment of partial onset seizure in adults with epilepsy

Dosages: 400, 600, 800 mg tablets for oral administration

Applicant: Sunovion

I. Summary:

A. Background

Sunovion submitted on December 2, 2011 requesting a Type C meeting to discuss Sunovion's proposed Abuse Potential Section for pending NDA 022416 resubmission in 2012. CSS denied the meeting because the abuse potential assessment of the drug is integral to the safety assessment conducted as part of the NDA review and the NDA has not been resubmitted and filed. In addition, some questions specifically relate to data from new studies and analysis and interpretation of the data cannot be answered apart from the NDA. However, CSS now provides comments for those questions that can be answered at this time and identifies which questions will have to be addressed during the NDA resubmission review cycle.

B. Questions

Question 1 –Overall Submission Organization

Does the Agency agree with the proposed, overall organization for the Abuse Potential Section (Module 1.11.4) and the plan to reference other supportive sections within the NDA resubmission?

CSS response:

No. The organization of the Module 1.11.4 might be acceptable. However, you must also include complete study reports of all nonclinical abuse potential studies in Module 4.2.3.7.4.

The recommended details of the submission of the abuse potential section are provided in the draft Guidance for Industry - Assessment of Abuse Potential of Drugs, January 2010:

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

To facilitate the Agency's review of NDA, you should provide hyperlinks in the text whenever any study is cited, and specifically, every individual study should contain primary data. From the draft *Guidance*, for NMEs, the NDA should include an abuse potential section with the following:

- 1. A summary, interpretation, and discussion of abuse potential data provided in the NDA.**
- 2. A proposal and rationale for placing (or not placing) a drug into a particular schedule of the Controlled Substances Act.**
- 3. All primary data related to the abuse potential characterization of the drug, organized under the following subheadings:**
 - a. Chemistry**
 - b. Preclinical Pharmacology**
 - c. Animal Behavioral and Dependence Pharmacology**
 - d. Pharmacokinetics/Pharmacodynamics**
 - e. Human Abuse Potential Laboratory Studies**
 - f. Clinical Trial Data Relative to Abuse and Dependence Potential**
 - g. Integrated Summaries of Safety and Efficacy**
 - h. Foreign Experience with the Drug (Adverse Events, Abuse Potential, Marketing and Labeling)**

For an NDA submitted in electronic format, the common technical document (CTD) you should address points 1, 2, and 3a-h (above) under the appropriate Modules 1, 2, 3, 4 and 5. These sections should contain links to the summary of abuse data in Module 2 and the proposal for scheduling and product labeling in Module 1.

The data and studies supporting sections 3 a-g (above) should be placed in the appropriate sections of the CTD: Chemistry (Module 3), preclinical and animal pharmacology (Module 4), pharmacokinetics/pharmacodynamics (Modules 4 and 5), human abuse and clinical studies (Module 5), and integrated summaries of safety and efficacy (Module 5). Foreign experience has no specific designated location, but would fit most appropriately under Module 5, postmarketing experience.

Question 2 –Potential for Physical Dependence

a) Does the FDA agree that these nonclinical data, along with the analysis of available human data regarding physical dependence and withdrawal are sufficient to be considered a complete response to the CSS request for data to evaluate physical dependence?

b) Does the FDA agree with the analysis plan and the format of the associated table shells for the clinical assessment of physical dependence?

CSS response:

You should consider submitting these questions for the pre-NDA meeting. At that time, we will review the meeting package, including any protocol and other

information the sponsor might submit. CSS will review that information in the context of the whole NDA and provide feedback.

Question 3 – Clinical Abuse Liability Study

a) Does the FDA agree that this constitutes a complete response to the Agency's request for a human abuse liability study?

b) Based on the Emax on Drug Liking VAS for both doses of alprazolam compared to placebo, does the Agency agree that alprazolam separates from placebo, and the study is valid?

c) Based on the Emax on Drug Liking VAS for eslicarbazepine acetate compared to alprazolam, does the Agency agree that eslicarbazepine acetate separates from alprazolam at all doses?

d) We interpret that the data indicate that the product does not demonstrate a meaningful potential for abuse. Pending review of the full data, does the Agency interpret the outcome of this study in a similar manner?

CSS response:

CSS provided earlier feedback regarding the design of clinical and nonclinical studies related to abuse potential. The evaluation of these studies is a review issue. Additionally, these studies will undergo independent analysis by the FDA statistical staff.

Question 4 – Assessment of adverse events potentially related to abuse

a) It is proposed that the assessment of adverse events potentially related to abuse will include an analysis of pooled data and a single cumulative table across all studies. The analysis will not be presented on an individual-study basis. Is this pooling strategy acceptable to the FDA?

b) Does the FDA agree with the analysis plan and the format of the associated table shells for the clinical assessment of abuse liability?

CSS response:

a) No. This is not an acceptable strategy. CSS requests that you provide the data for each individual study and cumulative tables broken down by population including: 1) healthy volunteers, 2) epilepsy patients, 3) non-epilepsy patients and 4) recreational drug users (from the human abuse potential study).

b) Additionally, you must ensure that the NDA submission provides complete information, including case report forms and final outcomes, on all instances of addiction, abuse, misuse, overdose, drug diversion/drug accountability,

discrepancies in amount of the clinical supplies of the study drug, noncompliance, protocol violations, lack of efficacy, individuals lost to follow-up, and any other reasons why subjects dropped out of the study.

- c) Consider submitting this question for the pre-NDA meeting and at that time, CSS will evaluate the protocols and any other information submitted by the sponsor in the context of the whole NDA and provide feedback.**

Question 5 – Foreign Postmarketing Experience with the Drug

Does the FDA agree with the proposed approach to assess foreign postmarketing experience with eslicarbazepine acetate?

CSS response:

Yes. This is an acceptable strategy. CSS requests that you provide a numerator for postmarketing adverse events which were reported in other countries relative to the population at risk. You should also be aware that FDA will perform an independent analysis of postmarketing adverse events reported that may relate to abuse potential.

Question 6 – Review of published literature, drug abuse and law enforcement data sources for other AEDs

a) Does the Agency agree that the review of published literature, drug abuse and law enforcement data sources for carbamazepine and oxcarbazepine should be summarized in Module 1.11.4?

b) A comparison between eslicarbazepine acetate and other AEDs that have been placed in or recommended for Schedule V will be summarized in the resubmission.

Does the FDA agree that this presentation would provide a useful context for the evaluation of the potential for abuse and potentially support a proposal that eslicarbazepine acetate be unscheduled?

CSS response:

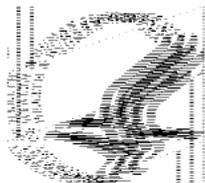
a) No. This information should be provided in Module 5, section 5.3.6.1 Reports of Postmarketing Experience (see response to the above question 1).

b) CSS suggests that you provide a comparison of eslicarbazepine with other drugs in various levels of control, such as Schedule 4 and 5, with similar general pharmacological activity, i.e. CNS depressants and not limit the drugs to anti-epileptic drugs.

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/s/

SU-LIN SUN
01/12/2012



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

M E M O R A N D U M

Date: November 29th, 2011
From: Virginia Elgin, M.D.
Through: Lisa Mathis, M.D.
To: Rusty Katz, M.D.
Director
Division of Neurology Products (DNP)
Re: Type C Meeting Request

Background:

Sponsor: Sunovion Pharmaceuticals, Inc.
Application: N-22-416

Drug: Eslicarbazepine Acetate

Indication: Adjunctive Therapy for Partial Onset Seizures

Dosage form and route of administration: tablets administered orally: 200, 400, 800, and 1200 mg.

Product Description: Anti-epileptic

Division's Consult Request

The Sponsor submitted an NDA which received a Complete Response (CR) on 3/30/2010.

(b) (4)

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/s/

VIRGINIA E ELGIN
12/15/2011

LISA L MATHIS
12/20/2011



NDA 022416

MEETING DENIED

Sunovion Pharmaceuticals Inc.
Attention: Karen Joyce
Director Regulatory Affairs
84 Waterford Drive
Marlborough, MA 01752

Dear Ms. Joyce:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Stedesa, (eslicarbazepine acetate) 400mg, 800mg, and 1200mg tablets.

We also refer to your December 2, 2011, correspondence requesting a type C meeting to discuss Sunovion's proposed Abuse Potential Section for pending NDA 022416 resubmission in 2012. We are denying the meeting because the abuse potential assessment of the drug is integral to the safety assessment conducted as part of the NDA review and the NDA has not been resubmitted and filed. In addition, some questions specifically relate to data from new studies and analysis and interpretation of the data cannot be answered apart from the NDA. The Agency will provide comments for those questions that can be currently answered within 30 days from this letter date. We will also identify which questions will have to be addressed during the NDA resubmission review cycle.

If you have any questions, call me at (301) 796-0036.

Sincerely,

{See appended electronic signature page}

Su-Lin Sun, PharmD
Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

SU-LIN SUN
12/20/2011

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Wednesday, October 05, 2011 12:10 PM
To: 'Karen.Joyce@sunovion.com'
Subject: NDA 22416

Dear Karen:

Below are the comments from our reviewer for your July 27, 2011 proposed PCS criteria submission:

With respect to the July 27, 2011 submission of proposed PCS criteria, please see the guidance document, Attachment B, Clinical Safety Review of an NDA or BLA, Table 12 (MAPP 6010.3 Rev 1). Modify the values you have proposed to be consistent with the values in that table. Also, see the guidance on drug induced liver injury and include an analysis as noted in section IV.E. of that document ("Drug-Induced Liver Injury: Premarketing Clinical Evaluation"). These documents are available through the FDA website. For the serum chemistry parameters not in Table 12 of Attachment B, for the hematology values, and for vital signs, the proposed criteria are acceptable. For EKG parameters, please also present the following.

- treatment emergent PR interval prolongations of > 200 ms, >220 ms, and > 250 ms by treatment group*
- For QTc intervals, present the number and percentage of patients with prolonged post-baseline QTc interval by drug group as follows: QTcB interval ≥ 500 ms, Max increase from BL < 30 ms, Max increase from BL ≥ 30 ms and ≤ 60 ms, Max increase from BL ≥ 60 ms, Max ≥ 500 ms and max increase from BL ≥ 60 ms; QTcF interval ≥ 500 ms, Max increase from BL < 30 ms, Max increase from BL ≥ 30 ms and ≤ 60 ms, Max increase from BL ≥ 60 ms, Max ≥ 500 ms and max increase from BL ≥ 60 ms*
- The number and percentage of patients with post-baseline ≥ 450 ms in males and ≥ 470 ms in females by drug group*
- The number and percentage of patients with post-baseline QTc shortening below 340 ms*

If you have any question, please feel free to contact me.

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
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/s/

SU-LIN SUN
10/05/2011

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Tuesday, December 13, 2011 12:58 PM
To: 'Karen.Joyce@sunovion.com'; 'Amy.LaForte@sunovion.com'
Subject: NDA 22416 preliminary comments

Importance: High

Attachments: NDA 022416--Type C meeting--preliminary comment 121011.pdf

Dear Karen or Amy:

Attached is the Division's preliminary comment for NDA 22416.



NDA 022416--Type
C meeting--pr...

By the way, the meeting room has been changed to room # 1417.

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
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Meeting Date: December 14, 2011

Time: 3:00-4:00 PM EST

Sponsor: Sunovion Pharmaceuticals Inc.

Product: Stedesa (eslicarbazepine acetate, SEP-0002093)

(b) (4)

Proposed Use:

(b) (4)

Introductory Comment: This material consists of our preliminary responses to your questions in preparation for the discussion at the meeting scheduled for December 14, 2011 from 3:00 – 4:00 PM with the Division of Neurology Products. This material is shared to promote a collaborative and successful discussion at the meeting. The minutes of the meeting will reflect agreements, key decisions and any action items discussed during the formal meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the Regulatory Project Manager, RPM). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. Please note that if there are any major changes to your development plan/the purpose of the meeting/the questions (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting. If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact the RPM to discuss the possibility of including these for further discussion at the meeting.

SUMMARY OF BACKGROUND INFORMATION PROVIDED BY THE SPONSOR/QUESTIONS AND FDA PRELIMINARY RESPONSES

(b) (4)

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/s/

SU-LIN SUN
12/13/2011



NDA 022416

INFORMATION REQUEST

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Sunovion Pharmaceuticals, Inc.
Attention: Karen Joyce
Director, Regulatory Affairs
84 Waterford Drive
Marlborough, MA 01752-7010

Dear Ms. Joyce:

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

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by Cetero Research in Houston, Texas (Cetero).¹ The pervasiveness and egregious nature of the violative practices by Cetero has led FDA to have significant concerns that the bioanalytical data generated at Cetero from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or "prep" run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or "prep" runs that prevented Cetero and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by Cetero Research in Houston, Texas during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is searching available documentation to determine which NDAs are impacted by the above findings.

¹ These violations include studies conducted by Bioassay Laboratories and BA Research International specific to the Houston, Texas facility.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by Cetero Research in Houston, Texas during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

Please respond to this query within 30 days from the date of this letter.

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

If you have questions, contact your designated Regulatory Project Manager, at (301) 796-2250.

Sincerely,

{See appended electronic signature page}

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

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/s/

JACQUELINE H WARE

09/15/2011

Signed for Dr. Russell G. Katz



NDA 022416

MEETING MINUTES

Sunovion Pharmaceuticals Inc.
Attention: Karen Joyce
Associate Director Regulatory Affairs
84 Waterford Drive
Marlborough, MA 01752-7010

Dear Ms. Joyce:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Stedesa, (eslicarbazepine acetate) 400mg, 600mg, and 800mg tablets.

We also refer to the meeting between representatives of your firm and the FDA on June 7, 2011. The purpose of the meeting was to discuss Sunovion's NDA resubmission plan, the revised ISS and ISE (including a new Phase III study (2093-304)), Sunovion's auditing plan for studies 2093-301, and 2093-302, and data requirements to address the CSS' request for any potential for physical dependence.

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 Sulin Sun, PharmD, Regulatory Project Manager at (301)796-0036.

Sincerely,

{See appended electronic signature page}

Russell G. 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
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C

Meeting Category: N/A

Meeting Date and Time: June 7, 2011 3:00-4:00 PM

Meeting Location: CDER White Oak Bldg # 22, Room 1309

Application Number: NDA 022416

Product Name: Stedesa (eslicarbazepine acetate)
400, 600, and 800mg tablets

Indication: Adjunctive therapy in the treatment of partial onset seizures
in adults with epilepsy

Sponsor/Applicant Name: Sunovion Inc.

Meeting Chair: Russell G. Katz, MD
DNP Division Director

Meeting Recorder: Su-Lin Sun, PharmD

FDA ATTENDEES

Ellis Unger, MD, Deputy Director, Office of Drug Evaluation-I
Norman Hershkowitz, MD, Ph.D., Clinical Team Leader
Teresa Podruchny, MD, Clinical Reviewer
Alicja Lerner, MD, Ph.D., Medical Officer (CSS)
Katherine Bonson, Ph.D., Pharmacologist (CSS)
Tejashri Purohit-Sheth, MD, Acting Division Director, Division of GCPC (Office of
Scientific Investigation, Office of Compliance/ CDER)
Antoine El Hage, Ph.D., Regulatory Pharmacologist (DSI)
Kun Jin, Ph.D., Biostatistics Team Leader
Xiang Ling, Ph.D., Biostatistics Reviewer
Tracey Peters, PharmD, Regulatory Project Manager
Su-Lin Sun, PharmD, Regulatory Project Manager

SPONSOR ATTENDEES

Attendees from Sepracor

Stewart Mueller, Senior Vice President, Global Regulatory Affairs and Quality
Antony Loebel, MD, Executive Vice President, Clinical Research and Medical Affairs
Amy LaForte, PhD, Vice President, Regulatory Affairs
Karen Joyce, Director, Regulatory Affairs
Mark Versavel, MD, PhD Vice President, Clinical Research and Medical Affairs
David Blum, MD Senior Medical Director, Clinical Research and Medical Affairs
David Reasner, PhD, Senior Vice President, Data Science-North America
Hailong Cheng, Director, Biostatistics
Lisa Organisak, RPh, Senior Program Director, Product Development

BIAL - Portela & C^a, S.A. Attendees

Paula Costa, PharmD, Director, Regulatory Affairs
Susana Tavares, PharmD, Quality Assurance Manager
Teresa Nunes, MD, Head of Clinical Development
Patricio Soares da Silva, MD, PhD, Director, R&D

1. BACKGROUND

On 29 March 2009, Sunovion submitted an NDA for eslicarbazepine acetate which was received by the Division on 30 March 2009. On the extended PDUFA Goal Date of 30 April 2010 Sunovion received a Complete Response letter and an End of Review Meeting took place on 30 July 2010. During the 30 July meeting FDA (both the Division and the Office of Drug Evaluation 1) advised that submission of a new adequate and well-controlled Phase III study would be very helpful to support successful review of this application, given the GCP compliance issues observed in the program, and that in accord with the intent of FDAMA a single new trial could be adequate to support NDA review.

As explained in Sunovion's 18 March 2011 submission requesting an extension for the deadline to resubmit the NDA, Sunovion intends to resubmit the eslicarbazepine acetate NDA with results from Study 2093-304, which is a new adequate and well-controlled Phase III study evaluating the safety and efficacy of eslicarbazepine acetate once daily at doses of 800 mg and 1200 mg. Study 2093-304, entitled *Efficacy and safety of eslicarbazepine acetate as adjunctive therapy for refractory partial seizures in a double-blind, randomized, placebo- controlled, parallel-group, multicentre clinical trial*, was submitted to the IND on 11 December 2009, Serial No. 120 and is expected to be complete and reported in Q1 2012. Study 2093-304 was amended to revise the design of the seizure diary in order to address the Division's concerns regarding the potential for missing seizure data associated with the original diary card design (amendment submitted 1 November 2010, Serial No. 0184).

Taking into account the Division's comments in the Complete Response letter and the End of Review meeting minutes regarding pooling of data, the outcomes of the audits of Studies 2093-301 and 2093-302 and the inclusion of results of an additional Phase III Study (2093-304), Sunovion has developed proposed pooling strategies for the Integrated Summary of Safety (ISS) and Integrated Summary of Efficacy (ISE) which are discussed in Sections 9.1.1 and 9.1.2.

As requested by the Division in the Complete Response letter and agreed to at the End of Review meeting, additional audits of all subjects at all sites for Studies 2093-301 and 2093-302, with the exception of the 4 sites inspected by DSI, have been conducted in order to provide the Agency with additional information adequate for FDA to reach a definitive conclusion about GCP compliance for these two studies. It was also agreed that Sunovion would request a face-to-face meeting to discuss the audit findings and Sunovion's overall conclusions regarding Studies 2093-301 and 2093-302. The audit reports were submitted on 28 March 2011 (eCTD Sequence No.0041) and a detailed analysis of the impact of the audit findings on safety and efficacy data is ongoing. Sunovion's summary of the audit findings and assessment of the impact on the safety and efficacy data will be submitted in the meeting briefing package.

The Complete Response letter also requested new clinical data addressing the potential for abuse and physical dependence. Specifically, the Controlled Substance Staff (CSS) requested a new study to assess abuse liability and a new two-week prospective evaluation of physical dependence, typically conducted at the conclusion of the clinical efficacy study. At the End of Review meeting Sunovion agreed to conduct the new abuse liability study. It was agreed at the End of Review meeting, however, that evaluation of physical dependence in an epilepsy

population would expose subjects to an unacceptable risk related to increased seizure frequency and that evaluation of physical dependence in a healthy normal population would be an acceptable alternative. Following submission of the protocol for the physical dependence study (2093-154) the FDA determined that the risk of exposing healthy normal subjects in study 2093-154 was not necessary (communication dated 8 March 2011) and instead requested a new nonclinical dependence study and a prospective evaluation of physical dependence in 20-30 non-epilepsy patients, in addition to an evaluation of data following abrupt discontinuation in completed studies. Sunovion wishes to discuss the feasibility and limitations of obtaining these new data.

Post Meeting Note: A statement is noted in the background material that the Division agreed “that submission of a new adequate and well-controlled Phase III study would be very helpful to support successful review of this application.” Although this is an accurate statement it should not be interpreted to mean that the division has agreed that a single additional trial is sufficient. This will have to remain a review issue, as noted in the referenced, July 30, 2010, meeting minutes.

2. DISCUSSION

I. Resubmission Plan (Questions # 1 to 9):

A. Integrated Summary of Efficacy Pooling Strategy:

Question 1:

The new ISE will include analyses of the primary and key secondary endpoints for pooled Phase III Studies 2093-301, -302, and -304. Analyses of the data for individual studies will also be provided. Is this pooling strategy acceptable to the Division?

Preliminary FDA Response:

While the ISE is of interest as a supportive document, data and analyses of the individual studies will be the primary source of clinical and statistical review. Please focus on the individual study report presentations, data listings, and datasets.

Although not directly related to this question, in addition to the routine sensitivity analyses, there should be sensitivity analyses for the concomitant medications used, including rescue benzodiazepine use, and for the impact of changes in concomitant medication. It is critical that the data allows evaluation of rescue benzodiazepine use and for the changes made in dosing of carbamazepine and/or phenytoin. Therefore, there has to be a record of the dosage and times of use (stop and start dates) for these medications. It is unclear whether the current diary will be sufficient to collect the detailed information that will be necessary to evaluate these issues. Also, we refer you also to the email communication of 4-28-11 regarding study 304 protocol amendment #3.

Sunovion's Response (June 6, 2011):

We understand that the primary efficacy conclusions are drawn from analyses of individual studies. We propose that the ISE will present both an integrated analysis for pooled epilepsy studies, and also will present individual study analyses for the primary and key secondary endpoints. The presentation of individual study results in the ISE will differ in minor ways from that in the original CSRs for Studies 301 and 302 (e.g. some subjects will be removed from the efficacy dataset as a result of the audit findings; definitions of the length of study periods and seizure data availability will be modified to reflect actual seizure diary card return dates; new seizure diaries discovered at audits will added in to efficacy data).

We have elected to leave the original CSRs and their respective databases in their current form, without revision, as these represent the only analysis of the efficacy data conducted prior to unblinding, and additionally these are based on individual databases, whereas the modifications to the efficacy data described above are executed, for consistency, to the integrated dataset. In the resubmission, we will provide documentation to highlight the differences between analyses of individual studies conducted for the ISE and analyses conducted in the CSRs.

Is this acceptable to the Division?

Meeting Discussion:

The Sponsor noted they will also (in addition to the proposal above) provide documentation that highlights the differences between the CSR and ISE analyses of efficacy. FDA agreed to the proposal with the request that the Sponsor send in new efficacy datasets for the individual studies (as well as the original efficacy datasets). The Division recommended that the Applicant follow GCP Process and rectify diary card problems to ensure data quality.

Question 2:

If Study 2093-304 demonstrates statistical significance for the primary endpoint of standardized seizure frequency using data collected in both new and old diary cards) and the effect size for the primary endpoint in subjects with the new diary card is consistent with that observed in Studies 2093-301 and 2093-302, does the Division agree that the resubmission plan is acceptable to evaluate safety and efficacy in support of approval of eslicarbazepine acetate?

Preliminary FDA Response:

On face it appears adequate, but this depends, to a large degree, on the final conclusions of DSI and the Division as to the reliability, usability, and interpretability of the safety and efficacy data from studies 301 and 302 as well as from study 304. We can not commit to a definitive decision on this point at this time.

Sunovion's Response (June 6, 2011):

Thank you for your comments. We do not need further clarification for Question 2.

Meeting Discussion: None

B. Integrated Summary of Safety Pooling Strategy:

Question 3:

The integrated re-analysis in the new ISS will include an analysis of pooled data from Phase III Studies 2093-301, -302, and -304 with a separate summary of data from Study 2093-303. Studies 2093-301 and -302 will not be provided as a separate pool. Is this pooling strategy acceptable to the Division?

Preliminary FDA Response:

On-face and without regard to possible data quality issues, this strategy is acceptable.

Sunovion's Response (June 6, 2011):

Thank you for your comments. We do not need further clarification for Question 3.

Meeting Discussion: None

Question 4:

The integrated re-analysis in the new ISS will include tables that summarize the following study pools: Phase III epilepsy controlled studies in adults (2093-301, -302 and -304), epilepsy uncontrolled studies (Phase III long term extension studies), Phase II non-epilepsy patient controlled studies, Phase II non-epilepsy patient uncontrolled studies and all Phase I studies. Is this pooling strategy acceptable to the Division?

Preliminary FDA Response:

Given the possible baseline differences in medical history and concomitant medications, the diabetic population should not be pooled with the other groups. This is discussed more below under "ii".

i) For the Phase 3 epilepsy data: add a presentation that pools the cumulative controlled and uncontrolled epilepsy data for unique patients. For analyses of special events, please include an analysis with and without study 303.

Sunovion's Response (June 6, 2011):

We agree to provide the analyses as requested.

Preliminary FDA Response:

ii) The following table represents pertinent information for the proposed pooling of non-epilepsy controlled populations (phase 2).

		expected n randomized /completed	duration	dose
203	bipolar DB, R, PC	162/123	3 weeks	Group I-800-2400 Group II-600 to 1800 Group III-Placebo
204	bipolar DB, R, PC	38/28	3 weeks	600, 1200, 1800, P
205	bipolar OL then DB, PG	87/35	OL=2 weeks DB, PG=up to 15 months	OLE=900 DB, PG=300, 900, 1800 QD
206	DN DB, R, PC	557/419	17 w: (2w BL, 1w titrate, 12w maint, 2 wk fu)	BID of 400 or 600 or800 or QD of 800 or 1200 or P
207	PHN DB, R, PC	567/438	13 w: (2w BL, 1w titration, 8w maint, 2w fu)	BID of 400 or 600 or800 or QD of 800 or 1200 or P
209	Migraine	410/355	22 w	QD: 800, 1200, P
210	FM	528/389	17 w	QD: 400, 800, 1200, P

Table information from information in Table 1, attachment 3, n=number of subjects, 3 w =weeks, fu-follow-up, DB=double-blind, PG=parallel group, PC=placebo-controlled, R=randomized, DN=diabetic neuropathy, PHN=post-herpetic neuropathy, FM=fibromyalgia

Based on the information in the table above, please add the following sub-pools: (1) studies 203, 204, and 205, (2) studies 209 and 210, (3) study 206 only and, (4) study 207 only.

Sunovion's Response (June 6, 2011):

Based on the Division's comments [first paragraph and (ii)], we seek clarification on the following with respect to the comments regarding the diabetic population. We understand your comments in total to mean that it is not necessary to provide an all non-epilepsy controlled Phase 2 study pool and that only the following pools are required for non-epilepsy patients.

- 1. Studies 203, 204, 207, 209, 210 – Non-epilepsy controlled Phase 2 study pool (excludes Study 206 in diabetic neuropathy and Study 205 as an uncontrolled study)*
- 2. Studies 203, 204, 205 – All bipolar controlled and uncontrolled study pool*
- 3. Studies 209, 210 – Migraine and fibromyalgia controlled study pool*
- 4. Study 206 – Diabetic neuropathy study alone*
- 5. Study 207 – Post herpetic neuralgia study alone*

We also seek agreement that we are not planning to remove subjects with a medical history of diabetes from the epilepsy study pools.

Preliminary FDA Response:

iii) For the phase 1 data: For deaths, serious adverse events, and discontinuations secondary to an adverse event, please also present a table that separates the special populations (hepatic and renal impaired) from the healthy volunteers.

*Sunovion's Response (June 6, 2011):
We agree to provide the analyses as requested.*

Preliminary FDA Response:

iv) Ongoing studies: Based on Table 1, there will be six ongoing non-IND studies and three ongoing IND studies at the time of the ISS cut-off date.

Non-IND

- **A pediatric cognition study performed in children with POS (study 208). This study will have 2 parts, a controlled phase and an open-label extension. The controlled phase consists of 4- week titrations, 8- week maintenance, 4-week taper, and 4-week follow-ups. It seems the controlled phase CSR will be completed in September 2012 with the LPO in May, 2012. The OLE CSR is expected in October, 2013.**
- **A phase 3 pediatric study (study 305) with expected CSR date of September 2012 for part 1 (controlled) and of October, 2013 for part 2 (the first of the planned open-label extensions).**
- **Another study in DN (phase 3, study 307) with expected completion of the CSR in October 2012.**

- **Another study in PHN (phase 3, study 308) also with expected completion date of the CSR in October 2012.**
- **One monotherapy in newly diagnosed POS (study 311) with CSR November 2013. This seems to be a different formulation ((b) (4))**
- **One OL study in 100 elderly subjects (study 401) with refractory POS with CSR April 2012.**

IND

- **Two phase 3 monotherapy studies in refractory POS (studies 45 and 46) using an (b) (4) formulation and historical control design. The dates of the CSRs are “TBD” and the LPOs are the 3rd quarter of 2012. The Annual report to IND 67466 (reporting period ends 12-19-10) indicates that either 59 or 62 of 174 subjects have received at least one dose in study 45, an 18-week study, and 24 have completed. For study 46, 35 sites had been initiated, although only one subject had been randomized. Do you have an estimate of when these trials will be completed?**
- **An open-label, one-year extension (study 50) of study 45. As per the referenced IND annual report, 41 of the planned 348 had enrolled in study 50 and no one had completed.**

Please submit a proposal for the presentation of data in the studies noted as ongoing.

As noted previously, please identify an expected completion date for studies 45 and 46.

Sunovion’s Response (June 6, 2011):

For the ongoing studies (both IND and non-IND), we plan to provide data regarding enrollment, deaths, serious adverse events, non-serious adverse events, and discontinuations due to adverse events. It must be noted that except for data regarding deaths, these data will be blinded to study treatment for most studies and blinded to dose for the monotherapy studies where all subjects are administered eslicarbazepine acetate. We plan to provide frequency tables for each parameter noted above by individual study, similar to that provided for an IND annual report. Since the studies are ongoing, we note that these data are preliminary and it is not feasible to generate integrated databases to include these ongoing studies, nor will the individual study datasets be provided.

We are currently targeting August 2012 for the planned resubmission date. In previous communication, the Division had indicated agreement that the cut-off date was acceptable if within a year of the planned submission date. Therefore, we were considering a December 2011 cut-off date to coincide with planned completion of Study 304 and the requirements for the IND annual report. However, we have moved the planned cut-off date to February 2012 based on current expected completion dates of Study 304 as well as the Division’s new comments regarding the timing of the cut-off date within 6 months of the submission date. Since the new planned cut-off date of February 2012 is only two months after the IND annual report cut-off

date of December 2011, we would like to request an extension of up to 90 days on the cut-off date of the annual report to align with the cut-off for the NDA, as the submission will primarily be repetitive of the IND Annual report. A 90 day extension is requested to allow for any minor delays in the planned completion of study 304, resulting in a minor delay in the resubmission, noting the Division's comment in Question 6 regarding a fluid cut-off date. The annual report will be submitted 60 days following the agreed cut-off date.

Studies 045 and 046 are not expected to complete last patient visit prior to December 2012 and therefore will not be available as completed studies reported prior to the planned resubmission date.

Preliminary FDA Response:

vi) Please do include one section in the ISS that has all of the pediatric study data as well as including these data in other places in the ISS as may be appropriate (such as overview tables that show cumulative information, deaths, and non-fatal SAEs).

Sunovion's Response (June 6, 2011):

We agree to provide the pediatric data in a single dedicated section as well as other places as appropriate. We propose that this section be located in the Special Populations section of the ISS. We seek clarification as to whether the Division prefers to review the pediatric ongoing studies in the Pediatric section or the Ongoing Study section.

(b) (4)

Preliminary FDA Response:

vii) Some of the phase 3 trials have more than one OLE phase. All data until the cut-off of the ISS should be included in appropriate places in the ISS.

Sunovion's Response (June 6, 2011):

We plan to provide all data up to the cut-off date for the resubmission. Data from completed studies will be presented by topic and then by study (e.g. a section for adverse events will be provided in the section on adverse events). For ongoing studies, we planed to provide the data in dedicated sections listed under Sections 2.1.2. Deaths, 2.1.3. Other Serious Adverse Events and 2.1.4. Other Significant Adverse Events (refer to ISS Template - Attachment 3 in Meeting Briefing Package), as these data are blinded and preliminary.

In summary, does the Division:

- 1) Agree with the planned study pools for non-epilepsy patients as outlined above?*
- 2) Agree that subjects with a medical history of diabetes should not be removed from the epilepsy study pools?*

- 3) *Agree with the proposed plan for providing data from ongoing studies?*
- 4) *Agree with the request to delay the annual report cut-off date for up to 90 days to synchronize with the planned cut-off date for the resubmission?*
- 5) *Prefer the data regarding ongoing pediatric studies to be located in the pediatric section or the ongoing study section of the ISS?*
- 6) [REDACTED] (b) (4)

Meeting Discussion:

(The 1-6 numbering corresponds to 1-6 summary above)

1. *The Applicant presented Sunovion's meeting slide # 3 and 4 for discussion of proposed non-epilepsy study pools. The Division agreed with the proposed non-epilepsy study pools.*
2. *The Division noted this is a correct interpretation (DNP does not want them to separate out diabetic epileptic patients but rather the trials of diabetic neuropathy patients from other trials that are not specifically in a diabetic population.).*
3. *The Division agreed with the Applicant's proposed plan for providing data from ongoing studies (enrollment, deaths, SAEs, non-serious AEs, discontinuations due to AEs).*
4. *The Division noted that the request to have a cut-off date within 6 months of NDA re-submission was a recommendation and not obligatory. Otherwise, the Division agreed with the Applicant's request for delaying the IND annual report cut-off date for up to 90 days to synchronize with the planned cut-off date for the resubmission of the NDA if the NDA cut-off is moved to six months before re-submission. The company noted that all of the data from the controlled phase of study 304 would be submitted with the initial re-submission of the NDA.*
5. *The company indicated they expected there would be only one ongoing pediatric study at the time of NDA resubmission. The Division stated a preference for all of the pediatric data to be in one section (the pediatric section) and the "ongoing section" referencing the pediatric section with respect to the ongoing pediatric study(ies).*

6. [REDACTED] (b) (4)

Question 5:

Safety information from Studies 2093-201, -202, and -303 will be presented based on findings from the final clinical study reports. Studies 2093-201 and -202 will not be included in any pools other than the overall (all studies) pool. Is this acceptable to the Division?

Preliminary FDA Response:

- i) **Please describe more fully what it means when you say that “relevant safety findings from these studies” will be based on the final clinical study reports. What is the source document for adverse events’ datasets? We note the briefing package appears to indicate there were some issues with CSRs for both studies 301 and 302, therefore we cannot assume the CSRs are adequate as a sole document for review. Please provide datasets for these studies.**

Sunovion’s Response (June 6, 2011):

Sunovion’s comment quoted above was meant to convey that the data presented in the ISS will be copied unchanged from or directly referenced to the CSR for Studies 201, 202 and 303. Data from the CSR will be placed in the matching (i.e. relevant) section of the ISS. Datasets have already been provided in the NDA.

Preliminary FDA Response:

- ii) **Where in the ISS will these data be presented?**

Sunovion’s Response (June 6, 2011):

The information will be provided in the locations noted in the ISS, by topic, then by study. In this way, for example, adverse event data from these studies will be presented in proximity to adverse event from study pools.

Preliminary FDA Response:

- iii) **Analyses of deaths, SAES, and discontinuations should be presented with and without study 303.**

Sunovion’s Response (June 6, 2011):

We agree to provide adverse event data for these parameters with and without Study 303, as well as Study 303 alone.

Meeting Discussion: *FDA inquired as to how the datasets would be populated-from CSR information and tables or from source documents such as the CRFs. Bial representatives indicated the datasets for the original NDA submission (and re-submission) were/are from source documents.*

C. Integrated Summary of Safety Outline:

Question 6: Does the Division agree with the structure and format of the ISS?
--

Preliminary FDA Response:

General comment: When reporting the events of death, non-fatal SAEs, and discontinuations secondary to an AE, provide summary, overview information, include both a numerator and denominator, and cover the entire development program (similar to Table 6-1 in the 9-29-09 information amendment and Tables 3 and 4 in the 8-28-09 information amendment 1.11). Provide the total number of deaths in the development of eslicarbazepine / # subjects exposed, # in phase 2 and 3 trials / # exposed in phase 2 and 3, # in phase 1/# exposed in phase 1. Please include all studies (completed and ongoing) in these overview type presentations. In ongoing studies, if the data are blinded, indicate this.

Sunovion's Response (June 6, 2011):

We agree to provide the analyses as requested.

Meeting Discussion: None

Preliminary FDA Response:

- Attachment 3 contains a high-level view of the ISS structure and anticipated pooling methodology. The last column is "CSR/LPO Status 09-10, 11, 12" CSR is clinical study report. What is LPO and is this for the status as of 9-10-11? What is the 12? Also, on Table 1, there is a superscript "a" but there is no "a" in the legend. Further, the column with the number of randomized subjects in the study indicates that 360 are planned for study 304. This contradicts the protocol, which indicates that 615 are expected to be randomized (p. 33/93 amendment #3 and also in amendment #4). Please clarify. Lastly, as noted in the CR letter, there were inconsistencies in the information in the application. Although we know some errors will occur, we expect the rate of errors will be minimal.

Sunovion's Response (June 6, 2011):

We apologize for the confusion and errors in this table. In the heading of the last column, the header meant to indicate the completion year of the CSR or last patient out (LPO). "09-10, 11, 12" should have been deleted from the header. These numbers referred to the expected year of completion: 2009, 2010, 2011 or 2012. The superscript 'a' should have stated in the footnote "(a) Sunovion Inc. is a co-sponsor (along with BIAL) of Study BIA-2093-304". As noted, the correct number of subjects planned for Study 304 is 615. The number 360 indicates those subjects that will be enrolled with the new diary. It is intended to include all subjects in the primary analysis and the table should have indicated the total number of subjects (615) to be enrolled.

Meeting Discussion: FDA inquired as to whether the dates in the table for the expected year of completion were accurate. The company responded that they think the dates are accurate.

Preliminary FDA Response:

- The proposed cut-off date for the ISS is December 2011. We encourage you to have a cut-off date within 6 months of the expected submission date. Also, the

cut-off date should be considered fluid in the sense that if the re-submission is later, the cut-off date will require modification accordingly.

Sunovion's Response (June 6, 2011):

As noted above, we are currently targeting August 2012 for the planned resubmission date. Based on current expected completion dates of Study 304 as well as the Division's new comments regarding the timing of the cut-off date within 6 months of the submission date, we have moved the planned cut-off date to February 2012.

Preliminary FDA Response:

- **For tables like Table 2.2.1.2 and 2.1.3.2 in attachment 3 of the ISS outline, respective line listings should also include the study number, the subject number, the preferred term, and the verbatim term.**

Sunovion's Response (June 6, 2011):

We will include the parameters as requested.

Preliminary FDA Response:

- **For the events “death”, “non-fatal SAEs”, and “Adverse Events leading to Discontinuation”, it appears that tables (such as Table 6.1.19.1) are incidence tables. Please also provide line listings and datasets. If the datasets include columns showing the study number, the assigned drug group at the time, and the actual drug and dose taken at the time, the datasets can be combined in terms of populations per event type (specifically, there could be a dataset for deaths, one for non-fatal SAEs, and one for discontinuations secondary to an AE). Also, if you choose, you could design the dataset so that the indication, study number, and unique patient number are also parameters in the datasets, thus possibly allowing a single dataset for deaths, non-fatal SAEs, and discontinuations secondary to an AE. We understand that it might be the case that the dataset for discontinuations would be too large to encompass all indications. Adverse event datasets and line listings should include verbatim as well as preferred terms. Line listings and datasets of EKG, vital sign, or lab data that led to discontinuation should be included in the adverse events leading to discontinuation and/or serious adverse events (or separately if you choose) if these occurrences did not end up listed in the respective adverse event dataset or listing.**
- **The primary data tables for adverse events should be those that include events from audit findings. Please also discuss how the audit findings impacted adverse events in a general way. For specific events that changed in incidence due to the audit findings, include a comparative table.**

Sunovion's Response (June 6, 2011):

We have created a separate dataset that includes the potential adverse events noted from the audits. This dataset includes available information regarding these events from the audit reports. It is not feasible to include these events in the primary integrated datasets, as the vast majority of events are missing associated information that would be collected on an adverse event case report form, such as start and stop dates, severity, outcome, etc. In addition, these events have not been confirmed to be actual adverse events (versus for example post-ictal events). Because of the limited information and lack of confirmation of the validity of the events, we propose the following analyses.

The primary table of all adverse events for the epilepsy controlled study pool and epilepsy uncontrolled study pool will be presented with and without the potential audit events. Comparative tables will be provided for any events that change in incidence due to the audit findings.

A medical review of the potential audit events by two Sunovion physicians who were unaware of treatment assignments has been conducted to determine if any available information suggests that the event potentially could have met the ICH criteria for classification as serious. The outcome indicates that very few of these events would be considered serious. As such, a listing of those events and the available information, including the Sunovion physician's comments will be provided.

No new unreported deaths were discovered during the audits.

The frequency table supporting the proposed labeling (ie. 2% table) will be run with and without the events, such that comparisons can be made. Additional new events not previously reported will be noted.

Due to the lack of accompanying information of the potential audit events, it is not possible to include the potential audit events in analyses of severity, study period within Part 1 (e.g., titration, maintenance) or association with discontinuation of study medication. As previously noted in the briefing document, inclusion of the potential audit events did not increase the incidence of any individual event by more than 2.5% and did not increase the placebo adjusted difference by more than 1.5%. Therefore, it is proposed that sub-group analyses will be based on the primary database. If desired, subgroup analyses can be conducted on those events where the incidence changed by more than 2% and comparative tables can be provided.

Meeting Discussion: FDA had been under the impression, until the Company's response of 6-6-11, that these events had been adjudicated and were known adverse events.

DNP requested the Company to provide one dataset for all potential and all "known" adverse events and include in that dataset a column that would identify the event as a "potential AE" (or "unadjudicated AE" or something of that nature), a column indicating whether it was serious, a column indicating whether it led to discontinuation, and a column indicating whether the patient was hospitalized because of it (yes-no). The company indicated an understanding and agreed.

DNP stated that the Sponsor should use medical and hospital records to try and adjudicate the potential AEs and determine seriousness.

Preliminary FDA Response:

- **The tables of presumed relatedness to study drug for AEs can be eliminated (e.g. Table 2.1.1.5).**
-

Sunovion's Response (June 6, 2011):

We agree to eliminate the tables regarding relatedness to study drug.

Preliminary FDA Response:

- **In addition to the special events of interest listed in attachment 3, section 2.1.5, special adverse events should include the following events: hepatotoxicity (and increase in transaminase), blood dyscrasias, cardiac rhythm and conduction disorders, new seizure type onset, renal toxicity, SUDEP, and psychiatric events. The allergic reactions should discriminate between anaphylaxis, angioedema, serious skin reactions (EM, SJS, and TENS), and DRESS reactions. The psychiatric section could have suicidality as a subsection. Please make some effort to distinguish between events such as agitation or psychosis that occur post-seizure (or immediately preceding a seizure) from those that occur outside of the context of a seizure. Please elaborate on what will be in the "Alterations in cognitive function" section? Specifically, what search strategy will you use for this search.**

Sunovion's Response (June 6, 2011):

We agree to include the terms noted above as adverse events of special interest and the suggestions provided. In the resubmission, we will provide a list of MedDRA terms that were utilized to search on events related to alterations in cognitive function.

Preliminary FDA Response:

- **What are the "Selected Treatment Emergent Adverse Events" (e.g. Table 6.1.13.1)?**

Sunovion's Response (June 6, 2011):

The selected treatment emergent adverse events refer to the adverse events of special interest.

Preliminary FDA Response:

- **In the laboratory, vital sign, and EKG sections, please provide an overview as to how testing was conducted. For example, please state how often labs were acquired in pivotal studies and which lab parameters were measured.**

Sunovion's Response (June 6, 2011):

We agree to provide the information as requested.

Preliminary FDA Response:

- **The sections for labs should be arranged as such**
 - **Within the clinical laboratory evaluation section, for a set of labs (such as chemistry labs), also present mean change data in a table (mean change from baseline off-drug to the worst on drug value), shift data in a table (normal to abnormal), and a table showing potentially clinically significant changes based on criteria agreed to by the Division in advance. Examples of a mean change table and a potentially clinically significant table are in the appendix of this document and are for illustrative purposes only.**
 - **Section 3, the clinical laboratory evaluations' section, includes a subsection for blood coagulation, thyroid function, and sodium analysis. Similar to the comment above, please also include a tables showing the mean change data, shift data, and potentially clinically significant data. For "sodium", please also list this parameter in the general chemistry tables.**
 - **As referred to above, outlier criteria for labs, EKG, and vital signs should be discussed in advance with the Division, and agreed to with us.**

Sunovion's Response (June 6, 2011):

We agree to provide the information as requested. Criteria are currently available for potentially clinically significant (PCS) changes for the Division's review. Upon submission, could the Division commit to provide comment within 30 days of receipt of the criteria?

Meeting Discussion: FDA indicated that it is likely we could provide a response to a submission of PCS criteria in 30 days but requested this be sent in sooner rather than later and not just before the NDA re-submission or with the NDA re-submission.

Preliminary FDA Response:

- **Attachment 3, sections 5.4 and 5.4: For the pregnancy data and for the overdose data, separate the trial data (by indication) from the post-marketing data. Within the post-marketing section, separate by populations (diabetics, bipolar, epilepsy, etc). For clinical trial data and separately for post-marketing data, also provide information about the overall experience with the drug in summary tables that include the total number of pregnancies, total pregnancies that miscarried, total pregnancies with healthy baby outcome, total pregnancies that were electively terminated, and total pregnancies with baby but with complications. To supplement the summary tables, provide line listings that include outcome information and patient identifiers. There should be a listing for trial data and one for post-marketing data. For overdose, discuss single drug versus multiple drug overdose, if such exists. If there is no single dose overdose experience, please state this.**

Sunovion's Response (June 6, 2011):

We agree to provide the information as requested.

Preliminary FDA Response:

- **Some patients who withdraw from trials will have been discontinued from medication because of adverse events. Make an effort to separate signs and symptoms that resulted in discontinuation (“symptoms of withdrawal”) from those that occurred because of discontinuation (timing issue).**

Sunovion's Response (June 6, 2011):

We agree to provide the information as requested.

Preliminary FDA Response:

- **For the post-marketing events section, please group events by event type, for example cardiac disorders, in one place. Provide summary tables.**

Sunovion's Response (June 6, 2011):

We agree to provide the information as requested.

Preliminary FDA Response:

The sample comment on page 70 of attachment 3 is for a relatively simple case in that there is only one event. If a person had an SAE and then finally discontinued due to this event or a different event or lab or EKG finding, please include this in the narrative comments. In the narrative template, please add a column for each concomitant medication that indicates whether the concomitant medication use preceded any study drug exposure. This additional column could be called something like “preceded any study drug exposure” and would be populated with either “yes” or “no”. “Any” means that this medication pre-existed use of the study medication. In the case of an event that occurred in open-label, “any” would mean that this concomitant medication use preceded the beginning of exposure to the study drug in either the controlled or open-label phase. In the narrative template on page 69, does the use of the word “none” mean there were no EKG abnormalities or no EKG was obtained? If it means there was no abnormality, does this mean there was never any PCS EKG abnormality in the study or that there was not one that would be either temporally related to the event or considered by a physician to be possibly related. Please define this term and keep the use of the term consistent across all narratives.

Sunovion's Response (June 6, 2011):

We agree to provide the information as requested and will provide the requested clarification in the resubmission.

Meeting Discussion: None.

D. Exposure Data:

Question 7:
Does the Division agree with the proposed ISS pooling strategy for analyzing exposure?

Preliminary FDA Response:

Yes, but in addition to what you are providing,

i) Please include exposure for 6 months and 1 year in epilepsy patients (unique patients) using the mean or modal daily dose for the 1200 mg group. Please provide this with and without study 303.

ii) Please provide an additional exposure table of the phase 3 epilepsy studies that includes data from the phase 2 POS study, study 201.

Meeting Discussion: None

Question 8:
Does the Division agree that the data from non-epilepsy patients with bipolar disorder and neuropathic pain who typically received doses equal to or greater than 1200 mg contribute to the Division's overall consideration of exposure with regard to ICH guidelines, particularly with regard to review of the safety profile for the 1200 mg dose?

Preliminary FDA Response:

On face, it appears adequate.

Meeting Discussion: None

Question 9:
Noting that the Complete Response did not include the concern regarding exposure at the 1200 mg dose that was originally raised in the filing review letter; did the 28 August 2009 response adequately address the Divisions concern?

Preliminary FDA Response:

The 8-28-09 response included a table (Table 2) that indicates there were 63 people with exposure \geq 52 weeks by "cumulative calculated dose" for ESL in studies 301 and 302. We assume these are unique subjects. Without regard to data quality issues, on face, it appears acceptable. Please see the comments to #7 and #8 above.

Sunovion's Response (June 6, 2011):

Thank you for your comments. We do not need further clarification for Questions 7, 8 and 9.

Meeting Discussion: None

II. Audit Results (Question 10 to 11):

Question 10:

We plan to exclude the two non-compliant sites in Poland (sites 174 and 175) in Study 2093-301 from the integrated analyses of efficacy, but we plan to include the safety data from these sites in the integrated analyses of safety, given that the protocol violation identified applied principally to the efficacy analysis and that study subjects were exposed to treatment per the protocol. Does the Division agree with this approach?

Preliminary FDA Response (FDA/DSI):

FDA/DSI is in agreement with your decision to exclude the two Polish sites. Please explain your intent to use the two sites in the integrated analyses for safety despite the absence of source documents/ seizure data for all subjects.

Sunovion's Response (June 6, 2011):

The audit findings for the two Polish sites that lead to the decision to exclude these sites from the efficacy analyses were related to the lack of source documentation to verify the seizure data. At these two sites, seizure data were improperly recorded by the investigators. The audits verified, however, that all subjects were exposed to study drug and source documents are available to verify the validity of the safety data. Of the 18 subjects enrolled at sites 174 and 175, 11 subjects experienced 38 adverse events during Part 1 which were properly reported and are accounted for in the database. As these represent valid data obtained from subjects with partial onset seizures exposed to eslicarbazepine acetate, we believe they are appropriate for inclusion in the safety analyses. The audits conducted at these sites identified 23 potential adverse events in 6 subjects; 16 events were experienced by 1 subject of which 10 reports were headache. The majority of these events occurred during Part 2 of the study and/or duplicated reports of events reported in Part 1. Further, as noted in our response to Question 6, we intend to include the potential events from the audit findings to understand the impact of these additional events on the safety profile.

Preliminary FDA Response (Clinical):

In addition to FDA/DSI comments, clinical notes the following.

For efficacy, the plan seems acceptable. Analyses of the individual study should include one using the full mITT population and these results will be considered. The weight of these analyses will be a review issue.

Sunovion's Response (June 6, 2011):

We agree to provide the analyses as requested.

Meeting Discussion: FDA asked that serious adverse events and events leading to discontinuation within these 23 potential adverse events be identified as such.

Preliminary FDA Response (Clinical):

With regard to safety, on face, this appears acceptable. However, there should be a separate presentation of all the AEs observed at this site.

Sunovion's Response (June 6, 2011):

We will provide a separate frequency table of all adverse events noted at each of these two sites.

Preliminary FDA Response (Clinical):

Also, although not directly related to this question, in study 301, there was an unblinded statistician apparently at a meeting to determine the seriousness of protocol violations (page 19 of 34 of attachment 4). Please describe the context of this and tell us why this unblinded statistician was present.

Sunovion's Response (June 6, 2011):

Bial queried [REDACTED]^{(b) (4)}, the CRO for Study 301, regarding the attendance of the unblinded statistical at a meeting to determine the seriousness of protocol violations. A note to file indicates that the role of the unblinded statistician [REDACTED]^{(b) (4)} was not to provide any information regarding treatment assignment, but is described as running and printing the listings for the review meeting (see attached).

Meeting Discussion: None

Post-meeting note: It is still not clear why the statistician was present as his/her stated role was to run and print meeting listings. This will be scrutinized upon review of the re-submission. The re-submission should explain in more detail exactly what the statistician did in the meeting.

Question 11:

Audit reports and tabulations of the GCP deficiencies observed are provided as originally requested in the Complete Response letter and confirmed at the 30 July 2010 End of Review Meeting. Are there additional analyses we could provide that will facilitate DSI evaluation of GCP compliance for each site and overall data integrity for Studies 2093-301 and -302?

Preliminary FDA Response (FDA/DSI):

Based on review of the Briefing Package and preliminary cursory review of a small sample of audit reports, DSI is concerned regarding the significant number of protocol violations noted. DSI requests an assessment as to why the data are considered reliable despite some sites having identified significant issues with respect to eligibility, maintenance of accurate study related records to include seizure diary data, documentation of concomitant AED, and drug accountability.

Sunovion's Response (June 6, 2011):

In order to provide a justification as to why the data are considered reliable, we will provide a detailed analysis of the impact of the protocol violations for each patient with regard to safety and efficacy, and provide a sensitivity analysis to determine the impact of removing subjects with major protocol violations. As this response does not rely on the acquisition or analysis of new data, and recognizing the amount of information required for review by the DSI, would the DSI be amenable to submission of this response prior to the resubmission? The resubmission would of course include this information and any additional information requested following DSI's review.

Additional DSI Comments to Sponsor:

- 1. It is expected that you will provide a response to Item 1 as requested in FDA's Complete Response Letter dated 4/30/10.**

Sunovion's Response (June 6, 2011):

We will provide a response to Item 1 of the Complete Response Letter as requested. As this response does not rely on the acquisition or analysis of new data, and recognizing the amount of information required for review by the DSI, would the DSI be amenable to submission of this response prior to the resubmission? The resubmission would of course include this information and any additional information requested following DSI's review.

Additional DSI Comments to Sponsor:

- 2. Your briefing package notes that for Studies 301 and 302, 25 % and 43% of the subjects did not meet eligibility criteria, respectively. In addition, we note that for Studies 301 and 302, there were 9% and 17 % of subjects who did not meet eligibility due to seizure count issues, respectively, and 9% and 13 % of subjects did not meet the requirement for stable AED concomitant therapy. Please explain why these subjects should be included in the safety and efficacy analyses. It is recommended that sensitivity analyses be conducted excluding these subjects.**

Sunovion's Response (June 6, 2011):

As noted above, we intend to provide a detailed analysis of the impact of the protocol violations for each patient and conduct analyses excluding subjects with major violations.

Additional DSI Comments to Sponsor:

- 3. Review of Tables 3-8 in your briefing package raises concerns regarding the utilization of data from certain sites where a significant number of subjects did not meet eligibility criteria (e.g. Study 301: Sites 101, 122, 123, 125, 143, 182; Study 302: Sites 304, 307, 398, 311, 312, 315, 334, 337, 351, 401); and/or had drug accountability issues (e.g. Study 301: Sites 112, 123, 181; Study 302: 362, 373); and/or randomization was not conducted in**

accordance with the protocol (e.g. Study 302: Site 334). Please explain why the data from these sites are considered reliable.

Sunovion's Response (June 6, 2011):

The resubmission will include an explanation as requested. Would it be helpful to provide this discussion ahead of the resubmission?

Additional DSI Comments to Sponsor:

- 4. Based on the audit findings there appears to be a lack of adequate monitoring by the sponsor/CROS involved in monitoring the sites of Studies 2093-301,302 and 303. What type of assurances/ corrective action plans have been implemented to ensure adequate monitoring of the additional pivotal study being considered in support of the proposed indication, Study 2093-304?**

Sunovion's Response (June 6, 2011):

Sunovion is the Sponsor for North American investigational sites in Study 304, while Bial is responsible for the Rest of World sites. The study is being conducted under a single global protocol to ensure a consistent approach to the conduct of the study in all regions. In addition to the responsibilities undertaken for North American sites, Sunovion has committed dedicated personnel to reviewing and providing feedback to Bial and the CROs regarding issues identified in the monitoring reports for all investigational sites (North American and Rest of World). Further, Sunovion and Bial have planned together, and are working on an ongoing basis, to conduct clinical site audits throughout the study, of more than 40% of the enrolling clinical sites, selecting sites to ensure audit coverage of high enrolling sites, monitors, countries and site initiation sequence. To date, 16 audits in 6 countries have been conducted. In addition to audits of clinical sites, Sunovion and Bial plan a joint audit of the CRO, to be conducted before the end of Part I of the study. This comprehensive monitoring and audit program will ensure corrective measures to monitoring and audit findings are implemented in real-time, during study conduct, to resolve issues prior to study completion and thereby ensure data integrity.

Preliminary FDA Response (Clinical):

In addition to FDA/DSI comments, for the tables of audit finding tabulations for studies 301 and 302 that begin on page 23/55 of the briefing package, please provide a more detailed breakdown of the eligibility issues (per issue).

Sunovion's Response (June 6, 2011):

A more detailed breakdown of the eligibility issues will be provided in the resubmission. Would it be helpful to the Division to provide this discussion ahead of the resubmission?

Meeting Discussion:

The Applicant presented Sunovion's meeting slide # 8, 9, 10, 11, and 12 for discussion of Study 2093-304's global monitoring plan, sponsor's oversight, and overview of the sponsor's audit program. The Applicant also discussed factors taken into consideration in their

assessment of data reliability of Studies 2093-301 and 302. DSI requested that the Applicant provide analyses of the impact on data reliability of identified GCP deficiencies with their NDA resubmission. The Applicant agreed with this request.

The DSI and Division requested the Applicant to provide information for the following based on the Applicant's audited data:

1. At the time of the CR submission, the Applicant was requested to provide for each of the studies audited above, the number of sites that the Applicant identified as non-GCP compliant.

2. For Study 2093-304, how many sites were terminated based on the Applicant's monitoring/audit findings?

The Applicant informed DSI and the Division that one US site has been terminated.

3. DSI inquired if the Applicant reported termination of the US site from Study 2093-304 to the Agency as required by regulations.

The Applicant informed DSI that it has not reported the termination of the referenced site to the Agency yet.

DSI requested that notification of the termination of this site be submitted to the Agency to both DSI and OND/DNP in accordance with regulatory requirements.

4. DSI requested clarification on the criteria the Applicant used in selection of sites for audits for audited studies as referenced above. The Applicant informed DSI that the decision was based on certain criteria, including the occurrence of serious AEs and/or deaths. The Applicant also indicated that more auditing will be performed.

5. The Applicant inquired if DSI will review the Applicant's audit findings and requested audit related summaries/analyses if submitted in advance of the NDA resubmission. DSI notified the Applicant that DSI will need to review the audit findings and requested audit related analyses in the context of the totality of the information in the NDA resubmission. Therefore, DSI will review the audit related findings upon NDA resubmission.

6. DSI recommended to the Applicant to focus on critical data that matters to the integrity of the key safety and efficacy parameters. DSI also requested the Applicant to submit a list of all sites enrolled in Study 2093-304, including the following: full address, their contact information, and the number of patients enrolled at each site, no later than January 1, 2012. The Applicant agreed with the DSI's request.

Post Meeting Clarification from Sunovion (June 28, 2011)

During the June 7, 2011 Type C Meeting it was stated by Sunovion that a clinical site in the BIA 2093-304 study had to be closed for non-compliance. After the meeting we determined that this statement is not correct and we wish to provide clarification. Monitoring visits at Site #14 (Dr. Fernando Miranda, San Francisco) found certain GCP deficiencies related to data quality and protocol compliance and the site was put on screening hold after enrollment of 1 subject. A corrective action plan has been implemented and we are working with Dr. Miranda to resolve the GCP deficiencies observed. The hold remains in place until we are satisfied with progress on corrective actions.

III. Abuse Liability (Question 12 to 14):

Question 12:

We are willing to conduct the requested nonclinical dependence study and we propose that the mouse is the most suitable species to evaluate the potential for physical dependence following administration of eslicarbazepine acetate. Do the Division and CSS have comments or recommendations regarding the design of the nonclinical physical dependence study?

Preliminary FDA Response: **CSS Response**

- **Based on the available information, including the information provided in the briefing document, the selection of the mouse as the test species for the nonclinical physical dependence study seem to be adequate. However, the choice of doses in the study should be based on AUC equivalence between mice and humans. Therefore, we believe that the 100 mg dose is too low. The high dose selected (250 mg titrated up to 600 mg/kg/day) may be appropriate, but the final dose should not produce toxicity, including death. A justification for dose and species selection should be included in the final study report.**

Sunovion's Response (June 6, 2011):

Based on CSS' comments, additional intermediate doses (between 100 mg and 600 mg) will be included in the study. A justification for dose and species selection will be included in the final study report as requested.

Preliminary FDA Response (CSS):

Tables 12 and 13 of the briefing document provide steady-state plasma exposure data for the racemate, licarbazepine. To support the physical dependence study, we ask that you provide data for the S- and R-licarbazepine separately for both mouse and human, particularly since the ratios of the enantiomers are different between species.

Sunovion's Response (June 6, 2011):

We agree to provide the information as requested.

Preliminary FDA Response (CSS):

- **You should provide the protocol for the dose-finding study with diazepam. Alternately, you may choose to select a dose of diazepam that will be used as the positive control in mice based on citations in the scientific literature.**

Sunovion's Response (June 6, 2011):

The dose-finding study with diazepam was recently completed and the data are being compiled. The preliminary data demonstrate doses of diazepam for use as a positive control that are consistent with the scientific literature.

Preliminary FDA Response (CSS):

- You should provide the plasma concentrations of eslicarbazepine and metabolites associated with each proposed dose and correlated to plasma concentrations produced in humans at proposed therapeutic doses of eslicarbazepine. This is relevant for animal doses of eslicarbazepine greater than 400 mg/kg, as your submission notes that these doses can lead to adverse events and death.

Sunovion's Response (June 6, 2011):

We agree to provide the information as requested.

Preliminary FDA Response (CSS):

- You should provide the pharmacokinetics data on eslicarbazepine during drug discontinuation so that drug plasma levels may be correlated to behavioral changes during discontinuation.

Sunovion's Response (June 6, 2011):

We agree to provide the information as requested.

Preliminary FDA Response (CSS):

- The behavioral observations should last at least 10-15 minutes and should occur every 30 minutes during the first four hours following drug discontinuation.

Sunovion's Response (June 6, 2011):

We agree to add the additional time points for assessment as requested.

Preliminary FDA Response (CSS):

- Pharmacokinetic blood draws should occur immediately prior to behavioral observations during the first four hours following drug discontinuation.

Sunovion's Response (June 6, 2011):

We agree to provide the information as requested.

Meeting Discussion: None

Question 13:

Data may be available from more 1,500 subjects who completed studies and abruptly discontinued eslicarbazepine acetate. Do the Division and CSS agree with the approach to evaluate potential signs of physical dependence and withdrawal?

Preliminary FDA Response:

CSS Response:

Our comments conveyed to you on April 28, 2010, regarding requests for data from subjects who completed clinical studies and abruptly discontinued eslicarbazepine acetate remain. You should collect and provide the following data to the Agency:

- **All adverse events and all signs and/or symptoms of withdrawal (as noted by the Investigator or experienced by the subject).**
- **Subjects who abruptly discontinue the drug should be followed for 2-4 weeks, and all adverse events after the discontinuation should be provided.**
- **Subjects who taper should be followed throughout the period of taper and for 2-4 weeks after the end of the taper; and all adverse events from the taper period and after the drug discontinuation should be reported.**
- **The time of onset of the adverse event (or of the signs and/or symptoms of withdrawal) so that you can evaluate temporal relationships to stopping study drug.**
- **Information on rescue medication use, such as dose, date, reason for use, day of use relative to stopping study drug, outcome of rescue medication use. Did it help?**
- **Information related to the reasons and conditions of discontinuation (e.g. sudden due to AE, tapered over 2 weeks, tapered over 3 weeks, etc).**
- **Adverse events, including occurrences of pain that were observed after study drug discontinuations not observed previously in the trial (prior to study drug discontinuation) In other words, please describe the discontinuation syndrome.**
- **If the adverse event is believed to result from rescue medication and not from study drug discontinuation, the basis for this opinion should be explained.**
- **Description of how use of rescue medications may affect the adverse events profile or withdrawal patterns (for example, mask a withdrawal symptom).**

Sunovion's Response (June 6, 2011):

We agree to provide the information as requested.

Below we are also providing responses to the other comments from the Division/CSS in the April 28, 2011 correspondence.

Division/CSS Clarification Comment from April 28, 2011:

1) For clarification: We are not requesting that you perform the proposed human dependency study described in protocol SEP093-154.

Your email of 4-1-11 indicates that the phase 3 studies of ESL for DPN or PHN include a three week taper. Please indicate when tapers were introduced into these studies? To be clear, we are not recommending or suggesting that these subjects undergo sudden discontinuation.

Provide the data on all adverse events which occurred during the withdrawal period in Studies 2093-206, 2093-207, 2093-209, 2093-2010 (End of Review meeting, July 30, 2010) where patients were abruptly discontinued and followed up for 2-4 weeks.

Even in studies in which there are planned drug tapers, some subjects may for a variety of unknown and unexpected reasons (e.g. lack of tolerability, serious adverse effects) still need to stop study drug abruptly. You should collect information from these subjects as is further described below in # 5 below.

In an email from Karen Joyce dated 4-1-11, Sunovion requested clarification of item 6 and argued against abrupt discontinuation. We understand your reasons for not abruptly discontinuing ESL. We are not asking you to abruptly discontinue ESL. We are asking that you collect data from subjects who do abruptly discontinue for some reason (such as an adverse event) as well as from subjects whom undergo tapers. We ask these data be collected in all studies in which humans are exposed to more than a few doses of eslicarbazepine (phases 1-4 of development, controlled, uncontrolled, open-label extension).

Lastly we ask you, in order to optimize data collection and presentation, that you please [provide the information listed]. [Please see Abuse Liability Question 13 above.]

Sunovion's Response (June 6, 2011):

We agree to provide the information as requested.

Regarding point #2, our partner Bial has confirmed that the three week taper periods were included in the original protocols for both the DPN and PHN phase 3 studies.

Regarding point #3, the analyses will be provided in accordance with the plan as described in Section 6.3.3 of the briefing document for the June 7, 2011 meeting.

Regarding point #4, data will be collected from subjects who discontinue due to any reason requiring abrupt discontinuation as well as from subjects who taper.

Meeting Discussion: None

Question 14:

It is not feasible to modify the ongoing Phase III ex-US clinical studies in non-epilepsy patients with neuropathic pain to evaluate physical dependence and there are no other ongoing or planned studies in non-epilepsy patients suitable to accommodate the CSS request. In light of the proposed labeling for eslicarbazepine acetate, consistent with all antiepileptic drugs recommending that patients taper the dose when discontinuing the product and in light of our agreement to analyze the available data from completed clinical studies, do the Division and CSS agree that the additional new nonclinical data would be sufficient to evaluate physical dependence despite the considerations in study design and that no further human data regarding physical dependence are necessary?

Preliminary FDA Response:

CSS Response:

We are hopeful that the preclinical and human safety data from clinical studies will be adequate for the evaluation of physical dependence. Although we are not requiring a new human physical dependence study, we may ask for additional data from clinical studies as necessary for our evaluation.

Sunovion's Response (June 6, 2011):

Thank you for your comments. We do not need further clarification for Question 14.

Meeting Discussion: None

Sunovion's Request (June 6, 2011):

CLARIFICATION REQUEST TO DIVISION'S COMMENTS ON CLINICAL PROTOCOL 2093-304

We would also like to discuss the Division's Clinical Comments #9 and #10 (dated 28 April 2011) to Clinical Protocol 2093-304 Amendments #3 and #4. Sunovion's responses to Comments #9 and #10 (submitted May 13, 2011, IND eCTD Sequence 221) are provided below.

Protocol 2093-304 Division's Clinical Comment #9

Follow SAEs for resolution/stabilization. Follow discontinuations and AEs in general for resolution or stabilization and for at least 4 weeks post the last of study drug.

Sunovion's Response (June 6, 2011):

We presently monitor SAEs until resolution or stabilization. Also, non-serious AEs are followed until 4 weeks (30 days in North America) following last dose. A post-treatment non-serious AE (for instance, a hypothetical withdrawal-emergent AE) would not be followed for a fixed timeframe, and would not necessarily be followed beyond the end-of-study follow-up visit. At that visit, the outcome of the non-serious AE would be marked "ongoing". If the non-serious AE progresses to an SAE within 4 weeks (30 days in North America) of the last visit, Investigators are instructed to report the SAE. This is standard industry practice and is consistent with ICH guidelines and we believe it is compliant with the request above.

Does the Division agree that the method described above for following SAE, non-serious AEs and discontinuations, which is consistent with ICH guidelines, is acceptable?

Meeting Discussion:

The Applicant presented Sunovion's meeting slide # 6 for discussion in regard to Study 2093-304.

The Division asked the Applicant what the process is for following up if a patient was categorized as having a non-SAE within 30 days and then developed a serious event after 30 days. What process will allow the Sponsor to identify such an SAE that developed post-30 days from the last dose?

The Applicant explained to the Division that the Applicant's proposed SAE monitoring plan is based on the current protocol standard in the industry, which is generally viewed as adequate.

Protocol 2093-304 Division's Clinical Comment #10

For CRF and safety reports, investigators should be advised to report signs and symptoms and not just final diagnoses (e.g. do not just report cerebellar syndrome, report the specific signs/symptoms as well). Also, investigators should provide concomitant medication information and pertinent medical information that would be required to support the diagnosis in the case of serious or medically significant adverse events, labs, EKG, or syncope. We need to understand the clinical event from a medical point of view. Please provide appropriate information to allow such. If this information is not available, please state this and state what efforts were made to acquire the information.

Sunovion's Response (June 6, 2011):

We will document the diagnosis where available, and collect narratives with more information for selected adverse events of special interest. At a minimum, we will gather additional information on the following adverse events of special interest:

*Rash
Hyponatremia
Cerebellar syndrome
Cognition disturbance
Withdrawal
Abuse*

It this approach acceptable to the Division?

Meeting Discussion:

The Applicant presented Sunovion's meeting slide # 7 for discussion of Study 2093-304. The Division requests the actual event description to be provided instead of the final diagnostic term for an AE event.

The Applicant presented CDASH slide and CDER DATA Acquisition Standard slides to inform the Division that data collection complied with CDER's standard and data was coded based on the MedDRA term selection. The applicant explained the provisional diagnosis term will be used if the sign and symptom matched with a diagnosis. If additional symptoms were not consistent with the diagnosis, then it will be coded as a second event.

The Division requested that the actual event the patient complained of be captured, instead of the diagnostic terminology, noting that not all diagnostic terms are defined by exactly the same signs and symptoms. FDA noted that if "myalgia" was always subsumed under an umbrella diagnostic term such as "flu syndrome", then a potential signal might be missed. FDA noted that it is imperative that reviewers have the data that allows for independent evaluation of

adverse events. Having final diagnostic terms instead of verbatim terms of the signs and symptoms the patient reported prevents independent evaluation.

Post-meeting discussion: While final diagnostic terms also should be submitted, it is necessary to have the signs and symptoms both captured as verbatim terms on source documents at the site and included in datasets. In addition to the FDA's concern as discussed in the meeting, it will not be possible to adequately characterize syndromes without the actual signs and symptoms/complaints/verbatim terms. For example, if a diagnosis of drug hypersensitivity is made, was this a rash, angioedema, SJS, anaphylaxis, or a rash with itching? It is unclear how one would be able to characterize common hypersensitivity reactions. Similarly, for drug toxicity; is this ataxia, nystagmus, nausea, vomiting, dizziness or some combination?

In terms of the list of terms sent (rash, hyponatremia, etc) FDA cannot blanket agree or disagree as we need the actual signs/symptom/complaints of the subject as well as any final diagnoses in order for us to independently evaluate adverse occurrences. As noted, not all diagnostic terms are defined by the exact same set of signs and symptoms and lumping may "dilute" a signal. FDA must be able to independently evaluate the complaints and adverse experiences that patients experience.

3.0

PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

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>

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

Sunovion’s meeting slide June 7, 2011. (See attachment).

APPENDIX

The tables below are illustrative and do not contain each parameter that might be measured. Actual NDA tables should include all of the chemistry panel and all of the hematology parameters (in separate tables, one for chemistry and one for hematology). As noted previously, the proposed criteria for potentially clinically significant values should be discussed with the Division in advance. For potentially clinically significant values, the example table is of subjects with normal baseline. Please also include tables with subjects who had abnormal values at baseline (one for low at baseline and one for high at baseline).

Table xx: Mean Change from Baseline for Serum Chemistry Parameters in Pool of Placebo-Controlled Clinical Trials Cutoff Date xx-xx-xxxx

Serum Chemistry Parameters and Units of Measure	New Drug			Placebo		
	n	BL	Change from BL	n	BL	Change from BL
Albumin (g/dL)						
Alkaline Phosphatase (U/L)						
Bilirubin (mg/dL)						

n=number of subjects with measure at baseline BL=baseline means for the parameter. Change from baseline= mean change from baseline to the subject’s worst on drug value for each of the serum chemistry parameters of interest.

Table xx: Incidence of Potentially Clinically Significant Change in Serum Chemistry Parameters for Pool of Placebo-Controlled Clinical Trials for New Drug Cut-off date: xx-xx-xxx

Serum Chemistry Parameters and PCS criteria	New Drug			Placebo		
	Total subjects	Abnormal		Total subjects	Abnormal	
		Nbr	%		Nbr	%
Albumin –L (<xx g/dL)						
Alkaline Phosphatase-H (>xx U/L)						
Bilirubin total – H (> x mg/dL)						
Total subjects=number of subjects for the group who had that parameter assessed at baseline and at least one follow-up time and fro whom the baseline was normal. Nbr= subset of the total number of subjects who met the criteria in question at least once during the treatment. A separate listing should provide the subject identification for those subjects meeting the criterion. %=round up to the nearest integer						

Sunovion Pharmaceuticals Inc June 7, 2011 Meeting Slides

11 pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

RUSSELL G KATZ
07/06/2011

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Thursday, June 02, 2011 5:26 PM
To: 'Karen.Joyce@sunovion.com'
Subject: NDA 22416

Importance: High

Attachments: NDA 022416--Type C meeting--preliminary responses 060211.pdf

Dear Karen:

Attached document is the Division's preliminary comments for June 7, 2011 Type C meeting.



NDA 022416--Type
C meeting--pr...

If you have any question, please feel free to contact me.

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
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Meeting Date: June 7, 2011

Time: 3:00-4:00 PM EST

Sponsor: Sunovion Inc.

Product: Stedesa (eslicarbazepine acetate) 400, 600, and 800mg tablets

Proposed Use: Adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy.

Introductory Comment: This material consists of our preliminary responses to your questions in preparation for the discussion at the meeting scheduled for June 7, 2011 from 3:00 – 4:00 PM with the Division of Neurology Products. This material is shared to promote a collaborative and successful discussion at the meeting. The minutes of the meeting will reflect agreements, key decisions and any action items discussed during the formal meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the Regulatory Project Manager, RPM). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. Please note that if there are any major changes to your development plan/the purpose of the meeting/the questions (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting. If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact the RPM to discuss the possibility of including these for further discussion at the meeting.

SUMMARY OF BACKGROUND INFORMATION PROVIDED BY THE SPONSOR/QUESTIONS AND FDA PRELIMINARY RESPONSES

On 29 March 2009, Sunovion submitted an NDA for eslicarbazepine acetate which was received by the Division on 30 March 2009. On the extended PDUFA Goal Date of 30 April 2010 Sunovion received a Complete Response letter and an End of Review Meeting took place on 30 July 2010. During the 30 July meeting FDA (both the Division and the Office of Drug Evaluation 1) advised that submission of a new adequate and well-controlled Phase III study would be very helpful to support successful review of this application, given the GCP compliance issues observed in the program, and that in accord with the intent of FDAMA a single new trial could be adequate to support NDA review.

As explained in Sunovion's 18 March 2011 submission requesting an extension for the deadline to resubmit the NDA, Sunovion intends to resubmit the eslicarbazepine acetate NDA with results from Study 2093-304, which is a new adequate and well-controlled Phase III study evaluating the safety and efficacy of eslicarbazepine acetate once daily at doses of 800 mg and 1200 mg. Study 2093-304, entitled *Efficacy and*

safety of eslicarbazepine acetate as adjunctive therapy for refractory partial seizures in a double-blind, randomized, placebo- controlled, parallel-group, multicentre clinical trial, was submitted to the IND on 11 December 2009, Serial No. 120 and is expected to be complete and reported in Q1 2012. Study 2093-304 was amended to revise the design of the seizure diary in order to address the Division's concerns regarding the potential for missing seizure data associated with the original diary card design (amendment submitted 1 November 2010, Serial No. 0184).

Taking into account the Division's comments in the Complete Response letter and the End of Review meeting minutes regarding pooling of data, the outcomes of the audits of Studies 2093- 301 and 2093-302 and the inclusion of results of an additional Phase III Study (2093-304), Sunovion has developed proposed pooling strategies for the Integrated Summary of Safety (ISS) and Integrated Summary of Efficacy (ISE) which are discussed in Sections 9.1.1 and 9.1.2.

As requested by the Division in the Complete Response letter and agreed to at the End of Review meeting, additional audits of all subjects at all sites for Studies 2093-301 and 2093-302, with the exception of the 4 sites inspected by DSI, have been conducted in order to provide the Agency with additional information adequate for FDA to reach a definitive conclusion about GCP compliance for these two studies. It was also agreed that Sunovion would request a face-to-face meeting to discuss the audit findings and Sunovion's overall conclusions regarding Studies 2093-301 and 2093-302. The audit reports were submitted on 28 March 2011 (eCTD Sequence No.0041) and a detailed analysis of the impact of the audit findings on safety and efficacy data is ongoing. Sunovion's summary of the audit findings and assessment of the impact on the safety and efficacy data will be submitted in the meeting briefing package.

The Complete Response letter also requested new clinical data addressing the potential for abuse and physical dependence. Specifically, the Controlled Substance Staff (CSS) requested a new study to assess abuse liability and a new two-week prospective evaluation of physical dependence, typically conducted at the conclusion of the clinical efficacy study. At the End of Review meeting Sunovion agreed to conduct the new abuse liability study. It was agreed at the End of Review meeting, however, that evaluation of physical dependence in an epilepsy population would expose subjects to an unacceptable risk related to increased seizure frequency and that evaluation of physical dependence in a healthy normal population would be an acceptable alternative. Following submission of the protocol for the physical dependence study (2093-154) the FDA determined that the risk of exposing healthy normal subjects in study 2093- 154 was not necessary (communication dated 8 March 2011) and instead requested a new nonclinical dependence study and a prospective evaluation of physical dependence in 20-30 non-epilepsy patients, in addition to an evaluation of data following abrupt discontinuation in completed studies. Sunovion wishes to discuss the feasibility and limitations of obtaining these new data.

I. Resubmission Plan (Questions # 1 to 9):

A. Integrated Summary of Efficacy Pooling Strategy:

Question 1:

The new ISE will include analyses of the primary and key secondary endpoints for pooled Phase III Studies 2093-301, -302, and -304. Analyses of the data for individual studies will also be provided. Is this pooling strategy acceptable to the Division?

Preliminary FDA Response:

While the ISE is of interest as a supportive document, data and analyses of the individual studies will be the primary source of clinical and statistical review. Please focus on the individual study report presentations, data listings, and datasets.

Although not directly related to this question, in addition to the routine sensitivity analyses, there should be sensitivity analyses for the concomitant medications used, including rescue benzodiazepine use, and for the impact of changes in concomitant medication. It is critical that the data allows evaluation of rescue benzodiazepine use and for the changes made in dosing of carbamazepine and/or phenytoin. Therefore, there has to be a record of the dosage and times of use (stop and start dates) for these medications. It is unclear whether the current diary will be sufficient to collect the detailed information that will be necessary to evaluate these issues. Also, we refer you also to the email communication of 4-28-11 regarding study 304 protocol amendment #3.

Question 2:

If Study 2093-304 demonstrates statistical significance for the primary endpoint of standardized seizure frequency using data collected in both new and old diary cards) and the effect size for the primary endpoint in subjects with the new diary card is consistent with that observed in Studies 2093-301 and 2093-302, does the Division agree that the resubmission plan is acceptable to evaluate safety and efficacy in support of approval of eslicarbazepine acetate?

Preliminary FDA Response:

On face it appears adequate, but this depends, to a large degree, on the final conclusions of DSI and the Division as to the reliability, usability, and interpretability of the safety and efficacy data from studies 301 and 302 as well as from study 304. We can not commit to a definitive decision on this point at this time.

B. Integrated Summary of Safety Pooling Strategy:

Question 3:

The integrated re-analysis in the new ISS will include an analysis of pooled data from Phase III Studies 2093-301, -302, and -304 with a separate summary of data from Study 2093-303. Studies 2093-301 and -302 will not be provided as a separate pool. Is this pooling strategy acceptable to the Division?

Preliminary FDA Response:

On-face and without regard to possible data quality issues, this strategy is acceptable.

Question 4:

The integrated re-analysis in the new ISS will include tables that summarize the following study pools: Phase III epilepsy controlled studies in adults (2093-301, -302 and -304), epilepsy uncontrolled studies (Phase III long term extension studies), Phase II non-epilepsy patient controlled studies, Phase II non-epilepsy patient uncontrolled studies and all Phase I studies. Is this pooling strategy acceptable to the Division?

Preliminary FDA Response:

Given the possible baseline differences in medical history and concomitant medications, the diabetic population should not be pooled with the other groups. This is discussed more below under “ii”.

i) For the Phase 3 epilepsy data: add a presentation that pools the cumulative controlled and uncontrolled epilepsy data for unique patients. For analyses of special events, please include an analysis with and without study 303.

ii) The following table represents pertinent information for the proposed pooling of non-epilepsy controlled populations (phase 2).

		expected n randomized/com pleted	duration	dose
203	bipolar DB, R, PC	162/123	3 weeks	Group I-800-2400 Group II-600 to 1800 Group III-Placebo
204	bipolar DB, R, PC	38/28	3 weeks	600, 1200, 1800, P
205	bipolar OL then DB, PG	87/35	OL=2 weeks DB, PG=up to 15 months	OLE=900 DB, PG=300, 900, 1800 QD
206	DN DB, R, PC	557/419	17 w: (2w BL, 1w titrate, 12w maint, 2 wk fu)	BID of 400 or 600 or 800 or QD of 800 or 1200 or P
207	PHN DB, R, PC	567/438	13 w: (2w BL, 1w titration, 8w maint, 2w fu)	BID of 400 or 600 or 800 or QD of 800 or 1200 or P
209	Migraine	410/355	22 w	QD: 800, 1200, P
210	FM	528/389	17 w	QD: 400, 800, 1200, P

Table information from information in Table 1, attachment 3, n=number of subjects, 3 w =weeks, fu= follow-up, DB=double-blind, PG=parallel group, PC=placebo-controlled, R=randomized, DN=diabetic neuropathy, PHN=post-herpetic neuropathy, FM=fibromyalgia

Based on the information in the table above, please add the following sub-pools: (1) studies 203, 204, and 205, (2) studies 209 and 210, (3) study 206 only and, (4) study 207 only.

iii) For the phase 1 data: For deaths, serious adverse events, and discontinuations secondary to an adverse event, please also present a table that separates the special populations (hepatic and renal impaired) from the healthy volunteers.

iv) Ongoing studies: Based on Table 1, there will be six ongoing non-IND studies and three ongoing IND studies at the time of the ISS cut-off date.

Non-IND

- A pediatric cognition study performed in children with POS (study 208). This study will have 2 parts, a controlled phase and an open-label extension. The controlled phase consists of 4- week titrations, 8- week maintenance, 4-week taper, and 4-week follow-ups. It seems the controlled phase CSR will be completed in September 2012 with the LPO in May, 2012. The OLE CSR is expected in October, 2013.

- A phase 3 pediatric study (study 305) with expected CSR date of September 2012 for part 1 (controlled) and of October, 2013 for part 2 (the first of the planned open-label extensions).
- Another study in DN (phase 3, study 307) with expected completion of the CSR in October 2012.
- Another study in PHN (phase 3, study 308) also with expected completion date of the CSR in October 2012.
- One monotherapy in newly diagnosed POS (study 311) with CSR November 2013. This seems to be a different formulation (over-encapsulated).
- One OL study in 100 elderly subjects (study 401) with refractory POS with CSR April 2012.
-

IND

- Two phase 3 monotherapy studies in refractory POS (studies 45 and 46) using an (b) (4) formulation and historical control design. The dates of the CSRs are “TBD” and the LPOs are the 3rd quarter of 2012. The Annual report to IND 67466 (reporting period ends 12-19-10) indicates that either 59 or 62 of 174 subjects have received at least one dose in study 45, an 18-week study, and 24 have completed. For study 46, 35 sites had been initiated, although only one subject had been randomized. Do you have an estimate of when these trials will be completed?
- An open-label, one-year extension (study 50) of study 45. As per the referenced IND annual report, 41 of the planned 348 had enrolled in study 50 and no one had completed.
-

Please submit a proposal for the presentation of data in the studies noted as ongoing.

As noted previously, please identify an expected completion date for studies 45 and 46.

vi) Please do include one section in the ISS that has all of the pediatric study data as well as including these data in other places in the ISS as may be appropriate (such as overview tables that show cumulative information, deaths, and non-fatal SAEs).

vii) Some of the phase 3 trials have more than one OLE phase. All data until the cut-off of the ISS should be included in appropriate places in the ISS.

Question 5:

Safety information from Studies 2093-201, -202, and -303 will be presented based on findings from the final clinical study reports. Studies 2093-201 and -202 will not be included in any pools other than the overall (all studies) pool. Is this acceptable to the Division?

Preliminary FDA Response:

- i) Please describe more fully what it means when you say that “relevant safety findings from these studies” will be based on the final clinical study reports. What is the source document for adverse events’ datasets? We note the briefing package appears to indicate there were some issues with CSRs for both studies 301 and 302, therefore we cannot assume the CSRs are adequate as a sole document for review. Please provide datasets for these studies.
- ii) Where in the ISS will these data be presented?
- iii) Analyses of deaths, SAES, and discontinuations should be presented with and without study 303.

C. Integrated Summary of Safety Outline:

Question 6:

Does the Division agree with the structure and format of the ISS?

Preliminary FDA Response:

General comment: When reporting the events of death, non-fatal SAEs, and discontinuations secondary to an AE, provide summary, overview information, include both a numerator and denominator, and cover the entire development program (similar to Table 6-1 in the 9-29-09 information amendment and Tables 3 and 4 in the 8-28-09 information amendment 1.11). Provide the total number of deaths in the development of eslicarbazepine / # subjects exposed, # in phase 2 and 3 trials / # exposed in phase 2 and 3, # in phase 1/# exposed in phase 1. Please include all studies (completed and ongoing) in these overview type presentations. In ongoing studies, if the data are blinded, indicate this.

- Attachment 3 contains a high-level view of the ISS structure and anticipated pooling methodology. The last column is “CSR/LPO Status 09-10, 11, 12” CSR is clinical study report. What is LPO and is this for the status as of 9-10-11? What is the 12? Also, on Table 1, there is a superscript “a” but there is no “a” in the legend. Further, the column with the number of randomized subjects in the study indicates that 360 are planned for study 304. This contradicts the protocol, which indicates that 615 are expected to be randomized (p. 33/93 amendment #3 and also in

amendment #4). Please clarify. Lastly, as noted in the CR letter, there were inconsistencies in the information in the application. Although we know some errors will occur, we expect the rate of errors will be minimal.

- The proposed cut-off date for the ISS is December 2011. We encourage you to have a cut-off date within 6 months of the expected submission date. Also, the cut-off date should be considered fluid in the sense that if the re-submission is later, the cut-off date will require modification accordingly.
- For tables like Table 2.2.1.2 and 2.1.3.2 in attachment 3 of the ISS outline, respective line listings should also include the study number, the subject number, the preferred term, and the verbatim term.
- For the events “death”, “non-fatal SAEs”, and “Adverse Events leading to Discontinuation”, it appears that tables (such as Table 6.1.19.1) are incidence tables. Please also provide line listings and datasets. If the datasets include columns showing the study number, the assigned drug group at the time, and the actual drug and dose taken at the time, the datasets can be combined in terms of populations per event type (specifically, there could be a dataset for deaths, one for non-fatal SAEs, and one for discontinuations secondary to an AE). Also, if you choose, you could design the dataset so that the indication, study number, and unique patient number are also parameters in the datasets, thus possibly allowing a single dataset for deaths, non-fatal SAEs, and discontinuations secondary to an AE. We understand that it might be the case that the dataset for discontinuations would be too large to encompass all indications. Adverse event datasets and line listings should include verbatim as well as preferred terms. Line listings and datasets of EKG, vital sign, or lab data that led to discontinuation should be included in the adverse events leading to discontinuation and/or serious adverse events (or separately if you choose) if these occurrences did not end up listed in the respective adverse event dataset or listing.
- The primary data tables for adverse events should be those that include events from audit findings. Please also discuss how the audit findings impacted adverse events in a general way. For specific events that changed in incidence due to the audit findings, include a comparative table.
- The tables of presumed relatedness to study drug for AEs can be eliminated (e.g. Table 2.1.1.5).
- In addition to the special events of interest listed in attachment 3, section 2.1.5, special adverse events should include the following events: hepatotoxicity (and increase in transaminase), blood dyscrasias, cardiac rhythm and conduction disorders, new seizure type onset, renal toxicity,

SUDEP, and psychiatric events. The allergic reactions should discriminate between anaphylaxis, angioedema, serious skin reactions (EM, SJS, and TENS), and DRESS reactions. The psychiatric section could have suicidality as a subsection. Please make some effort to distinguish between events such as agitation or psychosis that occur post-seizure (or immediately preceding a seizure) from those that occur outside of the context of a seizure. Please elaborate on what will be in the “Alterations in cognitive function” section? Specifically, what search strategy will you use for this search.

- What are the “Selected Treatment Emergent Adverse Events” (e.g. Table 6.1.13.1)?
- In the laboratory, vital sign, and EKG sections, please provide an overview as to how testing was conducted. For example, please state how often labs were acquired in pivotal studies and which lab parameters were measured.
- The sections for labs should be arranged as such
 - Within the clinical laboratory evaluation section, for a set of labs (such as chemistry labs), also present mean change data in a table (mean change from baseline off-drug to the worst on drug value), shift data in a table (normal to abnormal), and a table showing potentially clinically significant changes based on criteria agreed to by the Division in advance. Examples of a mean change table and a potentially clinically significant table are in the appendix of this document and are for illustrative purposes only.
 - Section 3, the clinical laboratory evaluations’ section, includes a sub-section for blood coagulation, thyroid function, and sodium analysis. Similar to the comment above, please also include a tables showing the mean change data, shift data, and potentially clinically significant data. For “sodium”, please also list this parameter in the general chemistry tables.
 - As referred to above, outlier criteria for labs, EKG, and vital signs should be discussed in advance with the Division, and agreed to with us.
- Attachment 3, sections 5.4 and 5.4: For the pregnancy data and for the overdose data, separate the trial data (by indication) from the post-marketing data. Within the post-marketing section, separate by populations (diabetics, bipolar, epilepsy, etc). For clinical trial data and separately for post-marketing data, also provide information about the overall experience with the drug in summary tables that include the total number of pregnancies, total pregnancies that miscarried, total pregnancies with healthy baby outcome, total pregnancies that were electively terminated, and total pregnancies with baby but with complications. To supplement the

summary tables, provide line listings that include outcome information and patient identifiers. There should be a listing for trial data and one for post-marketing data. For overdose, discuss single drug versus multiple drug overdose, if such exists. If there is no single dose overdose experience, please state this.

- Some patients who withdraw from trials will have been discontinued from medication because of adverse events. Make an effort to separate signs and symptoms that resulted in discontinuation (“symptoms of withdrawal”) from those that occurred because of discontinuation (timing issue).
- For the post-marketing events section, please group events by event type, for example cardiac disorders, in one place. Provide summary tables.

The sample comment on page 70 of attachment 3 is for a relatively simple case in that there is only one event. If a person had an SAE and then finally discontinued due to this event or a different event or lab or EKG finding, please include this in the narrative comments. In the narrative template, please add a column for each concomitant medication that indicates whether the concomitant medication use preceded any study drug exposure. This additional column could be called something like “preceded any study drug exposure” and would be populated with either “yes” or “no”. “Any” means that this medication pre-existed use of the study medication. In the case of an event that occurred in open-label, “any” would mean that this concomitant medication use preceded the beginning of exposure to the study drug in either the controlled or open-label phase. In the narrative template on page 69, does the use of the word “none” mean there were no EKG abnormalities or no EKG was obtained? If it means there was no abnormality, does this mean there was never any PCS EKG abnormality in the study or that there was not one that would be either temporally related to the event or considered by a physician to be possibly related. Please define this term and keep the use of the term consistent across all narratives.

D. Exposure Data:

Question 7: Does the Division agree with the proposed ISS pooling strategy for analyzing exposure?

Preliminary FDA Response:

Yes, but in addition to what you are providing,

- i) Please include exposure for 6 months and 1 year in epilepsy patients (unique patients) using the mean or modal daily dose for the 1200 mg group. Please provide this with and without study 303.
- ii) Please provide an additional exposure table of the phase 3 epilepsy studies that includes data from the phase 2 POS study, study 201.

Question 8:

Does the Division agree that the data from non-epilepsy patients with bipolar disorder and neuropathic pain who typically received doses equal to or greater than 1200 mg contribute to the Division's overall consideration of exposure with regard to ICH guidelines, particularly with regard to review of the safety profile for the 1200 mg dose?

Preliminary FDA Response:

On face, it appears adequate.

Question 9:

Noting that the Complete Response did not include the concern regarding exposure at the 1200 mg dose that was originally raised in the filing review letter; did the 28 August 2009 response adequately address the Divisions concern?

Preliminary FDA Response:

The 8-28-09 response included a table (Table 2) that indicates there were 63 people with exposure ≥ 52 weeks by "cumulative calculated dose" for ESL in studies 301 and 302. We assume these are unique subjects. Without regard to data quality issues, on face, it appears acceptable. Please see the comments to #7 and #8 above.

II. Audit Results (Question 10 to 11):

Question 10:

We plan to exclude the two non-compliant sites in Poland (sites 174 and 175) in Study 2093-301 from the integrated analyses of efficacy, but we plan to include the safety data from these sites in the integrated analyses of safety, given that the protocol violation identified applied principally to the efficacy analysis and that study subjects were exposed to treatment per the protocol. Does the Division agree with this approach?

Preliminary FDA Response:

FDA/DSI Response: FDA/DSI is in agreement with your decision to exclude the two Polish sites. Please explain your intent to use the two sites in the integrated analyses for safety despite the absence of source documents/ seizure data for all subjects.

Clinical:

In addition to FDA/DSI comments, clinical notes the following.

For efficacy, the plan seems acceptable. Analyses of the individual study should include one using the full mITT population and these results will be considered. The weight of these analyses will be a review issue.

With regard to safety, on face, this appears acceptable. However, there should be a separate presentation of all the AEs observed at this site.

Also, although not directly related to this question, in study 301, there was an unblinded statistician apparently at a meeting to determine the seriousness of protocol violations (page 19 of 34 of attachment 4). Please describe the context of this and tell us why this unblinded statistician was present.

Question 11:

Audit reports and tabulations of the GCP deficiencies observed are provided as originally requested in the Complete Response letter and confirmed at the 30 July 2010 End of Review Meeting. Are there additional analyses we could provide that will facilitate DSI evaluation of GCP compliance for each site and overall data integrity for Studies 2093-301 and -302?

Preliminary FDA Response:

FDA/DSI/Response: Based on review of the Briefing Package and preliminary cursory review of a small sample of audit reports, DSI is concerned regarding the significant number of protocol violations noted. DSI requests an assessment as to why the data are considered reliable despite some sites having identified significant issues with respect to eligibility, maintenance of accurate study related records to include seizure diary data, documentation of concomitant AED, and drug accountability.

Additional DSI Comments to Sponsor:

1. It is expected that you will provide a response to Item 1 as requested in FDA's Complete Response Letter dated 4/30/10.
2. Your briefing package notes that for Studies 301 and 302, 25 % and 43% of the subjects did not meet eligibility criteria, respectively. In addition, we note that for Studies 301 and 302, there were 9% and 17 % of subjects who did not meet eligibility due to seizure count issues, respectively, and 9% and 13 % of subjects did not meet the requirement for stable AED concomitant therapy. Please explain why these subjects should be included in the safety and efficacy analyses. It is recommended that sensitivity analyses be conducted excluding these subjects.
3. Review of Tables 3-8 in your briefing package raises concerns regarding the utilization of data from certain sites where a significant number of subjects did

not meet eligibility criteria (e.g. Study 301: Sites 101, 122, 123, 125, 143, 182; Study 302: Sites 304, 307, 398, 311, 312, 315, 334, 337, 351, 401); and/or had drug accountability issues (e.g. Study 301: Sites 112, 123, 181; Study 302: 362, 373); and/or randomization was not conducted in accordance with the protocol (e.g. Study 302: Site 334). Please explain why the data from these sites are considered reliable.

4. Based on the audit findings there appears to be a lack of adequate monitoring by the sponsor/CROS involved in monitoring the sites of Studies 2093-301,302 and 303. What type of assurances/ corrective action plans have been implemented to ensure adequate monitoring of the additional pivotal study being considered in support of the proposed indication, Study 2093-304?

Clinical:

In addition to FDA/DSI comments, for the tables of audit finding tabulations for studies 301 and 302 that begin on page 23/55 of the briefing package, please provide a more detailed breakdown of the eligibility issues (per issue).

APPENDIX

The tables below are illustrative and do not contain each parameter that might be measured. Actual NDA tables should include all of the chemistry panel and all of the hematology parameters (in separate tables, one for chemistry and one for hematology). As noted previously, the proposed criteria for potentially clinically significant values should be discussed with the Division in advance. For potentially clinically significant values, the example table is of subjects with normal baseline. Please also include tables with subjects who had abnormal values at baseline (one for low at baseline and one for high at baseline).

Table xx: Mean Change from Baseline for Serum Chemistry Parameters in Pool

Serum Chemistry Parameters and Units of Measure	New Drug			Placebo		
	n	BL	Change from BL	n	BL	Change from BL
Albumin (g/dL)						
Alkaline Phosphatase (U/L)						
Bilirubin (mg/dL)						

n=number of subjects with measure at baseline BL=baseline means for the parameter. Change from baseline= mean change from baseline to the subject's worst on drug value for each of the serum chemistry parameters of interest.

Table xx: Incidence of Potentially Clinically Significant Change in Serum Chemistry Parameters for Pool of Placebo-Controlled Clinical Trials for New Drug Cut-off date: xx-xx-xxx

Serum Chemistry Parameters and PCS criteria	New Drug			Placebo		
	Total subjects	Abnormal		Total subjects	Abnormal	
		Nbr	%		Nbr	%
Albumin –L (<xx g/dL)						
Alkaline Phosphatase-H (>xx U/L)						
Bilirubin total – H (> x mg/dL)						

Total subjects=number of subjects for the group who had that parameter assessed at baseline and at least one follow-up time and fro whom the baseline was normal. Nbr= subset of the total number of subjects who met the criteria in question at least once during the treatment. A separate listing should provide the subject identification for those subjects meeting the criterion. %=round up to the nearest integer

III. Abuse Liability (Question 12 to 14):

Question 12:
 We are willing to conduct the requested nonclinical dependence study and we propose that the mouse is the most suitable species to evaluate the potential for physical dependence following administration of eslicarbazepine acetate. Do the Division and CSS have comments or recommendations regarding the design of the nonclinical physical dependence study?

Preliminary FDA Response:

CSS Response

- Based on the available information, including the information provided in the briefing document, the selection of the mouse as the test species for the nonclinical physical dependence study seem to be adequate. However, the choice of doses in the study should be based on AUC equivalence between mice and humans. Therefore, we believe that the 100 mg dose is too low. The high dose selected (250 mg titrated up to 600 mg/kg/day) may be appropriate, but the final dose should not produce toxicity, including death. A justification for dose and species selection should be included in the final study report.

- Tables 12 and 13 of the briefing document provide steady-state plasma exposure data for the racemate, licarbazepine. To support the physical dependence study, we ask that you provide data for the S- and R-licarbazepine separately for both mouse and human, particularly since the ratios of the enantiomers are different between species.
- You should provide the protocol for the dose-finding study with diazepam. Alternately, you may choose to select a dose of diazepam that will be used as the positive control in mice based on citations in the scientific literature.
- You should provide the plasma concentrations of eslicarbazepine and metabolites associated with each proposed dose and correlated to plasma concentrations produced in humans at proposed therapeutic doses of eslicarbazepine. This is relevant for animal doses of eslicarbazepine greater than 400 mg/kg, as your submission notes that these doses can lead to adverse events and death.
- You should provide the pharmacokinetics data on eslicarbazepine during drug discontinuation so that drug plasma levels may be correlated to behavioral changes during discontinuation.
- The behavioral observations should last at least 10-15 minutes and should occur every 30 minutes during the first four hours following drug discontinuation.
- Pharmacokinetic blood draws should occur immediately prior to behavioral observations during the first four hours following drug discontinuation.

Question 13:

Data may be available from more 1,500 subjects who completed studies and abruptly discontinued eslicarbazepine acetate. Do the Division and CSS agree with the approach to evaluate potential signs of physical dependence and withdrawal?

Preliminary FDA Response:

CSS Response:

Our comments conveyed to you on April 28, 2010, regarding requests for data from subjects who completed clinical studies and abruptly discontinued eslicarbazepine acetate remain. You should collect and provide the following data to the Agency:

- All adverse events and all signs and/or symptoms of withdrawal (as noted by the Investigator or experienced by the subject).
- Subjects who abruptly discontinue the drug should be followed for 2-4 weeks, and all adverse events after the discontinuation should be provided.

- Subjects who taper should be followed throughout the period of taper and for 2-4 weeks after the end of the taper; and all adverse events from the taper period and after the drug discontinuation should be reported.
- The time of onset of the adverse event (or of the signs and/or symptoms of withdrawal) so that you can evaluate temporal relationships to stopping study drug.
- Information on rescue medication use, such as dose, date, reason for use, day of use relative to stopping study drug, outcome of rescue medication use. Did it help?
- Information related to the reasons and conditions of discontinuation (e.g. sudden due to AE, tapered over 2 weeks, tapered over 3 weeks, etc).
- Adverse events, including occurrences of pain that were observed after study drug discontinuations not observed previously in the trial (prior to study drug discontinuation) In other words, please describe the discontinuation syndrome.
- If the adverse event is believed to result from rescue medication and not from study drug discontinuation, the basis for this opinion should be explained.
- Description of how use of rescue medications may affect the adverse events profile or withdrawal patterns (for example, mask a withdrawal symptom).

Question 14:

It is not feasible to modify the ongoing Phase III ex-US clinical studies in non-epilepsy patients with neuropathic pain to evaluate physical dependence and there are no other ongoing or planned studies in non-epilepsy patients suitable to accommodate the CSS request. In light of the proposed labeling for eslicarbazepine acetate, consistent with all antiepileptic drugs recommending that patients taper the dose when discontinuing the product and in light of our agreement to analyze the available data from completed clinical studies, do the Division and CSS agree that the additional new nonclinical data would be sufficient to evaluate physical dependence despite the considerations in study design and that no further human data regarding physical dependence are necessary?

Preliminary FDA Response:

CSS Response:

We are hopeful that the preclinical and human safety data from clinical studies will be adequate for the evaluation of physical dependence. Although we are not requiring a new human physical dependence study, we may ask for additional data from clinical studies as necessary for our evaluation.

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/s/

SU-LIN SUN
06/02/2011

1. For clarification: We are not requesting that you perform the proposed human dependency study described in protocol SEP093-154.
2. Your email of 4-1-11 indicates that the phase 3 studies of ESL for DPN or PHN include a three week taper. Please indicate when tapers were introduced into these studies? To be clear, we are not recommending or suggesting that these subjects undergo sudden discontinuation.
3. Provide the data on all adverse events which occurred during the withdrawal period in Studies 2093-206, 2093-207, 2093-209, 2093-2010 (End of Review meeting, July 30, 2010) where patients were abruptly discontinued and followed up for 2-4 weeks.
4. Even in studies in which there are planned drug tapers, some subjects may for a variety of unknown and unexpected reasons (e.g. lack of tolerability, serious adverse effects) still need to stop study drug abruptly. You should collect information from these subjects as is further described below in # 5 below.
5. In an email from Karen Joyce dated 4-1-11, Sunovion requested clarification of item 6 and argued against abrupt discontinuation.

We understand your reasons for not abruptly discontinuing ESL. We are not asking you to abruptly discontinue ESL. We are asking that you collect data from subjects who do abruptly discontinue for some reason (such as an adverse event) as well as from subjects whom undergo tapers. We ask these data be collected in all studies in which humans are exposed to more than a few doses of eslicarbazepine (phases 1-4 of development, controlled, uncontrolled, open-label extension).

6. Lastly we ask you, in order to optimize data collection and presentation, that you please:
 - Collect and provide all adverse events and all signs and/or symptoms of withdrawal (as noted by the Investigator or experienced by the subject).
 - Subjects who abruptly discontinue should be followed for 2-4 weeks.
 - Subjects who taper should be followed during the taper and for 2-4 weeks after the end of the taper.

- Capture the time of the adverse event (or of the signs and/or symptoms of withdrawal) so that one can evaluate temporal relationships to stopping study drug.
- Collect information on rescue medication use such as dose, date, reason for use, day of use relative to stopping study drug, outcome of rescue medication use –did it help?).
- Collect information as to how discontinuation was performed (e.g. sudden due to AE, tapered over 2 weeks, tapered over 3 weeks, etc).
- Identify adverse events, including occurrences of pain, that were observed after study drug discontinuation that were not observed previously in the trial (prior to study drug discontinuation).
- In the event that an adverse event is believed to be from the rescue medication and not from study drug discontinuation, explain why this is thought to be the case.
- For rescue medications that are used, provide a discussion of how use may impact the assessment of adverse events or withdrawal patterns (for example, mask a withdrawal symptom).

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

/s/

SU-LIN SUN
04/28/2011

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Monday, January 31, 2011 12:11 PM
To: 'Karen.Joyce@sunovion.com'
Subject: IND 067466 & NDA 022416

Importance: High
Sensitivity: Confidential

Dear Karen:

Here is the requested information from our clinical reviewer. Please submit your response under IND 067466 and make a reference note to NDA 22416 (since NDA22416 is on CR status currently)

In the informed consent for study 120, there is a sentence that states (viewbox page 248/533, document [bia-2093-120.pdf](#), file 5334-extrin-factor-pd-stud-rep in module 5 of the 3-29-09 NDA submission), "The following rare, potentially fatal, adverse reactions have been reported in patients treated with eslicarbazepine. " The paragraph goes on to describe what patients should do if they notice any of the signs or symptoms that follow. The next page has six bulleted events. These include liver failure, agranulocytosis, serious skin lesions or rashes, and maybe angioedema. The wording seems to indicate that liver failure, and the other events, have been reported in patients treated with eslicarbazepine. Please address this. Please reference where in the original NDA submission, or any subsequent amendment, we may find case descriptions for the patients who experienced the events of liver failure, agranulocytosis, serious skin reactions, and angioedema. Thank you.

If you have any question, please feel free to contact me.

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
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/s/

SU-LIN SUN
01/31/2011



NDA 022416

**ACKNOWLEDGE CORPORATE
NAME/ADDRESS CHANGE**

Sunovion Pharmaceuticals Inc.
Attention: Amy J. LaForte, Ph.D.
Vice President, Regulatory Affairs
84 Waterford Drive
Marlborough, MA 01752-7010

Dear Dr. LaForte:

We acknowledge receipt on October 15, 2010 of your October 14, 2010 correspondence notifying the Food and Drug Administration that the corporate name and/or address has been changed from

Sepracor Inc
84 Waterford Drive
Marlborough, MA 01752-7010

to

Sunovion Pharmaceuticals Inc.
84 Waterford Drive
Marlborough, MA 01752-7010

for the following new drug application:

NDA 022416 for STEDESA (eslicarbazepine acetate) 400mg, 600mg, and 800mg tablets.
We have revised our records to reflect this change.

We request that you notify your suppliers and contractors who have DMFs referenced by your application of the change so that they can submit a new letter of authorization (LOA) to their Drug Master File(s).

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

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

If you have any questions, call me at (301) 796-0036.

Sincerely,

{See appended electronic signature page}

Su-Lin Sun, PharmD
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/

SU-LIN SUN
10/22/2010



NDA 22416

MEETING MINUTES

Sepracor Inc.
Attention: Karen Joyce
Associate Director Regulatory Affairs
84 Waterford Drive
Marlborough, MA 01752

Dear Ms. Joyce:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Stedesa, (eslicarbazepine acetate) 400mg, 600mg, and 800mg tablets.

We also refer to the meeting between representatives of your firm and the FDA on July 30, 2010. The purpose of the meeting was to clarify the issues identified in the Division's Complete Response letter of April 30, 2010, to discuss proposals from Sepracor on actions to be taken to address the outstanding issues, and to obtain feedback from the Division and the Controlled Substance Staff on the proposed actions or alternative actions that the Division may deem to be more appropriate.

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 Sulin Sun, PharmD, Regulatory Project Manager at (301)796-0036.

Sincerely,

{See appended electronic signature page}

Ellis F. Unger, M.D.
Deputy Director
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 C
Meeting Category: End of Review
Meeting Date and Time: July 30, 2010 3:00-4:00 PM
Meeting Location: CDER White Oak Bldg # 22, Room 1311
Application Number: NDA 22416
Product Name: Stedesa (eslicarbazepine acetate)
400, 600, and 800mg tablets
Indication: Adjunctive therapy in the treatment of partial onset seizures
in adults with epilepsy
Sponsor/Applicant Name: Sepracor Inc.
Meeting Chair: Ellis F. Unger, MD, Deputy Director
Office of Drug Evaluation-I
Meeting Recorder: Su-Lin Sun, PharmD

FDA ATTENDEES

Ellis Unger, MD, Deputy Director, Office of Drug Evaluation-I
Norman Hershkowitz, MD, Ph.D., Clinical Team Leader
Teresa Podruchny, MD, Clinical Reviewer
Lois Freed, Ph.D., supervisory Nonclinical Pharmacologist
Christopher Toscano, Nonclinical Reviewer
Michael Klein, Ph.D., Director (CSS)
Lori Love, MD, Ph.D., Lead Medical Officer (CSS)
Alicja Lerner, MD, Ph.D., Medical Officer (CSS)
Katherine Bonson, Ph.D., Pharmacologist (CSS)
Tejashri Purohit-Sheth, MD, Branch Chief (DSI)
Antoine El Hage, Ph.D., Regulatory Pharmacologist (DSI)
Kun Jin, Ph.D., Biostatistics Team Leader
Xiang Ling, Ph.D., Biostatistics Reviewer
Hari Sachs, MD, Medical Team Leader, (PMHS)
Lilly Mulugeta, PharmD, Senior Staff Fellow (PMHS)
Matthew Bacho, Senior Regulatory Health Project Manager (PMHS)
Su-Lin Sun, PharmD, Regulatory Project Manager

SPONSOR ATTENDEES

Attendees from Sepracor

Nobuhiko Tamura, Executive Vice President and Chief Scientific Officer
Stewart Mueller, Senior Vice President, Regulatory Affairs and Quality
Antony Loebel, MD, Executive Vice President, Clinical Research and Medical Affairs
Amy LaForte, PhD, Vice President, Regulatory Affairs
Karen Joyce, Director, Regulatory Affairs
Jean Clancy Senior Director, Research Quality Assurance
Mark Versavel, MD, PhD Vice President, Clinical Research and Medical Affairs
David Blum, MD Senior Medical Director, Clinical Research and Medical Affairs
Janet Price, MD Vice President, Drug Safety and Pharmacovigilance
Robert Tosiello, Executive Director, Biostatistics
Hailong Cheng, Associate Director, Biostatistics
Paul Tarantino, PhD, Senior Director, Preclinical Safety
Lisa Organisak, RPh, Senior Program Director, Product Development
Bradford Sippy Executive Director, Epilepsy Marketing

BIAL - Portela & C^a, S.A. Attendees

Paula Costa, PharmD Director, Regulatory Affairs
Roberto Pinto, MD Medical Monitor, Deputy Safety Manager
Susana Tavares, PharmD Quality Assurance Manager
Teresa Nunes, MD Head of Clinical Development
Patricio Soares da Silva, MD, PhD Director, R&D

1. BACKGROUND

On March 29, 2009, Sepracor submitted an NDA for eslicarbazepine acetate which was received by the Division on March 30, 2009. On the extended PDUFA Goal Date of April 30, 2010, Sepracor received a Complete Response letter identifying significant and serious clinical deficiencies in the application as well as other comments regarding Abuse Liability, Statistical, Clinical Pharmacology, Nonclinical, Labeling, Safety Update, (b) (4) and Risk Evaluation and Mitigation Strategy (REMS) Requirements.

The Division indicated in the Complete Response letter that the review team will be available to discuss the deficiencies with Sepracor and potential approaches to resolving them.

The purpose of the meeting is to clarify the issues identified in the Division's Complete Response letter of April 30, 2010, to discuss proposals from Sepracor on actions to be taken to address the outstanding issues, and to obtain feedback from the Division and the Controlled Substance Staff on the proposed actions or alternative actions that the Division may deem to be more appropriate.

2. DISCUSSION

Question 1: Does the Division agree with the proposed audit plan, the use of (b) (4) to conduct these audits and the rating plan for audit outcomes?

Preliminary FDA Response:

The proposed audit plan is generally acceptable, as written. We note, however, that the audit report templates do not include a section that addresses adequacy of randomization process (Item 2.c.vi in the Agency's CR letter dated April 30, 2010). Please ensure in your complete response that this issue is adequately addressed. In addition, in your complete response you should provide a summary of:

- 1. Any differences between the conduct of the proposed audits and those conducted previously by (b) (4) (e.g. differences in governing SOPs, items audited, audit report templates, etc).**
- 2. In addition to providing summaries of audit findings by site, at sites where prior (b) (4) audits were conducted, please provide summaries of results (findings) by site for subjects' records reviewed during prior audits and new audits separately, and combined across both audits.**

We also note that complete original audit reports for all newly conducted audits should be included in your complete response.

Regarding your use of (b) (4) to conduct the planned audits, your selection of a firm to conduct these audits should be in compliance with your internal SOPs for selection of third party vendors; the Agency does not endorse specific vendors.

Discussion at Meeting: none.

Question 2: Is the Division amenable to a future meeting to discuss the audit findings and Sepracor's overall conclusions prior to a potential NDA resubmission, in order to determine the adequacy of the audit outcomes to support the integrity of Studies 2093-301 and 2093-302?

Preliminary FDA Response:

DSI would be amenable to attending a meeting at which you provide a presentation related to audit results and your overall conclusion(s) regarding audit findings. We also encourage you to submit the ^{(b) (4)} audit reports with your evaluation of the audits as soon as they are available to facilitate our review of audit findings. However, DSI's comprehensive review of audit findings and resulting recommendations to the Review Division regarding the adequacy of the audits and specific audit findings will not be completed until full results of the independent audit are submitted in your complete response.

Meeting Discussion:

1. The Applicant inquired whether the audit data can be submitted as a small batch. FDA noted it is acceptable to submit audit data for Study 301 as one batch and Study 302 as another batch. FDA requested that the applicant provide specific details for each site audit report including, but not limited to:

- o Specific details of each finding*
- o The impact of each of the audit findings on assessment of data reliability*
- o The number of waivers issued for each study site and rationale for the issuance of waivers*

2. The applicant questioned the Division's likely course of action if only one of the two pivotal trials is deemed to be sufficient. Specifically, will a single trial be sufficient to complement the existing data? FDA noted that this is a review issue and recommended the applicant refer to Guidance on evidence of effectiveness.

3. The applicant inquired whether an additional study would be needed after audits have been completed. FDA noted that this is a review issue. FDA reiterated the need for the applicant to conduct comprehensive audits and to provide full audit reports, and to include analyses on the impact of noted deficiencies on data reliability by study site.

B. Clinical Deficiencies in the Structure of the Application:

Question 3: Can the Division advise if there are specific clarifications, analyses or other information that could further address these issues, or is resubmission of our response of January 25, 2010 (and perhaps certain subsequent responses) the appropriate course of action?

Preliminary FDA Response:

In addition to the possibility that we may still require another controlled trial (pending our review of your audit), the ISS re-submission should be a comprehensive, consolidated

document that includes all data up to a new-cut-off that FDA and you agree upon in advance. Ideally, information from 3rd party audits would be available and complete such that any new and pertinent information can be incorporated into the ISS. Otherwise, if these data are sent in the 120-day safety update and require extensive review, this may delay an action.

While FDA realizes that typically there will be clarifications and some additional data requests during review cycles, the extent of such in this application was an outlier. No single anomaly or deficiency in itself would have precluded review. However, the volume and persistence of errors eventually undermined FDA's confidence in the veracity of the data.

Examples of some of the corrections and deficiencies are listed below; some of which are known to you already either from your own discovery while compiling the 120-day safety update or through requests for additional information:

- **The 120-day safety update included 59 “Delayed-Reported Part 1 TEAEs”**
- **120-day safety update was missing 31 serious adverse events from one trial, which were reported only in response to clarify table 9.2-1.**
- **Trials completed before the cut-off of either the ISS or 120-day SU should have been reported. For example, you classified trial 206 as “clinically completed but not reported”. Trial 206 was clinically completed 11-18-08, which is before the 120-day safety update cut-off date of 3-30-09.**
- **The 120-day safety update of these ongoing or “clinically completed but not reported trials” and for part 3 of study did not include discontinuations secondary to an AE.**
- **A 2-4-10 submission continued to correct misinformation in Table 9.2-1.**
- **The 2-4-10 submission contains a narrative of a “new report of death”.**
- **A 2-22-10 submission notes a spelling error in the SAS code to flag “Articarias” (not “Urticarias” in the search strategy for hypersensitivity reactions. The result, as reported, is not significant but the error was noted only in February 2010.**
- **Suboptimal presentation and or quality control: Information was presented in ways that did not always highlight the salient or potential importance of an event relative to ESL, was not comprehensive/complete, was internally inconsistent, or was difficult to read. Examples are listed below:**

- **Subject 110-11 is from a healthy volunteer study with a crossover design of either ESL 900 mg daily, ESL 450 mg BID, or Trileptal. The narrative heading indicates the event of “Transaminases Increased” as occurring on Trileptal 450 mg BID and the text gives the values (without reference ranges). These are about 2x ULN for AST and ~ 5.4 x ULN for ALT. Bilirubin values are reported as within the normal range. It is the case that the subject sustained transaminase increases on Trileptal and discontinued from the study because of this instance of elevations and it is the case that the narrative notes “the subject had also experienced an increase in transaminases during Period 1”, however the narrative does not indicate that the increases on ESL were higher increases (3.6x ULN for AST and ~ 8 x ULN for ALT)**

and that it seems he also had decreasing transaminases levels during dechallenge (washout). This latter information should have been included as it puts the event leading to discontinuation in context.

- **Subject 203-337-203058- (bipolar trial) The narrative bolded header is vomiting. Vomiting is the stated reason this subject, with a history of chronic pancreatitis, was discontinued from the study. The text of the narrative indicates that transaminases were high (values of 1447 U/L and 1154 U/L for AST and ALT respectively, no reference range provided) and that both direct and total bilirubin were elevated (values are given, again no reference range). The events of vomiting and increased liver function tests occurred three days after starting ESL. All laboratory abnormalities appear to have resolved about a month after discontinuation of ESL. The narrative did not describe ALP results, did not give a reference range, and does not address why this event should not be considered as potential drug induced hepatotoxicity or cholestatic injury, especially since ALP is not provided in the narrative.**
- **Subject 303-701-70290, pancytopenia, [The SU subject number indicates this was in study 302, but site 701 was in study 303.] The subject is noted to be on valproic acid, which may confound the case or be contributory, but these types of events are rare and potentially serious and should be highlighted in presentations even if in the end, it seems unlikely the event is related to ESL. This case is somewhat hard to identify in the SU because the tables of TE AEs in the body of the SU are for incidence $\geq 2\%$ and the event is in text of the SU (panctyopenia). Also, it would seem, by the nature of the event, this might be an SAE, but there is no narrative in the SU.**
- **Tables:**
 - **SAES occurring within a week of study drug discontinuation are not reflected consistently in summary tables. Based on Table 9-4 of the 1-25-10 response, nine subjects with SAEs that onset within one week of the last dose of study medication are not reflected in Table 3 (non-fatal SAES) of the 8-28-09 submission. Further, it is unclear whether all of the information in Table 9-4 is accurate. For example, subject 303-601-70156 is listed in Table 9-4 as having hyponatremia on 11-25-06 and last dose on 11-11-05. The CRF and/or the study report seem to indicate that this subject's last dose of study medication was 9-26-06 and the CRF indicates that an event of worsening of hyponatremia onset in October, 2006 and either offset or was ongoing on 11-26-06.**
 - **Table 4 and Table 4.1.4.3-1 were AE discontinuation tables. These seemed to conflict in terms of numbers of placebo and ESL subjects. The response of 1-25-10 describes that one table was populated from the CRF termination page of primary and secondary reasons for discontinuation (Table 4) and one was from the AE page in the CRF (Table 4.1.4.3-1 respectively). Three subjects were in Table 4 but not in Table 4.1.4.3-1. With preliminary review, the responses do not resolve the issue other than to indicate that CRF information was internally inconsistent for**

these subjects with the CRF termination page having the subject discontinued in part 1 but no corresponding AE had the impact of “discontinuation” with respect to study medication. Specifically, the response also notes that for subject 301-112-90393, leukopenia was originally reported as an AE that led to withdrawal but that query resulted in the lab finding being considered NCS and the AE was removed from the AE page, but the completion page was left as withdrawal due to an AE. If it is case that the subject was withdrawn by the investigator because the investigator thought the lab value was an AE, this should not be changed after the fact if the subject was already discontinued. Additionally, FDA DSI noted that there is a value of 2.66 for this subject. This value is not in the dataset and is not in the integrated safety dataset of adverse events, ADAE2.xpt. With regard to subjects 301-192-90259 and 301-211-90059, they seem to have been discontinued from the study but not recorded as discontinued from study medication.

- **It appears from preliminary review of your 1-25-10 response that you acknowledge that 7 subjects who reported an AE that led to study drug discontinuation were not in Table 4, as expected.**
- **Table 9.2-1 was difficult to read. This has been addressed in a specific request, which has been received. Future tables of similar information should not be formatted like Table 9.2-1.**
- **Some CRFs have multiple data clarification forms (DCF) and/or strikethrough corrections made by study staff and/or auditors making it difficult to follow the CRFs. It would be helpful to hyperlink the actual data clarification form to the notation of the DCF (the inquiry). If there are only a few, 10-20 or so DCFs, this is not such a big issue, but when there are multiple DCFs, this is time-consuming. Also, there are entries that sometimes appear to eclipse and obscure an original entry in the text. Sometimes, after significant time expenditure going back and forth from the CRF to data clarification forms, it seems that what appeared to be obscured text might have been an effort to re-enter the data for readability or might have been an attempt to correct original entry because the events were initially recorded in the wrong section of the CRF or for some other reason that seemed acceptable. However, this is not always obvious or the case. Please explain what these entries represent, not just in the specific examples below but also in general. Are there other copies of the CRFs that do not have this appearance? Please see the table and or images below for examples of notably difficult CRFs.**

Subject number	#DCF	Other CRF
303-601-70156 for parts 1&2 of study	> 60	mark out change to initial SAE entry from yes to no, DCF seems to obscure an original entry, DCFs from page 244-380 of 380 page CRF. Page 63, seems to indicate patient also started topirimate within 2 months after visit 1 and was approved by medical monitor
303-611-70237 for parts 1&2 of study	~90	pages 402-528 are DCFs
302-351-80013 part 1	>30	see duplicated excerpt of piece of CRF page
303-703-70231	~34 + onsite queried	one DCF obscures a column see image below
302-336-80073	~45	handwritten entries marked through in red
302-384-80509	~61	
302-351-80002 parts 1 &2 of study	~100	CRF is 432 pages, DCF pages 277-432
302-301-80670	>36	CRF is 198 pages, DCF pages 135-198

From CRF for 302-351-80013



(b) (4)



- **ISS narratives included subjects from single-blind placebo labeled as “placebo”. This has been previously addressed by FDA and there has been a response, but these issues should be addressed in a re-submission. Additionally, there is no explanation as to how the ISS narrative is set-up (for example, is the bolded heading event the verbatim term, a preferred term, ad diagnosis? Is the bolded treatment group, the assigned treatment group or the actual treatment at the time?), narratives are not indexed and there is no tabulated summary page (or hyperlink) with a list of the subject numbers for whom there is a narrative.**

- **ISS narrative event terms such as “Unknown Adverse Event (303-709-70384) and “Adverse Event Leading to Discontinuation Not Defined” (study 203). Please explain.**
- **Content of some narratives is not very informative, such as subject 302-363-80581, subject 302-372-80363 (orthostatic hypotension but no blood pressure measurements are given and there is no description of the event itself except that it was moderate, did not require treatment, and was considered resolved about 7 days after the last dose of study medication). Narratives for subjects 301-153-1334 and subject 302-338-80164 are other examples.**
- **Upon FDA review, two subjects appear to have experienced SAEs but there are no narratives for these subjects in the ISS SAE narrative section, and in one case, it appears the event may have been an SAE but was not categorized as an SAE.**
 - ▶ **Subject 119-004 has a narrative in the discontinuation section of the ISS narratives. The heading of the narrative indicates the treatment group is eslicarbazepine acetate with another drug (lamotrigine). As one reads the listing 6.3, (listing of discontinuations in attachment 5 of 9-29-09 submission), the subject appears to have been on 1200 mg eslicarbazepine acetate. The ISS discontinuation narrative event is “hypersensitivity”. The narrative lacks a detailed clinical description of the event. The CRF indicates this subject may have been hospitalized and if this is the case (versus treatment in the E.R), hospitalization would define this as an SAE. Also, based on CRF entries and notes, the subject’s reaction course appears to have included an ulcer in the mucosa of the lower lip, perhaps an increased temperature, peeling skin, and liver enzyme elevations. Therefore, even though the subject reportedly was on a product associated with Steven’s Johnson/serious skin reactions (lamotrigine), the event should have been captured as an SAE.**
 - ▶ **Subject 117-005 apparently had a purulent tonsillitis considered an SAE. There is no narrative or CRF. This was noted in a table describing CPK elevations in the ISS and is also seen in Listing 6.2 (attachment 4 of 9-29-09 information amendment). Listing 6.2 was submitted in response to FDA request.**
- **Subject 301-211-90059- is listed in Listing 6.3 “All Treatment Emergent Adverse Events In Subjects Discontinued Due to Adverse Events” for the safety population. (This listing was submitted 9-29 as response to FDA.) This would seem to indicate the subject discontinued secondary to an adverse event, however, there is no narrative in either the ISS or the SU and there is no CRF. To further cloud the issue, the listing has a column for action taken and one for treatment. Neither of these columns indicates that the subject was discontinued or the medication withdrawn. The listed events are arterial hypertension, dizziness, and diplopia at 400 mg ESL and ataxia at 1200 mg. There are other subjects like this with events listed but no event labeled as leading to withdrawal (for example, subject 110-000-00011, 114-000-00007, 301-181-90013, and 302-313-80265).**

- **Subject 301-213-90055 is not in listing 6.3 and there is no ISS or SU narrative, yet a CRF was submitted. In the study report, it seems this subject was discontinued because of somnolence (Table 60, p.240/1074, 301a1-table not included in this review) and there is a narrative for discontinuation due to an AE in the study report for the subject (p.257/1074). The study report indicates that the subject received 1200 mg since 12-27-04 and on 4-1-05 experienced somnolence and that study medication was discontinued 4-14-05 although it does say the patient withdrew consent. The CRF adverse event pages indicate somnolence several times (12-30, 3-02, and 4-01) and withdrawal and discontinuation due to this event occurrence on 4-01. However, the CRF termination page has the reason for premature study termination as “withdrawal as consent”. Data clarification (duplicated below) noted the discrepancy. Correction is made such that “other” is chosen as reason for discontinuation with withdrawal of consent as impact on study treatment.**

(b) (4)

- **Subject 302-312-80299- ISS narrative heading for SAE narrative is “Gastroenteritis”. ADAE2.xpt has two terms as serious, Gastroenteritis and “Acute on Chronic Renal Failure” with equivalent for the preferred term as “Renal Failure Acute”. The text of the narrative includes hospitalization for 2 events (“gastroenteritis and acute chronic renal failure”) yet the ISS narrative heading is only of the SAEs.**
- **The process of translating verbatim terms to preferred terms is not described. This point is made because there are a few terms in the dataset that not commonly used in the U.S. and may/may not be used the same way in different countries. Examples include “esophageal stenosis” (subject 205-534-203144-is**

this reflux, the subject received omeprazole), amygdalitis, systemma, and nutcracker syndrome.

- **Treatment emergent adverse events in phase 1, single dose studies were not comprehensive. The image below is excerpted from Tables 8.3.5-1 in the ISS (p. 125). Additionally, as noted in image below, one cannot tell from this table what the common AE was for the subject in the ESL 400 mg group or the 2nd subject in the ESL 200 mg group. Table 8.3.5-3 describes the DDI studies and is similar.**



General Recommendations Regarding Presentation of Safety Data are described in the following bulleted points:

In addition to addressing both specific examples and the more global issues noted in the response to #3 above, ways to resolve deficiencies are listed below. This list may be redundant with some of the points in the response to #3, but the spirit of this list is to facilitate that issues are described.,

Ways to resolve deficiencies:

- 1) Include in one, consolidated ISS submission all of the concepts in the clarifications that have been requested during the initial review**
- 2) Enhance quality control such that you do not have “delayed” event reporting or the discovery of SAEs during the review cycle. Re-examine the data for the accuracy and consistency of adverse event coding and reporting. Make sure any serious adverse events are consistently labeled as such. Make sure all deaths have been reported. If an event term will infer a potential SAE and yet for some reason the event was not one, then explicitly describe why the event was not an SAE (for example, pancytopenia as discussed above).**
- 3) In the ISS, include finalized data from all trials completed within cut-off dates and world-wide, post-marketing data. Your cut-off dates for trial data should be at maximum,**

one year, before the submission is submitted. Cut-off dates for post-marketing data should be within 6 months of the submission date with the exception that serious or rare, significant medical events known to you that may have occurred after the cut-off dates should be reported.

4) Discontinuation tables should reflect discontinuation from study medication, whether it means patients discontinued medication but are still in the study or discontinued medication and was discontinued from the study.. If there indeed were subjects who left a study but stayed on study drug, please note this and explain. This applies to all trials, not just the pivotal epilepsy trials.

6) Include over-view tables of all deaths by indication and trial, all SAEs by indication and trial, all discontinuations from study medication by indication and trial. Separate the controlled data from the non-controlled data. Provide line listings or datasets that provide the subject numbers and events for the subjects in the summary tables and reference the datasets in the legends of the tables. Datasets should contain the assigned treatment group, the actual treatment the subject was on at the time, and onset off set dates of treatment and the event.

7) In addition to the pivotal trial data integrated datasets, please provide an integrated dataset of adverse events that includes all adverse events from all epilepsy studies and one for events from all other studies. The datasets should include, but are not limited to, a column that indicates whether the event was a death, non-fatal SAE, or discontinuation from study drug secondary to an AE, a column that indicates in what study phase the event occurred (open-label or controlled), a column with the assigned treatment, a column noting the actual treatment and dose at the time of the event, a column with the trial number, a column with a unique subject identifier, a column of whether another action was taken (yes or no), and a column describing such action (for example, treated with a medication, referred to a doctor), a column with the outcome, and columns with verbatim and MedDRA coded terms.

8) If a subject discontinued because seizures changed in a negative way either in number, type, time (for example, nocturnal only and now also in the day), or because the subject thought that he/she was not doing well from a seizure point of view, this should be captured in some way as discontinuation secondary to increased seizures. It must not be the case that to be considered discontinued because of a seizure or to count the seizure as an AE requires doubling of the baseline seizure frequency.

9) Provide a tabulated index to the narratives (preferably with hyperlinks) and arrange them by the treatment group they were on at the time of the event.

10) Please do not parse the presentations of the mean change and shift summary tables for hematology and chemistry data as was the case in the ISS. For example, the ISS presentation of chemistry labs, sodium, chloride, and potassium are presented for part 1 phase 3 epilepsy studies, then for part 2, phase 3 epilepsy, then phase 2 adult epilepsy, phase 2 pediatric epilepsy, phase 1 healthy volunteers, and phase 1 populations studies. Please also do not parse out vital signs and EKGs and AEs.

11) Please put all of the lab data (or EKG or VS data or AE data) for all indications in one section in the submission. For presentations of special safety issues, please put all the information for an event of interest in one section of the ISS (for example, when describing hypersensitivity, put all of the experience (phase 1-3 and post-marketing) in the

hypersensitivity section and provide an overview summary before the detailed sub-sections).

12) The 1-25-10 information amendment notes that it is apparent that placebo rates of the individual common AEs for a given product are typically lower in non-US studies than US studies and that placebo rates of the individual AEs for the eslicarbazepine studies are similar to those of non-US studies of approved AEs. An argument is made that this may reflect lower doses in non-US studies.

In Table 2-1 “Summary of Safety Data from Pivotal Studies for Last 5 new AEDs Approved in US Compared with Stedesa (eslicarbazepine Acetate) Phase III Studies” it is noted that the non-fatal SAE placebo reporting rate is 0 for 2 of three ESL studies. No other product in the referenced table has 0 SAEs reported. Discontinuation rates also are lower than most other products in the table with the exception of ZONEGRAN (one US and one EUR study). Study 303 was within the range of other development programs. It is unclear how to consider this information (does it represent general under-reporting in non-US trials, specific under-reporting in ESL trials, or some other factor?) Briefly, please describe why you believe these data are sufficient to characterize serious events and events that led to discontinuation in ESL groups when placebo group data for ESL differs from placebo data from other trial programs.

Post-meeting errata: The following sentence, from the preliminary comments that were sent to the applicant, is inaccurate without modification: “In addition to the possibility that we may still require another controlled trial (pending our review of your audit), the ISS re-submission should be a comprehensive, consolidated document that includes all data up to a new-cut-off that FDA and you agree upon in advance.” This sentence should read, “In addition to the possibility that we may still require other controlled trial(s), (pending our review of your audits), the ISS re-submission should be a comprehensive, consolidated document that includes all data up to a new-cut-off that FDA and you agree upon in advance.”

Meeting Discussion:

- 1) *The Applicant asked for verification of their understanding that the next ISS should incorporate all of the information requested during the first review process as well as the 120-day safety update from that cycle. FDA clarified that this is the case, and post-marketing data also should be submitted. FDA reiterated that the next ISS should group data by topic, not by trial. FDA noted that it would be optimal if the ISS could include any additional data from audit findings. [Post-meeting note: It should be very clear in the ISS whether changes in audits resulted in changes in the final conclusions of the ISS]*
- 2) *FDA agreed to an email exchange to clarify “minor points” with respect to the next ISS.*

- 3) The applicant inquired as to the acceptable cut-off date for inclusion of studies. FDA agreed to a cut-off date for trial data of within one year prior to the re-submission date. The applicant anticipates re-submission in mid-2011.*

C. Abuse Liability (Question 4 to 9):

Question 4: Does CSS agree that the following features of the proposed study are adequate to determine an appropriate recommendation regarding abuse potential?

- a. Selected doses for eslicarbazepine acetate (800 mg, 1200 mg, and 1600 mg)
- b. Comparator drugs and comparator doses
- c. Sample size
- d. Washout interval between doses
- e. Inclusion & exclusion criteria for adequately defining appropriate subjects, including appropriateness of screening based on ability to detect effects of alprazolam 2.0 mg versus placebo
- f. Study assessments and primary endpoint
- g. Sparse PK sample procedures to document eslicarbazepine exposure
- h. Statistical Analysis

Preliminary FDA Response:

No, we do not agree that the submitted Concept Protocol No. SEP093-153 is adequate to evaluate the abuse potential of this drug. The proposed Concept Protocol is missing a number of important details that can influence the study results and interpretation. When the Sponsor officially submits a complete protocol to the IND, we will review this and provide feedback.

The Sponsor should be aware that data from the human abuse potential study will undergo a statistical analysis by Agency statisticians when it is submitted. This analysis will include an evaluation of whether the study is validated (as determined by statistical differentiation between placebo and positive control on primary measures) and will use Effect Maximum (Emax) values for all evaluation of subjective measures.

The details of abuse potential evaluation are described in Guidance for Industry Assessment of Abuse Potential of Drugs, January 2010:

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

Meeting Discussion:

The applicant asked if it would be possible to obtain CSS feedback on their draft concept protocol to study human abuse potential. CSS was unwilling to provide comments on the concept protocol, even comments of a general nature, without a full review of a complete protocol. CSS will provide comment only after the full protocol has been submitted. CSS

agreed to review and provide comments within 30 days after receiving the applicant's full protocol submission for a human abuse potential study under IND.

Question 5: If the study results demonstrate that eslicarbazepine acetate does not show a potential for abuse are these data sufficient to support a recommendation to not schedule the product?

Preliminary FDA Response:

No.

Cumulative data from all pre-clinical and clinical studies, as well as the scientific literature and other postmarketing surveillance information are considered in the evaluation of the abuse potential of the drug.

Discussion at Meeting: none.

Question 6: Given this background information, does CSS concur that there are sufficient human data available to evaluate the potential for physical dependence?

Preliminary FDA Response:

No.

Rather than submitting data from a formally designed study to evaluate withdrawal, the sponsor has submitted information from patients who were abruptly withdrawn from the drug because of an adverse event. The complexity of these cases prevents adequate evaluation of withdrawal and dependence. Consequently a two-week prospective evaluation of physical dependence is necessary to adequately evaluate withdrawal and dependence. We note that besides providing information on this drug's abuse potential, this information supplies critical information for the label/labeling to assure safe use of the product in the indicated population.

We are available to evaluate the protocol design and provide feedback prior to the start of this study.

Meeting discussion:

The Applicant asked for specific details on the type of physical dependence study. FDA recommended a prospective study design. It is acceptable to conduct a withdrawal/dependence study in a normal healthy population. The Applicant inquired whether a 4-week maintenance period was acceptable. FDA recommends that the sponsor submit the full protocol, providing rationale for specific protocol design (e.g., treatment period, study site description, etc.). FDA will provide feedback within 30 days after the full submission has been received by CSS. The applicant inquired whether data from the former non-epilepsy study will be of value; the FDA noted any data submitted will be reviewed and considered.

Question 7: Will it be acceptable to re-code all adverse events from the clinical studies to MedDRA Version 12.1 to be used in the safety update?

Preliminary FDA Response:

Yes, this is acceptable, as long the MedDRA terms are translated from verbatim descriptions.

Additional comment from Clinical:

Recoding should be done from the verbatim terms, not from previously recoded terms. Please submit datasets that include verbatim terms, the coded term from the first NDA, and the coded MedDRA 12.1 term. Notable differences should be highlighted.

Discussion at Meeting: none.

Question 8: Given Sepracor's commitment to re-code all adverse events into a single MedDRA version and reanalyze the abuse related adverse events in a single cumulative table across all studies, does CSS agree with the methodology we have utilized to assure all terms are included in the table of adverse events? If not, please provide additional detail as to how we can address the concern that all terms are included?

Preliminary FDA Response:

No.

Analyze abuse related adverse events (CSS list is included) of all studies broken down by the individual studies, and the dose of the drug in addition to providing a single cumulative table across all studies.

Please include the following abuse-related MedDRA terms: "psychosis: psychotic episode or disorder", and "aggression".

Discussion at Meeting: none.

Question 9: Does CSS concur that Study 2093-303 should be excluded from the abuse liability reanalysis since the Agency has determined that the study is not sufficient to support safety?

Preliminary FDA Response:

No.

All data are included in our evaluation of safety, which includes the abuse potential of a drug.

Discussion at Meeting: none.

D: Statistical:

Question 10: Does the Division agree that the distribution of missing seizure diary card returns is likely indicative of a similar random distribution of individual missing seizure diary entries and can be taken as evidence of lack of bias in the distribution of possible missing seizure entries to interpret the efficacy endpoint?

Preliminary FDA Response:

No. Please see our responses to Questions 11.

Meeting Discussion:

Please see Question # 11.

Question 11: Does the Division agree that the results of simulations of the effects of missing data, under various plausible assumed patterns, support the robustness of efficacy in the 800mg and 1200mg compared to placebo? If not, please provide further guidance on possible methods or analyses to address this issue?

Preliminary FDA Response:

No. First of all, efficacy assessments are primarily based on individual studies. Your simulations used a larger sample size by pooling studies hence increased the power. Your simulation does not mimic the actual studies.

Secondly, we do not agree with your approach of randomly selecting a portion of patients in your simulations. We are concerned about the potential bias in your study dataset due to underreporting seizures. However, all your simulations were generated based on this potentially biased dataset.

We would like to defer the discussion after seeing the audit results. At that time we can discuss possible worst case scenario analyses.

Meeting Discussion:

The Applicant inquired as to the need for additional studies if the third party audits resurrect data for Study 301 & Study 302. FDA re-iterated that all of the missing data (missing diary cards and missing seizure records on returned diary cards) limited our evaluation of the robustness of the efficacy results. The simulation provided by the sponsor was not helpful. The applicant will need to provide specific detail on the extent of missing data for further evaluation.

Question 12: Does the Division agree that the analysis of efficacy with and without the hard codes, as described in the November 24, 2009 submission demonstrated no significant impact on the conclusions regarding efficacy? If not, please provide further clarification of the Division's concerns regarding the use of hard codes in the analysis of Study 2093-301 and guidance on potential approaches to addressing this issue.

Preliminary FDA Response:

Yes. However, as we mentioned in the CR letter, the extensive use of hardcodes supports our concern regarding the data quality.

Discussion at Meeting: none.

Question 13: Please provide more specific information regarding the deficiencies in the presentation of data and recommend potential approaches for resolving them so that the complete response submission addresses the issues at hand to allow for an adequate assessment of data reliability and approvability of the NDA based on studies 2093-301 and 2093-302?

Preliminary FDA Response:

Please see our response to Questions 11.

Discussion at Meeting: none.

E. Nonclinical:

Question 14: Does the Division concur that the in vitro chromosomal aberration study of the active moiety, eslicarbazepine, in human peripheral lymphocytes using human liver S9 mix will be adequate for assessing the genotoxic potential of eslicarbazepine?

Preliminary FDA Response:

We concur with your proposal, but suggest that you provide data to demonstrate that human liver S9 is an appropriate metabolic activation system. The adequacy of the study will be a matter of review.

Discussion at Meeting: none.

Post-Meeting Nonclinical Clarification Comment:

Our comment regarding the use of human liver S9 was based on the lack of information regarding the in vitro metabolic profile of eslicarbazepine using this metabolic activation system. You have provided in vitro metabolism data for human liver microsomes, but not human liver S9. Since there may be differences in the metabolic profile using different metabolic activation systems, we request confirmation that the metabolic profile for human liver S9 is similar to that in humans in vivo, in order to aid interpretation of the data.

F. Safety Update:

Question 15: Given the Division's determination that Study 2093-303 should not be relied upon to support safety conclusions, we propose to compare the re-tabulated frequencies to the pooled analysis of 2093-301 and 2093-302. Does the Division agree?

Preliminary FDA Response:

Yes. FDA does want to see the data from study 303, although separate from pooled 301-302, similar to way this was handled in the 120-day safety update (for example, Table 4.1.2-1).

Discussion at Meeting: none.

Question 16: Should the safety data from Study 2093-303 be included in any integrated re-analyses in the Safety Update, for example summary of exposure?

Preliminary FDA Response:

Please provide the data from study 303 as compared to combined 301-302 as described above. This includes exposure data.

Discussion at Meeting: none.

G. [redacted] (b) (4)

Question 17: [redacted] (b) (4)

Preliminary FDA Response:

[redacted] (b) (4)

Meeting Discussion:

[redacted] (b) (4)

3. ATTACHMENTS AND HANDOUTS

Attachment # 1 is Abuse Potential Term Update 09/2009

Attachment # 2 is Stedesa meeting slides 07/30/10

Attachment- The following list of terms provides a general guide of terms suggestive of abuse potential. This list has been compiled based on our experience to date and is not intended to be inclusive of all possible abuse related MedDRA terms.

Terms suggestive of abuse potential:

- *EUPHORIA-RELATED TERMS:*

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

Elevated mood: mood elevate, elation.

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

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

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

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

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

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

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

- *SUBJECTIVE RESPONSE TERMS INDICATIVE OF IMPAIRED ATTENTION, COGNITION, MOOD, AND PSYCHOMOTOR EVENTS WHICH ARE OFTEN ASSOCIATED WITH DRUGS OF ABUSE):*

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

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

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

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

- *DISSOCIATIVE/PSYCHOTIC* (TERMS OFTEN ASSOCIATED PCP, AND KETAMINE):

Psychosis: psychotic episode or disorder.

Aggressive: hostility, anger, paranoia

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22416	GI-1	SEPRACOR INC	SEP-0002093 ESLICARBAZEPINE ACETATE

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

/s/

ELLIS F UNGER
09/09/2010



NDA 022416

Sepracor Inc.
Attention: Karen Joyce
Associate Director Regulatory Affairs
84 Waterford Drive
Marlborough, MA 01752

GENERAL ADVICE

Dear Ms. Joyce:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Stedesa (eslicarbazepine acetate) 400 mg, 600 mg and 800 mg tablets.

We also refer to your February 10, 2010 submission notifying us of your concern involving the CSS' interpretations of data submitted to this NDA.

We acknowledge and appreciate your submission of February 10, 2010. We will consider your comments and concerns in our review of your application.

If you have any questions, call Dorothy Demczar, Pharm.D., Regulatory Project Manager, at (301) 796-2263.

Sincerely,

{See appended electronic signature page}

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



NDA 22416

MEETING PRELIMINARY COMMENTS

Sepracor Inc.
Attention: Karen Joyce
Associate Director Regulatory Affairs
84 Waterford Drive
Marlborough, MA 01752

Dear Ms. Joyce:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Stedesa, (eslicarbazepine acetate) 400mg, 600mg, and 800mg Tablets.

We also refer to your May 11, 2010, correspondence, received May 11, 2010, requesting a meeting to clarify the issues identified in the Division's Complete Response letter of April 30, 2010, and to discuss proposals from Sepracor on actions to be taken to address the outstanding issues, and to obtain feedback from the Division and the Controlled Substance Staff on the proposed actions or alternative actions that the Division may deem to be more appropriate.

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for July 30, 2010 between 2 and 3 PM, at FDA White Oak Building 22, room# 1311 between Sepracor and the Division of Neurology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me at (301) 796-0036.

Sincerely,

{See appended electronic signature page}

Su-Lin Sun, PharmD
Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Meeting Date: July 30, 2010

Time: 2:00-3:00 PM EST

Sponsor: Sepracor Inc.

Product: Stedesa (eslicarbazepine acetate) 400, 600, and 800mg tablets

Proposed Use: Adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy.

SUMMARY OF BACKGROUND INFORMATION PROVIDED BY THE SPONSOR/QUESTIONS AND FDA PRELIMINARY RESPONSES

On March 29, 2009, Sepracor submitted an NDA for eslicarbazepine acetate which was received by the Division on March 30, 2009. On the extended PDUFA Goal Date of April 30, 2010, Sepracor received a Complete Response letter identifying significant and serious clinical deficiencies in the application as well as other comments regarding Abuse Liability, Statistical, Clinical Pharmacology, Nonclinical, Labeling, Safety Update, [REDACTED] (b) (4) and Risk Evaluation and Mitigation Strategy (REMS) Requirements.

The Division indicated in the Complete Response letter that the review team will be available to discuss the deficiencies with Sepracor and potential approaches to resolving them.

The purpose of the meeting is to clarify the issues identified in the Division's Complete Response letter of April 30, 2010, to discuss proposals from Sepracor on actions to be taken to address the outstanding issues, and to obtain feedback from the Division and the Controlled Substance Staff on the proposed actions or alternative actions that the Division may deem to be more appropriate.

Question 1: Does the Division agree with the proposed audit plan, the use of [REDACTED] (b) (4) to conduct these audits and the rating plan for audit outcomes?

Preliminary FDA Response:

The proposed audit plan is generally acceptable, as written. We note, however, that the audit report templates do not include a section that addresses adequacy of randomization process (Item 2.c.vi in the Agency's CR letter dated April 30, 2010). Please ensure in your complete response that this issue is adequately addressed. In addition, in your complete response you should provide a summary of:

- 1. Any differences between the conduct of the proposed audits and those conducted previously by [REDACTED] (b) (4) (e.g. differences in governing SOPs, items audited, audit report templates, etc).**

- 2. In addition to providing summaries of audit findings by site, at sites where prior (b) (4) audits were conducted, please provide summaries of results (findings) by site for subjects' records reviewed during prior audits and new audits separately, and combined across both audits.**

We also note that complete original audit reports for all newly conducted audits should be included in your complete response.

Regarding your use of (b) (4) to conduct the planned audits, your selection of a firm to conduct these audits should be in compliance with your internal SOPs for selection of third party vendors; the Agency does not endorse specific vendors.

Question 2: Is the Division amenable to a future meeting to discuss the audit findings and Sepracor's overall conclusions prior to a potential NDA resubmission, in order to determine the adequacy of the audit outcomes to support the integrity of Studies 2093-301 and 2093-302?

Preliminary FDA Response:

DSI would be amenable to attending a meeting at which you provide a presentation related to audit results and your overall conclusion(s) regarding audit findings. We also encourage you to submit the (b) (4) audit reports with your evaluation of the audits as soon as they are available to facilitate our review of audit findings. However, DSI's comprehensive review of audit findings and resulting recommendations to the Review Division regarding the adequacy of the audits and specific audit findings will not be completed until full results of the independent audit are submitted in your complete response.

B. Clinical Deficiencies in the Structure of the Application:

Question 3: Can the Division advise if there are specific clarifications, analyses or other information that could further address these issues, or is resubmission of our response of January 25, 2010 (and perhaps certain subsequent responses) the appropriate course of action?

Preliminary FDA Response:

In addition to the possibility that we may still require another controlled trial (pending our review of your audit), the ISS re-submission should be a comprehensive, consolidated document that includes all data up to a new-cut-off that FDA and you agree upon in advance. Ideally, information from 3rd party audits would be available and complete such

that any new and pertinent information can be incorporated into the ISS. Otherwise, if these data are sent in the 120-day safety update and require extensive review, this may delay an action.

While FDA realizes that typically there will be clarifications and some additional data requests during review cycles, the extent of such in this application was an outlier. No single anomaly or deficiency in itself would have precluded review. However, the volume and persistence of errors eventually undermined FDA's confidence in the veracity of the data.

Examples of some of the corrections and deficiencies are listed below; some of which are known to you already either from your own discovery while compiling the 120-day safety update or through requests for additional information:

- **The 120-day safety update included 59 “Delayed-Reported Part 1 TEAEs”**
- **120-day safety update was missing 31 serious adverse events from one trial, which were reported only in response to clarify table 9.2-1.**
- **Trials completed before the cut-off of either the ISS or 120-day SU should have been reported. For example, you classified trial 206 as “clinically completed but not reported”. Trial 206 was clinically completed 11-18-08, which is before the 120-day safety update cut-off date of 3-30-09.**
- **The 120-day safety update of these ongoing or “clinically completed but not reported trials” and for part 3 of study did not include discontinuations secondary to an AE.**
- **A 2-4-10 submission continued to correct misinformation in Table 9.2-1.**
- **The 2-4-10 submission contains a narrative of a “new report of death”.**
- **A 2-22-10 submission notes a spelling error in the SAS code to flag “Articarias”(not “Urticarias” in the search strategy for hypersensitivity reactions. The result, as reported, is not significant but the error was noted only in February 2010.**
- **Suboptimal presentation and or quality control: Information was presented in ways that did not always highlight the salient or potential importance of an event relative to ESL, was not comprehensive/complete, was internally inconsistent, or was difficult to read. Examples are listed below:**

- **Subject 110-11 is from a healthy volunteer study with a crossover design of either ESL 900 mg daily, ESL 450 mg BID, or Trileptal. The narrative heading indicates the event of “Transaminases Increased” as occurring on Trileptal 450 mg BID and the text gives the values (without reference ranges). These are about 2x ULN for AST and ~ 5.4 x ULN for ALT. Bilirubin values are reported as within the normal range. It is the case that the subject sustained transaminase increases on Trileptal and discontinued from the study because of this instance of elevations and it is the case that the narrative notes “the subject had also experienced an increase in transaminases during Period 1”, however the narrative does not indicate that the increases on ESL were higher increases (3.6x ULN for AST and ~ 8 x ULN for ALT) and that it seems he also had decreasing transaminases levels during**

dechallenge(washout). This latter information should have been included as it puts the event leading to discontinuation in context.

- **Subject 203-337-203058- (bipolar trial) The narrative bolded header is vomiting. Vomiting is the stated reason this subject, with a history of chronic pancreatitis, was discontinued from the study. The text of the narrative indicates that transaminases were high (values of 1447 U/L and 1154 U/L for AST and ALT respectively, no reference range provided) and that both direct and total bilirubin were elevated (values are given, again no reference range). The events of vomiting and increased liver function tests occurred three days after starting ESL. All laboratory abnormalities appear to have resolved about a month after discontinuation of ESL. The narrative did not describe ALP results, did not give a reference range, and does not address why this event should not be considered as potential drug induced hepatotoxicity or cholestatic injury, especially since ALP is not provided in the narrative.**
- **Subject 303-701-70290, pancytopenia, [The SU subject number indicates this was in study 302, but site 701 was in study 303.] The subject is noted to be on valproic acid, which may confound the case or be contributory, but these types of events are rare and potentially serious and should be highlighted in presentations even if in the end, it seems unlikely the event is related to ESL. This case is somewhat hard to identify in the SU because the tables of TE AEs in the body of the SU are for incidence $\geq 2\%$ and the event is in text of the SU (panctyopenia). Also, it would seem, by the nature of the event, this might be an SAE, but there is no narrative in the SU.**
- **Tables:**
 - **SAES occurring within a week of study drug discontinuation are not reflected consistently in summary tables. Based on Table 9-4 of the 1-25-10 response, nine subjects with SAEs that onset within one week of the last dose of study medication are not reflected in Table 3 (non-fatal SAES) of the 8-28-09 submission. Further, it is unclear whether all of the information in Table 9-4 is accurate. For example, subject 303-601-70156 is listed in Table 9-4 as having hyponatremia on 11-25-06 and last dose on 11-11-05. The CRF and/or the study report seem to indicate that this subject's last dose of study medication was 9-26-06 and the CRF indicates that an event of worsening of hyponatremia onset in October, 2006 and either offset or was ongoing on 11-26-06.**
 - **Table 4 and Table 4.1.4.3-1 were AE discontinuation tables. These seemed to conflict in terms of numbers of placebo and ESL subjects. The response of 1-25-10 describes that one table was populated from the CRF termination page of primary and secondary reasons for discontinuation (Table 4) and one was from the AE page in the CRF (Table 4.1.4.3-1 respectively). Three subjects were in Table 4 but not in Table 4.1.4.3-1. With preliminary review, the responses do not resolve the issue other than to indicate that CRF information was internally inconsistent for these subjects with the CRF termination page having the subject**

discontinued in part 1 but no corresponding AE had the impact of “discontinuation” with respect to study medication. Specifically, the response also notes that for subject 301-112-90393, leukopenia was originally reported as an AE that led to withdrawal but that query resulted in the lab finding being considered NCS and the AE was removed from the AE page, but the completion page was left as withdrawal due to an AE. If it is case that the subject was withdrawn by the investigator because the investigator thought the lab value was an AE, this should not be changed after the fact if the subject was already discontinued. Additionally, FDA DSI noted that there is a value of 2.66 for this subject. This value is not in the dataset and is not in the integrated safety dataset of adverse events, ADAE2.xpt. With regard to subjects 301-192-90259 and 301-211-90059, they seem to have been discontinued from the study but not recorded as discontinued from study medication.

- It appears from preliminary review of your 1-25-10 response that you acknowledge that 7 subjects who reported an AE that led to study drug discontinuation were not in Table 4, as expected.**
- Table 9.2-1 was difficult to read. This has been addressed in a specific request, which has been received. Future tables of similar information should not be formatted like Table 9.2-1.**
- Some CRFs have multiple data clarification forms (DCF) and/or strikethrough corrections made by study staff and/or auditors making it difficult to follow the CRFs. It would be helpful to hyperlink the actual data clarification form to the notation of the DCF (the inquiry). If there are only a few, 10-20 or so DCFs, this is not such a big issue, but when there are multiple DCFs, this is time-consuming. Also, there are entries that sometimes appear to eclipse and obscure an original entry in the text. Sometimes, after significant time expenditure going back and forth from the CRF to data clarification forms, it seems that what appeared to be obscured text might have been an effort to re-enter the data for readability or might have been an attempt to correct original entry because the events were initially recorded in the wrong section of the CRF or for some other reason that seemed acceptable. However, this is not always obvious or the case. Please explain what these entries represent, not just in the specific examples below but also in general. Are there other copies of the CRFs that do not have this appearance? Please see the table and or images below for examples of notably difficult CRFs.**

Subject number	#DCF	Other CRF
303-601-70156 for parts 1&2 of study	> 60	mark out change to initial SAE entry from yes to no, DCF seems to obscure an original entry, DCFs from page 244-380 of 380 page CRF. Page 63, seems to indicate patient also started topirimate within 2 months after visit 1 and was approved by medical monitor
303-611-70237 for parts 1&2 of study	~90	pages 402-528 are DCFs
302-351-80013 part 1	>30	see duplicated excerpt of piece of CRF page
303-703-70231	~34 + onsite queried	one DCF obscures a column see image below
302-336-80073	~45	handwritten entries marked through in red
302-384-80509	~61	
302-351-80002 parts 1 &2 of study	~100	CRF is 432 pages, DCF pages 277-432
302-301-80670	>36	CRF is 198 pages, DCF pages 135-198

From CRF for 302-351-80013

(b) (4)



(b) (4)



- **ISS narratives included subjects from single-blind placebo labeled as “placebo”. This has been previously addressed by FDA and there has been a response, but these issues should be addressed in a re-submission. Additionally, there is no explanation as to how the ISS narrative is set-up (for example, is the bolded heading event the verbatim term, a preferred term, ad diagnosis? Is the bolded treatment group, the assigned treatment group or the actual treatment at the time?), narratives are not indexed and there is no tabulated summary page (or hyperlink) with a list of the subject numbers for whom there is a narrative.**

- **ISS narrative event terms such as “Unknown Adverse Event (303-709-70384) and “Adverse Event Leading to Discontinuation Not Defined” (study 203). Please explain.**
- **Content of some narratives is not very informative, such as subject 302-363-80581, subject 302-372-80363 (orthostatic hypotension but no blood pressure measurements are given and there is no description of the event itself except that it was moderate, did not require treatment, and was considered resolved about 7 days after the last dose of study medication). Narratives for subjects 301-153-1334 and subject 302-338-80164 are other examples.**
- **Upon FDA review, two subjects appear to have experienced SAEs but there are no narratives for these subjects in the ISS SAE narrative section, and in one case, it appears the event may have been an SAE but was not categorized as an SAE.**
 - ▶ **Subject 119-004 has a narrative in the discontinuation section of the ISS narratives. The heading of the narrative indicates the treatment group is eslicarbazepine acetate with another drug (lamotrigine). As one reads the listing 6.3, (listing of discontinuations in attachment 5 of 9-29-09 submission), the subject appears to have been on 1200 mg eslicarbazepine acetate. The ISS discontinuation narrative event is “hypersensitivity”. The narrative lacks a detailed clinical description of the event. The CRF indicates this subject may have been hospitalized and if this is the case (versus treatment in the E.R), hospitalization would define this as an SAE. Also, based on CRF entries and notes, the subject’s reaction course appears to have included an ulcer in the mucosa of the lower lip, perhaps an increased temperature, peeling skin, and liver enzyme elevations. Therefore, even though the subject reportedly was on a product associated with Steven’s Johnson/serious skin reactions (lamotrigine), the event should have been captured as an SAE.**
 - ▶ **Subject 117-005 apparently had a purulent tonsillitis considered an SAE. There is no narrative or CRF. This was noted in a table describing CPK elevations in the ISS and is also seen in Listing 6.2 (attachment 4 of 9-29-09 information amendment). Listing 6.2 was submitted in response to FDA request.**
- **Subject 301-211-90059- is listed in Listing 6.3 “All Treatment Emergent Adverse Events In Subjects Discontinued Due to Adverse Events” for the safety population. (This listing was submitted 9-29 as response to FDA.) This would seem to indicate the subject discontinued secondary to an adverse event, however, there is no narrative in either the ISS or the SU and there is no CRF. To further cloud the issue, the listing has a column for action taken and one for treatment. Neither of these columns indicates that the subject was discontinued or the medication withdrawn. The listed events are arterial hypertension, dizziness, and diplopia at 400 mg ESL and ataxia at 1200 mg. There are other subjects like this with events listed but no event labeled as leading to withdrawal (for example, subject 110-000-00011, 114-000-00007, 301-181-90013, and 302-313-80265).**

- **Subject 301-213-90055 is not in listing 6.3 and there is no ISS or SU narrative, yet a CRF was submitted. In the study report, it seems this subject was discontinued because of somnolence (Table 60, p.240/1074, 301a1-table not included in this review) and there is a narrative for discontinuation due to an AE in the study report for the subject (p.257/1074). The study report indicates that the subject received 1200 mg since 12-27-04 and on 4-1-05 experienced somnolence and that study medication was discontinued 4-14-05 although it does say the patient withdrew consent. The CRF adverse event pages indicate somnolence several times (12-30, 3-02, and 4-01) and withdrawal and discontinuation due to this event occurrence on 4-01. However, the CRF termination page has the reason for premature study termination as “withdrawal as consent”. Data clarification (duplicated below) noted the discrepancy. Correction is made such that “other” is chosen as reason for discontinuation with withdrawal of consent as impact on study treatment.**

(b) (4)

- **Subject 302-312-80299- ISS narrative heading for SAE narrative is “Gastroenteritis”. ADAE2.xpt has two terms as serious, Gastroenteritis and “Acute on Chronic Renal Failure” with equivalent for the preferred term as “Renal Failure Acute”. The text of the narrative includes hospitalization for 2 events (“gastroenteritis and acute chronic renal failure”) yet the ISS narrative heading is only of the SAEs.**
- **The process of translating verbatim terms to preferred terms is not described. This point is made because there are a few terms in the dataset that not commonly used in the U.S. and may/may not be used the same way in different countries. Examples include “esophageal stenosis” (subject 205-534-203144-is**

this reflux, the subject received omeprazole), amygdalitis, systemma, and nutcracker syndrome.

- **Treatment emergent adverse events in phase 1, single dose studies were not comprehensive. The image below is excerpted from Tables 8.3.5-1 in the ISS (p. 125). Additionally, as noted in image below, one cannot tell from this table what the common AE was for the subject in the ESL 400 mg group or the 2nd subject in the ESL 200 mg group. Table 8.3.5-3 describes the DDI studies and is similar.**



General Recommendations Regarding Presentation of Safety Data are described in the following bulleted points:

In addition to addressing both specific examples and the more global issues noted in the response to #3 above, ways to resolve deficiencies are listed below. This list may be redundant with some of the points in the response to #3, but the spirit of this list is to facilitate that issues are described.,

Ways to resolve deficiencies:

- 1) Include in one, consolidated ISS submission all of the concepts in the clarifications that have been requested during the initial review**
- 2) Enhance quality control such that you do not have “delayed” event reporting or the discovery of SAEs during the review cycle. Re-examine the data for the accuracy and consistency of adverse event coding and reporting. Make sure any serious adverse events are consistently labeled as such. Make sure all deaths have been reported. If an event term will infer a potential SAE and yet for some reason the event was not one, then explicitly describe why the event was not an SAE (for example, pancytopenia as discussed above).**
- 3) In the ISS, include finalized data from all trials completed within cut-off dates and world-wide, post-marketing data. Your cut-off dates for trial data should be at maximum,**

one year, before the submission is submitted. Cut-off dates for post-marketing data should be within 6 months of the submission date with the exception that serious or rare, significant medical events known to you that may have occurred after the cut-off dates should be reported.

4) Discontinuation tables should reflect discontinuation from study medication, whether it means patients discontinued medication but are still in the study or discontinued medication and was discontinued from the study.. If there indeed were subjects who left a study but stayed on study drug, please note this and explain. This applies to all trials, not just the pivotal epilepsy trials.

6) Include over-view tables of all deaths by indication and trial, all SAEs by indication and trial, all discontinuations from study medication by indication and trial. Separate the controlled data from the non-controlled data. Provide line listings or datasets that provide the subject numbers and events for the subjects in the summary tables and reference the datasets in the legends of the tables. Datasets should contain the assigned treatment group, the actual treatment the subject was on at the time, and onset off set dates of treatment and the event.

7) In addition to the pivotal trial data integrated datasets, please provide an integrated dataset of adverse events that includes all adverse events from all epilepsy studies and one for events from all other studies. The datasets should include, but are not limited to, a column that indicates whether the event was a death, non-fatal SAE, or discontinuation from study drug secondary to an AE, a column that indicates in what study phase the event occurred (open-label or controlled), a column with the assigned treatment, a column noting the actual treatment and dose at the time of the event, a column with the trial number, a column with a unique subject identifier, a column of whether another action was taken (yes or no), and a column describing such action (for example, treated with a medication, referred to a doctor), a column with the outcome, and columns with verbatim and MedDRA coded terms.

8) If a subject discontinued because seizures changed in a negative way either in number, type, time (for example, nocturnal only and now also in the day), or because the subject thought that he/she was not doing well from a seizure point of view, this should be captured in some way as discontinuation secondary to increased seizures. It must not be the case that to be considered discontinued because of a seizure or to count the seizure as an AE requires doubling of the baseline seizure frequency.

9) Provide a tabulated index to the narratives (preferably with hyperlinks) and arrange them by the treatment group they were on at the time of the event.

10) Please do not parse the presentations of the mean change and shift summary tables for hematology and chemistry data as was the case in the ISS. For example, the ISS presentation of chemistry labs, sodium, chloride, and potassium are presented for part 1 phase 3 epilepsy studies, then for part 2, phase 3 epilepsy, then phase 2 adult epilepsy, phase 2 pediatric epilepsy, phase 1 healthy volunteers, and phase 1 populations studies. Please also do not parse out vital signs and EKGs and AEs.

11) Please put all of the lab data (or EKG or VS data or AE data) for all indications in one section in the submission. For presentations of special safety issues, please put all the information for an event of interest in one section of the ISS (for example, when describing hypersensitivity, put all of the experience (phase 1-3 and post-marketing) in the

hypersensitivity section and provide an overview summary before the detailed sub-sections).

12) The 1-25-10 information amendment notes that it is apparent that placebo rates of the individual common AEs for a given product are typically lower in non-US studies than US studies and that placebo rates of the individual AEs for the eslicarbazepine studies are similar to those of non-US studies of approved AEs. An argument is made that this may reflect lower doses in non-US studies.

In Table 2-1 “Summary of Safety Data from Pivotal Studies for Last 5 new AEDs Approved in US Compared with Stedesa (eslicarbazepine Acetate) Phase III Studies” it is noted that the non-fatal SAE placebo reporting rate is 0 for 2 of three ESL studies. No other product in the referenced table has 0 SAEs reported. Discontinuation rates also are lower than most other products in the table with the exception of Zonegran (one US and one EUR study). Study 303 was within the range of other development programs. It is unclear how to consider this information (does it represent general under-reporting in non-US trials, specific under-reporting in ESL trials, or some other factor?) Briefly, please describe why you believe these data are sufficient to characterize serious events and events that led to discontinuation in ESL groups when placebo group data for ESL differs from placebo data from other trial programs.

C. Abuse Liability (Question 4 to 9):

Question 4: Does CSS agree that the following features of the proposed study are adequate to determine an appropriate recommendation regarding abuse potential?

- a. Selected doses for eslicarbazepine acetate (800 mg, 1200 mg, and 1600 mg)
- b. Comparator drugs and comparator doses
- c. Sample size
- d. Washout interval between doses
- e. Inclusion & exclusion criteria for adequately defining appropriate subjects, including appropriateness of screening based on ability to detect effects of alprazolam 2.0 mg versus placebo
- f. Study assessments and primary endpoint
- g. Sparse PK sample procedures to document eslicarbazepine exposure
- h. Statistical Analysis

Preliminary FDA Response:

No, we do not agree that the submitted Concept Protocol No. SEP093-153 is adequate to evaluate the abuse potential of this drug. The proposed Concept Protocol is missing a number of important details that can influence the study results and interpretation. When the Sponsor officially submits a complete protocol to the IND, we will review this and provide feedback.

The Sponsor should be aware that data from the human abuse potential study will undergo a statistical analysis by Agency statisticians when it is submitted. This analysis will include an evaluation of whether the study is validated (as determined by statistical differentiation between placebo and positive control on primary measures) and will use Effect Maximum (Emax) values for all evaluation of subjective measures.

The details of abuse potential evaluation are described in Guidance for Industry Assessment of Abuse Potential of Drugs, January 2010:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>

Question 5: If the study results demonstrate that eslicarbazepine acetate does not show a potential for abuse are these data sufficient to support a recommendation to not schedule the product?

Preliminary FDA Response:

No.

Cumulative data from all pre-clinical and clinical studies, as well as the scientific literature and other postmarketing surveillance information are considered in the evaluation of the abuse potential of the drug.

Question 6: Given this background information, does CSS concur that there are sufficient human data available to evaluate the potential for physical dependence?

Preliminary FDA Response:

No.

Rather than submitting data from a formally designed study to evaluate withdrawal, the sponsor has submitted information from patients who were abruptly withdrawn from the drug because of an adverse event. The complexity of these cases prevents adequate evaluation of withdrawal and dependence. Consequently a two-week prospective evaluation of physical dependence is necessary to adequately evaluate withdrawal and dependence. We note that besides providing information on this drug's abuse potential, this information supplies critical information for the label/labeling to assure safe use of the product in the indicated population.

We are available to evaluate the protocol design and provide feedback prior to the start of this study.

Question 7: Will it be acceptable to re-code all adverse events from the clinical studies to MedDRA Version 12.1 to be used in the safety update?

Preliminary FDA Response:

Yes, this is acceptable, as long the MedDRA terms are translated from verbatim descriptions.

Additional comment from Clinical:

Recoding should be done from the verbatim terms, not from previously recoded terms. Please submit datasets that include verbatim terms, the coded term from the first NDA, and the coded MedDRA 12.1 term. Notable differences should be highlighted.

Question 8: Given Sepracor's commitment to re-code all adverse events into a single MedDRA version and reanalyze the abuse related adverse events in a single cumulative table across all studies, does CSS agree with the methodology we have utilized to assure all terms are included in the table of adverse events? If not, please provide additional detail as to how we can address the concern that all terms are included?

Preliminary FDA Response:

No.

Analyze abuse related adverse events (CSS list is included) of all studies broken down by the individual studies, and the dose of the drug in addition to providing a single cumulative table across all studies.

Please include the following abuse-related MedDRA terms: "psychosis: psychotic episode or disorder", and "aggression".

Question 9: Does CSS concur that Study 2093-303 should be excluded from the abuse liability reanalysis since the Agency has determined that the study is not sufficient to support safety?

Preliminary FDA Response:

No.

All data are included in our evaluation of safety, which includes the abuse potential of a drug.

D: Statistical:

Question 10: Does the Division agree that the distribution of missing seizure diary card returns is likely indicative of a similar random distribution of individual missing seizure diary entries and can be taken as evidence of lack of bias in the distribution of possible missing seizure entries to interpret the efficacy endpoint?

Preliminary FDA Response:

No. Please see our responses to Questions 11.

Question 11: Does the Division agree that the results of simulations of the effects of missing data, under various plausible assumed patterns, support the robustness of efficacy in the 800mg and 1200mg compared to placebo? If not, please provide further guidance on possible methods or analyses to address this issue?

Preliminary FDA Response:

No. First of all, efficacy assessments are primarily based on individual studies. Your simulations used a larger sample size by pooling studies hence increased the power. Your simulation does not mimic the actual studies.

Secondly, we do not agree with your approach of randomly selecting a portion of patients in your simulations. We are concerned about the potential bias in your study dataset due to underreporting seizures. However, all your simulations were generated based on this potentially biased data set.

We would like to defer the discussion after seeing the audit results. At that time we can discuss possible worst case scenario analyses.

Question 12: Does the Division agree that the analysis of efficacy with and without the hard codes, as described in the November 24, 2009 submission demonstrated no significant impact on the conclusions regarding efficacy? If not, please provide further clarification of the Division's concerns regarding the use of hard codes in the analysis of Study 2093-301 and guidance on potential approaches to addressing this issue.

Preliminary FDA Response:

Yes. However, as we mentioned in the CR letter, the extensive use of hardcodes supports our concern regarding the data quality.

Question 13: Please provide more specific information regarding the deficiencies in the presentation of data and recommend potential approaches for resolving them so that the complete response submission addresses the issues at hand to allow for an adequate assessment of data reliability and approvability of the NDA based on studies 2093-301 and 2093-302?

Preliminary FDA Response:
Please see our response to Questions 11.

E. Nonclinical:

Question 14: Does the Division concur that the in vitro chromosomal aberration study of the active moiety, eslicarbazepine, in human peripheral lymphocytes using human liver S9 mix will be adequate for assessing the genotoxic potential of eslicarbazepine?

Preliminary FDA Response:
We concur with your proposal, but suggest that you provide data to demonstrate that human liver S9 is an appropriate metabolic activation system. The adequacy of the study will be a matter of review.

F. Safety Update:

Question 15: Given the Division's determination that Study 2093-303 should not be relied upon to support safety conclusions, we propose to compare the re-tabulated frequencies to the pooled analysis of 2093-301 and 2093-302. Does the Division agree?

Preliminary FDA Response:
Yes. FDA does want to see the data from study 303, although separate from pooled 301-302, similar to way this was handled in the 120-day safety update (for example, Table 4.1.2-1).

Question 16: Should the safety data from Study 2093-303 be included in any integrated re-analyses in the Safety Update, for example summary of exposure?

Preliminary FDA Response:
Please provide the data from study 303 as compared to combined 301-302 as described above. This includes exposure data.

G. [Redacted] (b) (4)

Question 17: [Redacted] (b) (4)

Preliminary FDA Response: [Redacted] (b) (4)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22416	GI-1	SEPRACOR INC	SEP-0002093 ESLICARBAZEPINE ACETATE

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/s/

SU-LIN SUN
07/28/2010

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Meeting Request Granted Form**

(Use this form to document the meeting granted via telephone.)

Complete the information below and check form into DFS.

Application Type	NDA
Application Number	022416
DATE Sponsor informed of meeting granted	5-11-10
Sponsor was informed of: <ul style="list-style-type: none">• date/time & meeting location• expected FDA attendees• meeting briefing package due date• number of copies	<input type="checkbox"/> Yes <input type="checkbox"/> <input type="checkbox"/> Yes <input type="checkbox"/> Yes (date: _____) <input type="checkbox"/> <input type="checkbox"/> Yes
Project Manager	Sponsor notified by D. Demczar RPM

Any follow-up letter must be checked into DFS as an advice letter, **NOT as a meeting request granted letter.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22416	GI-1	SEPRACOR INC	SEP-0002093 ESLICARBAZEPINE ACETATE

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SU-LIN SUN
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NDA-22416	ORIG-1	SEPRACOR INC	SEP-0002093 ESLICARBAZEPINE ACETATE

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/s/

RUSSELL G KATZ
04/16/2010

Demczar, Dorothy

From: Demczar, Dorothy
Sent: Wednesday, March 31, 2010 2:22 PM
To: 'karen.joyce@sepracor.com'
Subject: NDA 22416 Stedesa (eslicarbazepine acetate) - FDA labeling edits 3/30/10

Attachments: Eslicarbazepine Label 3 30 10_FDA track change edits_TL reviewed.doc

Hi Karen,

As mentioned last week, I am sending you a copy of the Division's labeling edits for NDA 22416.



Eslicarbazepine
Label 3 30 10_...

Thanks,
Dorothy

Dorothy Demczar, BS, PharmD
*Regulatory Project Manager
Food and Drug Administration
Division of Neurology Products
Bldg. 22, Rm. 4211
10903 New Hampshire Ave
Silver Spring, MD 20993
Phone: (301) 796-2263
Fax: (301) 796-9842
Email: Dorothy.Demczar@fda.hhs.gov*

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27 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22416	ORIG-1	SEPRACOR INC	SEP-0002093 ESLICARBAZEPINE ACETATE

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/s/

JACQUELINE H H WARE
04/13/2010

Demczar, Dorothy

From: Demczar, Dorothy
Sent: Wednesday, June 03, 2009 12:53 PM
To: Hershkowitz, Norman; Podruchny, Teresa; El Hage, Antoine N
Subject: FW: NDA 22-416 - Summary Information for Telecon Tomorrow
Importance: High
Attachments: NDA 22-416 Study 303 - Mexico Sites Audit Findings.pdf

hello all,

I am forwarding additional information that Sepracor has just provided regarding the Mexico site audit, for the telecon scheduled tomorrow morning. Apparently the person who performed the audit from Sepracor put together a presentation for internal staff at Sepracor.

they have taken pertinent information from this presentation and have forwarded it to us hoping to provide some additional detail.

Dorothy

From: karen.joyce@sepracor.com [mailto:karen.joyce@sepracor.com]
Sent: Wednesday, June 03, 2009 12:25 PM
To: Demczar, Dorothy
Subject: NDA 22-416 - Summary Information for Telecon Tomorrow
Importance: High

Hi Dorothy,

As discussed, attached please find summary information to facilitate the discussion at tomorrow's 9:00 AM teleconference. The document provides a summary of overall audit results for Study 303 Mexico sites as well as a listing for each site outlining the specific observations that were made.

The attendees from Sepracor will be:

Stu Mueller	Regulatory Affairs
Jean Clancy	Regulatory Quality Assurance
Amy LaForte	Regulatory Affairs
Karen Joyce	Regulatory Affairs
Janet Price	Drug Safety and Pharmacovigilance

Would you be able to send a list of FDA attendees in advance?

Please use the call in number that was provided in my May 28, 2009 e-mail (below).

Thanks,

Karen

From: Joyce, Karen
Sent: Thursday, May 28, 2009 5:07 PM

3/23/2010

To: 'Demczar, Dorothy'

Subject: RE: Confirmation of Telecon for Thursday June 4, 2009

Hello Dorothy,

Thank you for providing clarification around the nature of the question for next week's telecon. Moving the telecon to 9:00 AM is not a problem on this end. Please use the following call-in number and PIN:

Call-in Number: (b) (4)

Participant PIN: (b) (4)

Thanks,

Karen

From: Demczar, Dorothy [mailto:Dorothy.Demczar@fda.hhs.gov]

Sent: Thursday, May 28, 2009 4:46 PM

To: Joyce, Karen

Subject: RE: Confirmation of Telecon for Thursday June 4, 2009

hi Karen,

Regarding more detail about nature of the questions for next week's telecon, the team primarily wants more information on why the mexican sites were determined to be inadequate.

I was able to block off 8:30 - 9:00, as our internal discussion time, so if it's not a problem, perhaps we can move the telecon to 9:00am? If not, no problem.

Also, would it be easier if we just called into a number set up on your end?

thanks,
Dorothy

From: karen.joyce@sepracor.com [mailto:karen.joyce@sepracor.com]

Sent: Wednesday, May 27, 2009 2:16 PM

To: Demczar, Dorothy

Subject: Confirmation of Telecon for Thursday June 4, 2009

Hi Dorothy,

I am confirming Sepracor's attendance at the telecon with the agency on Thursday, June 4, 2009 at 9:15 AM.

I will send a list of Sepracor attendees prior to the telecon.

Karen

Karen Joyce

Associate Director, Regulatory Affairs

s Sepracor, Inc.

Improving Health Through Innovation™

3/23/2010

84 Waterford Drive
Marlborough, MA 01752
Tel: (508) 357-7856
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8 pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

Demczar, Dorothy

From: Demczar, Dorothy
Sent: Friday, June 05, 2009 3:13 PM
To: 'karen.joyce@sepracor.com'
Subject: Additional requests related to June 4, 2009 telecon

Follow Up Flag: Follow up
Flag Status: Red

Dear Karen:

I am sending a follow-up email to the Division's June 4, 2009 teleconference with Sepracor regarding the integrity of the safety data in study 303. In addition to the requests discussed during the telecon, the clinical team has the following:

1. We note that there were deficiencies at a site in Portugal and Spain. As these were not discussed at the teleconference, please send us a description of what exactly these problems were and at which sites. We see that you inspected site 501 in Portugal, but do not see a site in Spain in Table 2 of the clinical overview document, GCP compliance statement section. To facilitate selection of sites for FDA inspection, we would like this as soon as possible.
2. Based on the clinical-overview.pdf document, Sepracor did not perform audits of phase 1 studies, the pediatric epilepsy study, or the bipolar studies. If this is not the case, please advise. Please indicate whether these studies included data generated from Mexico. You may submit this with the package you are sending in July. We remind you that as non-pivotal phase 3 trials studies make up part of the safety database, you should address the integrity of all such studies in the analysis of the integrity database that we are requesting.
3. As we understood you, if study 303 data are dropped from the exposure numbers, there are 563 subjects with 6 months exposure and 333 with one-year. Are these all epilepsy subjects? If not, please detail the study populations for the 6 month and 1-year exposure data and indicate the doses. Please send a preliminary response to this with your question 1 response and put a final response in the package you are sending by the end of August.

Thanks,
Dorothy

Dorothy Demczar, PharmD
*Regulatory Project Manager
Food and Drug Administration
Division of Neurology Products
Bldg. 22, Rm. 4211
10903 New Hampshire Ave
Silver Spring, MD 20993
Phone: (301) 796-2263
Fax: (301) 796-9842
Email: Dorothy.Demczar@fda.hhs.gov*

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Demczar, Dorothy

From: karen.joyce@sepracor.com
Sent: Thursday, June 11, 2009 3:30 PM
To: Demczar, Dorothy
Subject: NDA 22-416 Response to additional requests related to June 4, 2009 telecon
Follow Up Flag: Follow up
Flag Status: Red
Attachments: Audit Summaries Study 303 Spain and Portugal.pdf; Table 2 - Table of Studies_Audits Conducted by Sepracor.pdf; Table 3 - Integrated Table of Studies_Audits Bial+Sepracor.pdf

Dear Dorothy,

Below is Sepracor's response to Questions 1 - 3 from your June 5, 2009 e-mail requesting additional information related to the June 4, 2009 telecon:

Division Request #1

We note that there were deficiencies at a site in Portugal and Spain. As these were not discussed at the teleconference, please send us a description of what exactly these problems were and at which sites. We see that you inspected site 501 in Portugal, but do not see a site in Spain in Table 2 of the clinical overview document, GCP compliance statement section. To facilitate selection of sites for FDA inspection, we would like this as soon as possible.

Sepracor Response #1

Attached are summary sheets for the sites in Spain and Portugal that Sepracor audited for Study 2093-303. Please note that an error was found in Tables 2 and 3 submitted in the original NDA (Module 2.5, Clinical Overview) where Study 303 Site 611 was listed as being located in Mexico but the site was actually located in Spain. As a result, Tables 2 and 3 have been revised to reflect the change and are attached as follows:

Table 2: Table of Studies/Audits Conducted by Sepracor

Table 3: Integrated Table of Studies/Audits Conducted by Bial and Sepracor

The revised tables will also be formally submitted to the NDA along with the audit reports.

Division Request #2

Based on the clinical-overview.pdf document, Sepracor did not perform audits of phase 1 studies, the pediatric epilepsy study, or the bipolar studies. If this is not the case, please advise. Please indicate whether these studies included data generated from Mexico. You may submit this with the package you are sending in July. We remind you that as non-pivotal phase 3 trials studies make up part of the safety database, you should address the integrity of all such studies in the analysis of the integrity database that we are requesting.

Sepracor Response #2

We are confirming that Sepracor did not perform audits of the Phase 1, pediatric epilepsy or bipolar studies and none of those studies included data generated from Mexico.

Division Request #3

As we understood you, if study 303 data are dropped from the exposure numbers, there are 563 subjects with 6 months exposure and 333 with 1 year. Are these all epilepsy subjects? If not, please detail the study populations for the 6 month and 1 year exposure data and indicate the doses. Please send a preliminary response to this with your question 1 response and put a final response in the package you are sending by the end of August.

Sepracor Response #3

As requested, below is the 6-month and 1-year exposure data for epilepsy subjects from Studies 2093-301 and 2093-302 Parts 1 and 2:

- 588 epilepsy subjects with exposure for more than 6 months

- 442 epilepsy subjects with exposure for more than 1 year

Please note that the numbers above are higher than the preliminary numbers provided during the telecon because we had mistakenly not accounted for placebo patients when subtracting out the 303 study.

We will provide additional information regarding exposure and dosage in the subsequent submission.

Please do not hesitate to contact me if you have any questions with the above.

Also, I see that tomorrow is Day 74 and was hoping you could send me a courtesy e-mail copy of the Day 74 letter when it is finalized.

Kind regards,

Karen

Karen Joyce

Associate Director, Regulatory Affairs

s Sepracor, Inc.

Improving Health Through Innovation™

84 Waterford Drive

Marlborough, MA 01752

Tel: (508) 357-7856

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From: Demczar, Dorothy [mailto:Dorothy.Demczar@fda.hhs.gov]

Sent: Friday, June 05, 2009 3:13 PM

To: Joyce, Karen

Subject: Additional requests related to June 4, 2009 telecon

Dear Karen:

I am sending a follow-up email to the Division's June 4, 2009 teleconference with Sepracor regarding the integrity of the safety data in study 303. In addition to the requests discussed during the telecon, the clinical team has the following:

1. We note that there were deficiencies at a site in Portugal and Spain. As these were not discussed at the teleconference, please send us a description of what exactly these problems were and at which sites. We see that you inspected site 501 in Portugal, but do not see a site in Spain in Table 2 of the clinical overview document, GCP compliance statement section. To facilitate selection of sites for FDA inspection, we would like this as soon as possible.
2. Based on the clinical-overview.pdf document, Sepracor did not perform audits of phase 1 studies, the pediatric epilepsy study, or the bipolar studies. If this is not the case, please advise. Please indicate whether these studies included data generated from Mexico. You may submit this with the package you are sending in July. We remind you that as non-pivotal phase 3 trials studies make up part of the safety database, you should address the integrity of all such studies in the analysis of the integrity database that we are requesting.

3/16/2010

- 3. As we understood you, if study 303 data are dropped from the exposure numbers, there are 563 subjects with 6 months exposure and 333 with one-year. Are these all epilepsy subjects? If not, please detail the study populations for the 6 month and 1-year exposure data and indicate the doses. Please send a preliminary response to this with your question 1 response and put a final response in the package you are sending by the end of August.

Thanks,
Dorothy

Dorothy Demczar, PharmD
Regulatory Project Manager
Food and Drug Administration
Division of Neurology Products
Bldg. 22, Rm. 4211
10903 New Hampshire Ave
Silver Spring, MD 20993
Phone: (301) 796-2263
Fax: (301) 796-9842
Email: Dorothy.Demczar@fda.hhs.gov

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8 pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

Demczar, Dorothy

From: Demczar, Dorothy
Sent: Tuesday, June 23, 2009 11:26 AM
To: 'karen.joyce@sepracor.com'
Subject: RE: NDA 22-416 - Filing Review Letter - Request for clarification
Follow Up Flag: Follow up
Flag Status: Red

hi Karen,

In response to your request for clarification email below, the division has the following response:

In terms of our request for monitoring reports, we would like the monitoring reports from sites 211 and 181 in study 301 and sites 351, 372, 392, and 301 in study 302. Thank you

thanks,

Dorothy

From: karen.joyce@sepracor.com [mailto:karen.joyce@sepracor.com]
Sent: Monday, June 22, 2009 2:37 PM
To: Demczar, Dorothy
Subject: NDA 22-416 - Filing Review Letter - Request for clarification

Dear Dorothy,

Reference is made to the Division's Filing Review Letter for NDA 22-416 for Stedesa (eslicarbazepine acetate) dated June 12, 2009. We are requesting clarification on Clinical Request #3a which states:

3. The clinical overview document states that your view is that study 303 is not "sufficiently compliant" to be formally relied upon for a conclusion of safety and efficacy, but that the study can be supportive. On June 3, 2009, in advance of the teleconference we had with you to discuss this on June 4, 2009, you submitted a document detailing problems found at the Mexican sites. Please submit this document formally to the NDA with the cover letter noting that the document is identical to the emailed version of June 3, 2009.

As per the teleconference discussion, please send the following:

a. A copy of the CRO site initiation and monitoring reports as well as the Sponsor audit reports; both Bial and your audit reports.

As discussed during the teleconference on June 4, 2009, Sepracor will submit all Bial and Sepracor audit reports. Would you please confirm that the Division is requesting the CRO site initiation and morning reports for all sites that were audited for Studies 2093-201, 2093-301, 2093-302, and 2093-303?

3/16/2010

Thanks,

Karen

Karen Joyce
Associate Director, Regulatory Affairs

s Sepracor, Inc.

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Tel: (508) 357-7856

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Demczar, Dorothy

From: karen.joyce@sepracor.com
Sent: Tuesday, June 23, 2009 12:01 PM
To: Demczar, Dorothy
Subject: RE: NDA 22-416 - Filing Review Letter - Request for clarification

Hello Dorothy,

Thanks for the quick response.

Karen

From: Demczar, Dorothy [mailto:Dorothy.Demczar@fda.hhs.gov]
Sent: Tuesday, June 23, 2009 11:26 AM
To: Joyce, Karen
Subject: RE: NDA 22-416 - Filing Review Letter - Request for clarification

hi Karen,

In response to your request for clarification email below, the division has the following response:

In terms of our request for monitoring reports, we would like the monitoring reports from sites 211 and 181 in study 301 and sites 351, 372, 392, and 301 in study 302. Thank you

thanks,

Dorothy

From: karen.joyce@sepracor.com [mailto:karen.joyce@sepracor.com]
Sent: Monday, June 22, 2009 2:37 PM
To: Demczar, Dorothy
Subject: NDA 22-416 - Filing Review Letter - Request for clarification

Dear Dorothy,

Reference is made to the Division's Filing Review Letter for NDA 22-416 for Stedesa (eslicarbazepine acetate) dated June 12, 2009. We are requesting clarification on Clinical Request #3a which states:

3. The clinical overview document states that your view is that study 303 is not "sufficiently compliant" to be formally relied upon for a conclusion of safety and efficacy, but that the study can be supportive. On June 3, 2009, in advance of the teleconference we had with you to discuss this on June 4, 2009, you submitted a document detailing problems found at the Mexican sites. Please submit this document formally to the NDA with the cover letter noting that the document is identical to the emailed version of June 3, 2009.

3/23/2010

As per the teleconference discussion, please send the following:

a. A copy of the CRO site initiation and monitoring reports as well as the Sponsor audit reports; both Bial and your audit reports.

As discussed during the teleconference on June 4, 2009, Sepracor will submit all Bial and Sepracor audit reports. Would you please confirm that the Division is requesting the CRO site initiation and morning reports for all sites that were audited for Studies 2093-201, 2093-301, 2093-302, and 2093-303?

Thanks,

Karen

Karen Joyce
Associate Director, Regulatory Affairs

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Demczar, Dorothy

From: karen.joyce@sepracor.com
Sent: Monday, August 03, 2009 1:21 PM
To: Demczar, Dorothy
Subject: RE: NDA 22416 - follow-up comment to 7/22/09 telecon

Dear Dorothy,

In response to your e-mail of July 27, 2009, this is confirmation that the errors which were discovered in the population PK datasets are isolated to those datasets generated by (b) (4) and that (b) (4) was not involved in the data collection or construction of any other datasets in the eslicarbazepine acetate development program. Please do not hesitate to contact me if you have any additional questions.

Kind regards,

Karen

From: Demczar, Dorothy [mailto:Dorothy.Demczar@fda.hhs.gov]
Sent: Monday, July 27, 2009 5:37 PM
To: Joyce, Karen
Subject: NDA 22416 - follow-up comment to 7/22/09 telecon

Dear Karen:

In follow-up to our July 22, 2009 teleconference, the Division has the following comment:

At the teleconference of 7-22-09 regarding the cause of the errors in the PK datasets, our understanding is that you believe the problem was specific to data processed by a vendor in (b) (4) (b) (4) and that this problem is not more systemic and does not impact efficacy and safety datasets. Please confirm that the vendor in (b) (4) that you believe is responsible for the error(s) was not involved in the data collection or construction of any other datasets in any other studies. If this is not the case, please advise and indicate which studies and datasets were handled by this vendor. Thank you.

Thanks,
Dorothy

Dorothy Demczar, PharmD
Regulatory Project Manager
Food and Drug Administration
Division of Neurology Products
Bldg. 22, Rm. 4211
10903 New Hampshire Ave
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Demczar, Dorothy

From: karen.joyce@sepracor.com
Sent: Friday, June 26, 2009 3:52 PM
To: Demczar, Dorothy
Subject: NDA 22-416: Summary of discussions from June 4, 2009 Telecon and upcoming submissions
Follow Up Flag: Follow up
Flag Status: Red

Dear Dorothy,

I would like to briefly summarize the discussion at the teleconference on June 4, 2009 during which the Division requested clarification of the GCP audit findings for the Mexico sites in Study 2093-303.

Attendees from Sepracor:

Stewart Mueller	Senior Vice President, Regulatory Affairs and Quality Assurance
Amy LaForte, PhD	Executive Director, Regulatory Affairs
Karen Joyce	Associate Director, Regulatory Affairs
Jean Clancy	Senior Director, Research Quality Assurance
Janet Price, MD	Executive Medical Director, Drug Safety and Pharmacovigilance

Attendees from FDA

Eric Bastings, MD	Medical Officer, DNP
Norman Hershkowitz, MD	Clinical Team Leader, DNP
Teresa Podruchny	Clinical Reviewer, DNP
Tony El Hage	Pharmacologist, DSI
Dorothy Demczar, PharmD	Regulatory Project Manager, DNP

In advance of the teleconference, Sepracor provided a document summarizing the overall audit results for Study 2093-303 Mexico sites as well as a listing for each site outlining the specific observations that were made.

During the teleconference, the Division expressed concern regarding the audit findings for the Mexico sites in Study 2093-303 and the extent to which the findings may be representative of non-Mexican sites in Study 2093-303 and other studies.

Sepracor provided an overview of the audit program and clarified that the findings appeared to be related to a failure of (b) (4) (CRO) to adequately monitor the Mexican sites in Study 2093-303. Sepracor confirmed that all of the other sites in the Phase II and III epilepsy studies were monitored by either (b) (4) or (b) (4) and that the findings for sites in Mexico, as monitored by (b) (4) are distinctly different from the findings at the other sites, as monitored by (b) (4) or (b) (4). (b) (4) was not involved in the study conduct or monitoring of any non-Mexican sites in Studies 2093-301, -302 or -303, nor were any sites in Mexico included in Studies 2093-301 or -302.

The Division requested copies of all audit reports. Sepracor agreed to provide the reports from audits conducted by Sepracor and further agreed to request the audit reports from Bial. Agreement was made to provide these by July (June if possible).

The Division also requested an ISS-type of analysis of key safety data comparing pooled data from 2093-301 and 2093-302 to data from 2093-303. It was also suggested that if Sepracor can make an argument that the non-Mexico sites for 2093-303 showed similar behavior as 2093-301 and 2093-302 sites the information would be very helpful. Agreement was made to delay the submission of the 120-Day safety update until late August so the additional analyses

could be submitted with the safety update as one package.

The Division also expressed the concern that should Study 2093-303 be excluded, the number of epilepsy subjects in the safety database may be marginal. Sepracor estimated that approximately 563 and 333 epilepsy subjects from Studies 2093-301 and -302 (Parts 1 and 2) would have 6- and 12-month exposure, respectively.

Following the teleconference, we have received a follow-up email with additional questions, as well as the 74-day filing review letter.

Despite the extension of the due date for the 120-day safety update to August, significant non-clinical data intended for the 120-day safety update will be available in July. Sepracor proposes to submit these data in July along with responses to some of the information requested in the 74-day letter.

In an effort to provide an expectation with regard to the timing of our responses, we thought it would be helpful to provide the following table describing the anticipated submissions.

Submission Timing & Contents	Source of Request
Early July Submission	
Analysis of audits conducted by Bial and Sepracor and all audit reports	June 4, 2009 Telecon Filing Review Letter
Description of the missing adverse events in Study 2093-303, sites 702 and 703	Filing Review Letter
Location of sensitivity analysis regarding Mexico sites in the ISS	June 4, 2009 Telecon
Listing of the page numbers of sections that are not searchable for study reports and the ISS and ISE	Filing Review Letter
USAN status for eslicarbazepine acetate	Filing Review Letter
Copies of the drug product stability data tables in PDF format.	Filing Review Letter
End July Submission	
Non-clinical data intended for submission in the 120 day safety update	120-Day Safety Update (SU) - Nonclinical
Results from the non-clinical abuse liability studies requested by CSS and update to abuse liability summary document (Module 4.2.3.7.4). Please note that Module 1.11.4 will be updated in August when the clinical data are also available.	Filing Review Letter
Update to Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods, as it relates to the non-clinical studies utilizing human biomaterials, included in the non-clinical update.	120-Day SU - Nonclinical
Assay validation report for lamotrigine (Study 2093-119) and topiramate (Study 2093-120)	Filing Review Letter
Assay validation reports for other AEDs evaluated in the population analysis	Filing Review Letter
CRO site initiation and monitoring reports for Sites 211 and 181 in Study 2093-301 and Sites 351, 372, 392, and 301 in Study 2093-302	Filing Review Letter

End August Submission	
120-day safety update including: data from Part 2 extensions of Studies 2093-302 and 2093-303 studies, integrated analyses of these Part 2 data with Study 2093-301 Part 2 data, and data from 3 additional Phase I studies	120-Day SU - Clinical
Analyses of key safety data comparing pooled studies 2093-301 and 2093-302 to Study 2093-303	June 4, 2009 Telecon Filing Review Letter
Number of subjects who meet ICH guidelines at 6- and 12-months by dose and categorization regarding epilepsy and non-epilepsy subjects	June 4, 2009 Telecon June 5, 2009 E-mail Filing Review Letter
Total number of non-fatal SAEs in the entire development program of Eslicarbazepine Acetate by phase and per study as well as a listing of discontinuations secondary to an adverse event	Filing Review Letter
New datasets for Studies 2093-201, -202, and -203 and Study 301 Parts 1 and 2, for adverse events, laboratory data, and EKG data	Filing Review Letter
Description of training provided on MedDRA at all sites and the methodology used for translating all of the different versions of MedDRA into the most recent version contained in the original submission and demonstrate that the applicable terms were handled consistently in the different MedDRA versions	Filing Review Letter
Tabulated summary of patients who were discontinued or dropped for reasons related to potential abuse and diversion along with case report forms for each of the patients. An explanation for all reports of discontinuation or drop outs that were due to administrative reasons or unknown	Filing Review Letter
Updated financial disclosure document (financial-cert.pdf) to address missing principal investigator and sub-investigator disclosures for Studies 2093-301, -302, and -303	Filing Review Letter
Updated scheduling proposal based on the requested information	Filing Review Letter

Please do not hesitate to contact me if you have any questions regarding the above.

Kind regards,

Karen

Karen Joyce

Associate Director, Regulatory Affairs

s Sepracor, Inc.

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3/16/2010

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Demczar, Dorothy

From: karen.joyce@sepracor.com
Sent: Tuesday, July 07, 2009 9:19 AM
To: Demczar, Dorothy
Subject: NDA 22-416 (eslicarbazepine acetate) Population PK
Follow Up Flag: Follow up
Flag Status: Red

Dear Dorothy,

As a part of efforts to further investigate eslicarbazepine acetate for use in new indications, a comprehensive review of the data elements relevant to eslicarbazepine pharmacokinetic (PK) modeling was conducted for the previous population PK analyses of Phase III clinical trial data (Studies 2093-301, 2093-302, and 2093-303) submitted in the original NDA. During this review, systematic errors were found in the datasets with regard to dosing history, demographics, and derived variables indicating the treatment dose amount and the time in study. No systematic errors in eslicarbazepine concentrations, AED concomitant medication data, or laboratory data were found. As part of our investigation, appropriate parts of the NONMEM datasets were re-built based on the raw source data and merged with portions of the existing datasets to create new NONMEM datasets for population modeling.

Based on the nature and extent of the errors, we have determined the need to re-analyze the population PK using these updated datasets and to evaluate the impact of these analyses on the proposed labeling. The analyses include 1) assessment of the population PK for eslicarbazepine (the active metabolite of SEP-0002093) in the target patient population, including the effects of other AEDs on the PK and exposure of eslicarbazepine, 2) the effect of SEP-0002093 on the PK characteristics and exposure of these other AEDs, and 3) the PK/PD relationships between patient-specific estimates of SEP-0002093 exposure and selected efficacy endpoints related to seizure frequency.

Preliminary results of the analyses show that some of the numerical outcomes of these analyses have changed but that the impact on overall conclusions and subsequent labeling is minimal. The majority of changes are specific to the drug-drug interactions section of the label, noting that none are seen to be clinically significant. There is no change to the special populations section of the label.

We wanted to alert the Division of this issue and notify you of our plan to submit new datasets and population PK reports to the NDA. We are targeting the end of July.

If needed, we are available for a teleconference at the Division's convenience to answer any questions.

Kind regards,

Karen

Karen Joyce

Associate Director, Regulatory Affairs
s Sepracor, Inc.

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Demczar, Dorothy

From: Demczar, Dorothy
Sent: Monday, July 27, 2009 2:43 PM
To: 'karen.joyce@sepracor.com'
Subject: NDA 22416- Controlled substance recommendation

Follow Up Flag: Follow up
Flag Status: Red

Dear Karen:

In follow-up to the phone call on March 10, 2009 in which Dr. Katz and I relayed to you that the controlled substance data are no longer being considered a filing issue, I am forwarding a recommendation to Sepracor from the Controlled Substance Staff (CSS) regarding your monotherapy historical North America controlled trial.

They note that it has also come to their attention that you are planning to conduct a confirmatory safety and efficacy trial that includes North American subjects, which will be initiated after submission of the NDA. CSS requests that you closely monitor and report all events related to abuse of the drug in this study.

Thanks,
Dorothy

Dorothy Demczar, PharmD
Regulatory Project Manager
Food and Drug Administration
Division of Neurology Products
Bldg. 22, Rm. 4211
10903 New Hampshire Ave
Silver Spring, MD 20993
Phone: (301) 796-2263
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Email: Dorothy.Demczar@fda.hhs.gov

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Demczar, Dorothy

From: karen.joyce@sepracor.com
Sent: Monday, August 03, 2009 1:21 PM
To: Demczar, Dorothy
Subject: RE: NDA 22416 - follow-up comment to 7/22/09 telecon

Dear Dorothy,

In response to your e-mail of July 27, 2009, this is confirmation that the errors which were discovered in the population PK datasets are isolated to those datasets generated by (b) (4), and that (b) (4), was not involved in the data collection or construction of any other datasets in the eslicarbazepine acetate development program. Please do not hesitate to contact me if you have any additional questions.

Kind regards,

Karen

From: Demczar, Dorothy [mailto:Dorothy.Demczar@fda.hhs.gov]
Sent: Monday, July 27, 2009 5:37 PM
To: Joyce, Karen
Subject: NDA 22416 - follow-up comment to 7/22/09 telecon

Dear Karen:

In follow-up to our July 22, 2009 teleconference, the Division has the following comment:

At the teleconference of 7-22-09 regarding the cause of the errors in the PK datasets, our understanding is that you believe the problem was specific to data processed by a vendor in (b) (4), (b) (4), and that this problem is not more systemic and does not impact efficacy and safety datasets. Please confirm that the vendor in (b) (4) that you believe is responsible for the error(s) was not involved in the data collection or construction of any other datasets in any other studies. If this is not the case, please advise and indicate which studies and datasets were handled by this vendor. Thank you.

Thanks,
Dorothy

Dorothy Demczar, PharmD
*Regulatory Project Manager
Food and Drug Administration
Division of Neurology Products
Bldg. 22, Rm. 4211
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Silver Spring, MD 20993
Phone: (301) 796-2263
Fax: (301) 796-9842
Email: Dorothy.Demczar@fda.hhs.gov*

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3/23/2010

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Demczar, Dorothy

From: Demczar, Dorothy
Sent: Monday, August 24, 2009 12:45 PM
To: 'karen.joyce@sepracor.com'
Subject: Dataset request - NDA 22416

Hello Karen,

I have a request from the Clinical Pharmacology reviewer regarding the dataset and program for the population PK analysis for NDA 22416 (eslicarbazepine). They are specifically requesting the dataset and the program for the population PK analysis, which are referenced in appendix (3-6) of the report "Pooled Population Pharmacokinetic/Pharmacodynamic Analysis of Eslicarbazepine Acetate in Patients With Epilepsy: SCO/BIA-2093-301, (b) (4)/BIA-2093-302, and (b) (4)/BIA-2093-303, report date : July 16, 2009".

Thanks,
Dorothy

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Demczar, Dorothy

From: Demczar, Dorothy
Sent: Monday, August 24, 2009 1:51 PM
To: 'karen.joyce@sepracor.com'
Subject: NDA 22416 - eslicarbazepine

Hello Karen,

I have a question from the clinical reviewer for NDA 22426 that I am forwarding to you:

In the study report for study 302, in appendix 16.1.4, there are superscripts "a" and "b". Superscript a is explained as "Site initiated, but did not enroll patients for whom data were reported from the double blind phase." Does this mean that patients were enrolled but not randomized? Please clarify.

Thanks,
Dorothy

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Demczar, Dorothy

From: Demczar, Dorothy
Sent: Tuesday, September 08, 2009 4:20 PM
To: 'karen.joyce@sepracor.com'
Subject: NDA 22416 - request for information

Follow Up Flag: Follow up
Flag Status: Red

Hello Karen,

I have the following questions for Sepracor, regarding NDA 22416, from the biostatistics reviewer:

- As zeros are not recorded on diary cards and in the dataset, please explain how 'missing seizure records' (for example, a diary card not returned for a visit) and 'no occurrence of seizure' are differentiated. If they cannot be differentiated, please assess its impact on the efficacy results.
- Please explain, for subjects who withdrew early, how the end dates were determined for the purpose of calculating the number of days and for deriving the seizure frequency.
- For study 302, you indicated that "Bial and its partner (b) (4) (CRO) held meetings to identify records which are not regarded as seizures". Please clarify the definition of seizure and how the flag variable "noseiz" was generated. Please submit evidence that this was done before the study was unblinded.
- The disposition table for study 301 indicates that only 82 subjects entered maintenance period in 1200 mg group. However, the primary efficacy result shows that 94 subjects had efficacy measures during maintenance period (without imputation). Please explain the discrepancy.
- Explain the discrepancies in the disposition tables from individual studies and ISE. For example, based on the tables of individual studies, 87 subjects (33 and 54 from study 301 and 302 respectively) withdrew due to unacceptable adverse event based on the individual table. However, the pooled analysis shows that only 73 subjects withdrew due to AE.

Thanks!

Dorothy

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Demczar, Dorothy

From: Demczar, Dorothy
Sent: Friday, September 11, 2009 10:29 AM
To: 'karen.joyce@sepracor.com'
Subject: NDA 22416- Request for Information

Hello Karen,

I am forwarding a Request for Information (below) containing several questions from the clinical team regarding NDA 22416 (eslicarbazepine). As always, please submit your responses to these questions in archival format as an amendment to this NDA. You can email the responses to me in advance of the submission, as long as both communications (email and archive) contain identical information.

- 1) The safety update indicates that additional part 1 double-blind adverse events were discovered while evaluating the part 2 data. After eliminating errors or duplications, you indicated there were 59 additional adverse events in 48 subjects. On preliminary review, we are unable to locate these events and subjects. Please send a list of the subjects, by unique id and by trial, with the adverse event verbatim term and coded preferred term. If the event was an SAE, indicate this in the line listing.
- 2) Please provide a listing of all subjects who became pregnant, with outcomes, while exposed to active drug or placebo in the development program (phase 1 through phase 3 open-label). If there already is a comprehensive listing, please specify the location.
- 3) The literature review submitted with the safety update basically is a list of references. Please discuss the literature and summarize any findings. Please also make a statement as to whether you believe any of the literature changes the overall safety profile of the product or presents a new or unusual finding.
- 4) As we understand it, eslicarbazepine acetate received marketing approval in Europe in April (authorization date 4-21-09). If the product has been launched, please indicate whether you have had any post-marketing reports of serious or medically significant events.
- 5) We are not able to locate a presentation of QT data from the controlled trials that includes all patients who experienced a QT interval ≥ 450 msec, ≥ 500 msec, 30-60 msec, and ≥ 60 msec. Such a presentation should include placebo incidences, discuss the correction used, and include mean change from baseline for controlled data. We are also looking for the number of subjects and a listing of any subject meeting these outlier criteria in any study of eslicarbazepine or BIA2093. Please indicate where we may find such listings. If these are not currently in a submission, please submit such a presentation formally to the NDA within the next two weeks of 9-08-09.
- 6) Please indicate where we may find a comprehensive summary (in the ISS and the SU), that states how many people have died in any study of eslicarbazepine (and indicate the drug treatment group), experienced an SAE, or discontinued secondary to an adverse event. Please also indicate where we might find comprehensive line listings of these events. If such listings are not currently included in either the ISS or the SU, please submit.
- 7) On preliminary review, we are having a difficult time reconciling the data in Table 3.2-1 of the SU with that in Table 3.1-1 of the SU. Specifically, in Table 3.1-1 it looks like there is only one person with >52 week exposure to doses above 1100mg. In Table 3.2-1, it seems there are 75. This may be due to the definitions (for example of "category" or "cumulative calculated dose") or the way the calculations were made. Please address. Also, please state the number of subjects in any trial (controlled or open-label) who have been exposed to 1200 mg (using the mean daily dose) for ≥ 52 weeks and the number of subjects in any trial (controlled or open-label) who have been exposed to a mean daily dose of >1000 mg ≥ 52 weeks. If this information is already in the application, please reference where we may find it.

Thanks very much!
Dorothy

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Demczar, Dorothy

From: Demczar, Dorothy
Sent: Wednesday, September 23, 2009 1:39 PM
To: 'karen.joyce@sepracor.com'
Subject: NDA 22416 - Request for Information -ClinPharm

Hello Karen,

I am forwarding a Request for Information (below) from the Clinical Pharmacology group regarding NDA 22416 (eslicarbazepine). As always, please submit your response in archival format as an amendment to this NDA. You can email the response to me in advance of the submission, as long as both communications (email and archive) contain identical information.

The 'pkp' analysis dataset for bioequivalence Study 122 appears to be incomplete. There are only 2 subjects on Test in group 3. Please submit the complete correct dataset for the 'pkp' file as soon as possible.

Thanks!
Dorothy

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Demczar, Dorothy

From: Demczar, Dorothy
Sent: Thursday, September 24, 2009 12:36 PM
To: 'karen.joyce@sepracor.com'
Subject: NDA 22416 - Request for Information - Clinical

Follow Up Flag: Follow up
Flag Status: Red

Hi Karen,

I am forwarding the following question to Sepracor from the clinical reviewer:

In the document, multi-mod-info-amend.pdf in the 7-31-09 submission, on page 31/31, it indicates that there are planned additional GCP audits of clinical sites in study 302, overview compliance audits of (b) (4) and (b) (4) translations of two Bial audits (pre-2006), and translated site monitoring reports that are pending submission to the NDA. What is the status of these documents in terms of submission dates to the NDA?

Thanks,
Dorothy

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Demczar, Dorothy

From: Demczar, Dorothy
Sent: Thursday, October 08, 2009 9:37 AM
To: 'karen.joyce@sepracor.com'
Subject: NDA 22416 (eslicarbazepine) - Request for information- Biostatistics and CMC

Follow Up Flag: Follow up
Flag Status: Red

Hello Karen,

I am forwarding a Request for Information (below) from the Biostatistics and CMC groups regarding NDA 22416 (eslicarbazepine). As always, please submit your response in archival format as an amendment to this NDA. You can email the response to me in advance of the submission, as long as both communications (email and archive) contain identical information.

Biostatistics

Question 1

The sponsor has performed a large degree of hardcoding in the program that essentially changed the values of the variables in the database. For example, the dataset creation program for study 2093_301 ([sco_bia_2093_301_derived_data_part_i.pdf](#)) has 193 places with "if patid=xxx then variable ABC=zzz" indicating a value for a specific subject is changed in the program. Hardcoding is generally discouraged because 1) too much hard coding over rides the database controls in the clinical data management systems and may compromise study data integrity and 2) other people can not replicate the results based on the raw datasets without knowing all the data changes.

We request the following:

- 1) Please, explain when and how the hard coded values are determined.
- 2) Please submit one dataset (or a few datasets if necessary) with original variables (not derived variables) and a program to generate the final efficacy variables (seizure frequency during maintenance period, and seizure frequency during titration and maintenance period) based on this dataset. Use the last diary return date as the end date of early terminated subjects.
- 3) Please list the source (CRF, team meeting, etc) of each variable in this dataset, and the hardcodes used in the program. Give explanations/source documents of the hardcodes when necessary.
- 4) Please provide primary efficacy analysis results using the newly derived efficacy variable for each of the three phase 3 studies.

Question 2

The period for the purpose of counting the number of days does not seem to be consistent with the period for counting the number of seizures for early terminated subjects in ISE. For example, for subject 90040 (study 301/1200mg group) the 5 seizures after 22DEC04 were not counted as maintenance seizures for the reason of EOT. However, the number of days after 22DEC04 was counted as part of the maintenance period, resulting in the dilution of the standardized seizure to 1.7.

Please explain or correct when deriving the new efficacy variables mentioned in Question 1.

Question 3

You mentioned in your reply to Biostatistics question 3 on September 8 that duplicate seizures are identified in the blinded data review meetings. This process, however, does not seem to be followed in the ISE. For example, there seems to be 128 duplicate seizures counted for the maintenance period for subject 2093301-172-90435.

Make sure duplicate seizures are handled correctly when deriving the new efficacy variables mentioned in Question 1.

Question 4

As handling of the cluster seizures is not pre-specified in the SAP, please conduct a sensitivity analysis in which each individual seizure is counted instead of each cluster group.

Please respond to our requests as soon as possible.

CMC:

Please provide representative data for the (b) (4) of the 400 mg tablets (b) (4). Also provide comparison dissolution data for the (b) (4). Provide friability data for the (b) (4).

Thanks,
Dorothy

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Demczar, Dorothy

From: Demczar, Dorothy
Sent: Monday, October 19, 2009 10:59 AM
To: 'karen.joyce@sepracor.com'
Subject: NDA 22416 - Eslicarbazepine - Clin Pharm Request

Follow Up Flag: Follow up
Flag Status: Red

Hello Karen,

I have the following request from the Clinical Pharmacology reviewer regarding NDA 22416:

In the Clinical Pharmacology summary on page 80, you mention

(b) (4)

(b) (4)

(b) (4) Please clarify your rationale and intent of dosing recommendation in the renally impaired patients.

Thanks,
Dorothy

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NDA 22-416- (b) (4) submission Page 1 of 2
Demczar, Dorothy

From: karen.joyce@sepracor.com
Sent: Wednesday, October 28, 2009 12:14 PM
To: Demczar, Dorothy
Subject: RE: NDA 22416- (b) (4)
Follow Up Flag: Follow up
Flag Status: Red

Hello Dorothy,

This e-mail is confirmation that the August 28, 2009 submission (eCTD Submission Sequence 0007) to NDA 22-416 contained a (b) (4) (Module 1.9).

Yes, the clin pharm request is outstanding. We anticipate submitting a response on Monday, November 2, 2009.

Kind regards,

Karen

From: Demczar, Dorothy [mailto:Dorothy.Demczar@fda.hhs.gov]
Sent: Tuesday, October 27, 2009 3:39 PM
To: Joyce, Karen
Subject: NDA 22416- (b) (4)

Hi Karen,

Regarding our conversation the other day - could you please just send me an email that would clearly state that the August 28, 2009 submission (the safety update submission since there was another submission that day) also contained (b) (4) I need to code this internally since the cover letter isn't clear and I just need to make a clear path to it.

Also, I believe there was a clin pharm request that I had sent ealier, I don't think you mentioned it when we spoke. I think it's still outstanding.

Thanks,
Dorothy

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Demczar, Dorothy

From: Demczar, Dorothy
Sent: Wednesday, November 04, 2009 11:29 AM
To: 'karen.joyce@sepracor.com'
Cc: Demczar, Dorothy
Subject: NDA 22416 - Eslicarbazepine - Biostats Information Request

Follow Up Flag: Follow up
Flag Status: Red

Hello Karen,

I am forwarding the following Request for Information from the biostatistics team for NDA 22416 (eslicarbazepine). As always, please submit your response in archival format as an amendment to this NDA. You can email the response to me in advance of the submission, as long as both communications (email and archive) contain identical information.

We have received your response to FDA Sept. 8 Biostatistics Question 1. In your reply you indicated that the studies were to collect all diaries (used or un-used). Please provide a summary of patient diary compliance (e.g., percentage of diaries returned) and assess the impact of non-compliance on efficacy results. For each phase 3 study, please provide us the following analysis results, derived datasets for these analyses, listing of involved raw datasets, the involved raw datasets if they are not already submitted, and programs.

1. Summary of Patient Diary Compliance. The following table is an example and the sponsor can provide other tables such as summaries by study visit/phase if deemed necessary.

Percentage of Diaries Returned	Placebo n(%)	ESL 400 mg n(%)	ESL 800 mg n(%)	ESL 1200 mg n(%)
All patients				
100%				
80-100%				
60-80%				
<60%				

2. Analysis of the primary efficacy endpoint for subsets of ITT patients with 100% diary compliance and patients with >80% diaries returned.
3. Please provide a worst case analysis. The worst case scenario analysis may include an analysis that assumes rates for times that the diaries were missing as follows:

Missing diary during the experimental period:

- a) On placebo - assume missing diary rates are 0.
- b) On drug- assume missing diary rates are equivalent to the baseline rate.

Missing Diary during the baseline:

- a) On placebo- assume rates equivalent to rate during experimental period
- b) On drug- assume rates are 0.

For periods with no single diary card returned and no seizure reported (refer to table 1 in your response to Sept. 8 Biostatistics Question 1), exclude such periods from all the efficacy analyses requested.

Thanks,
Dorothy

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Demczar, Dorothy

From: Demczar, Dorothy
Sent: Monday, January 04, 2010 4:31 PM
To: 'karen.joyce@sepracor.com'
Subject: NDA 22416-Briefing document for 1/11/10 meeting

Attachments: MTG w Sepracor on 011110.pdf

Hi Karen,

In preparation for our scheduled meeting on Monday, January 11, 2010, attached is the document detailing the Division's concerns regarding NDA 22416.



TG w Sepracor
n 011110.pdf (..

Thanks,
Dorothy

Dorothy Demczar, PharmD
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The primary reason FDA requested the upcoming meeting is to address deficiencies noted during recent inspections of two sites (study 301-site 112, study 302-site 395). Although the final inspection review is pending, these deficiencies appear potentially serious, limiting, and may impact safety and/or efficacy data quality. FDA notes that recently you submitted a response to inspection report 483 forms and defers further communication about these issues until the scheduled meeting. We are awaiting review of this by our DSI staff. In addition to inspection deficiencies, there are issues in other review disciplines that have been identified. These are described below.

As the main focus of the scheduled January meeting is to discuss potentially serious inspection findings, Clinical issues #1 and #2 will be the main focus of the meeting; the other issues outlined below may not be discussed at the meeting in much detail or at all pending time constraints. For the clinical issues outlined below, please submit a formal response to the EDR by January 18, 2010. If there is not time to discuss the clinical issues described below at the January meeting, please feel free to email for clarifications.

CSS:

1. There are limitations in the design of pre-clinical abuse studies. These studies do not provide enough data to fully assess the abuse potential of eslicarbazepine acetate.
2. There are significant problems in the methodology and conduct of the clinical studies that prevent an accurate and adequate assessment of abuse potential. These include:

- Serious under-reporting of all adverse events, particularly in the pivotal safety and efficacy trials 2093-301, 2093-302 and 2093-303, which even the sponsor recognized.
- Inadequate and inaccurate information by which to assess abuse related AEs:
 - a. Not including in the integrated table of abuse related AEs from pooled clinical studies **all** abuse related MedDRA terms provided to the sponsor by CSS (communication from Nov 28, 2008).
 - b. Omitting and minimizing number of AEs potentially related to abuse.
- Use of different versions of MedDRA system (4.0 to 10.0) throughout the drug development which potentially could underestimate abuse related adverse events and makes the interpretation of these data difficult.

Clinical:

1. Suboptimal coding or inadequate adverse event documentation- For example, in study 303, site 501, subject screening #70099 (randomization # 3165), the audit report dated 10-2-08 (hyperlinked from the multi-mod-info-amend.pdf submitted 7-13-09) indicates that the termination reason in the CRF is "withdrawal of consent". Source documents indicated the subject did not continue in the study because he began to have daytime seizures instead of only nocturnal as they had occurred historically. This patient's primary reason for discontinuation is coded in the ADEX.xpt dataset (exposure) as "withdrawal of consent" and the patient is not in the AE dataset.

The audit reports hyperlinked from the multi-mod-info-amend.pdf of 7-13-09 for study 303, site 501 and 611 indicate that in both parts 1 and 2, for sampled subjects, the AE and SAE reporting was considered as “significant noncompliance”. Problems included adverse events in the source documents that were not in the CRFs. In Attachment 1 of the June submission (saf-info-amend.pdf), under “Data Integrity”, it is stated that at site 611, in general, good documentation practices were not employed with most source document entries not dated and many were not signed.

In addition to FDA inspections, there is evidence that data integrity issues may not be limited to study 303. For example, at site 195 in study 301, the report of inspection by Sepracor through (b) (4) of 9/16-18/2008 indicates that the CRFs of three subjects were audited using complete source documents and that AEs/SAEs were not properly reported for these sampled subjects. Details were not provided in the report section.

As noted previously, there is general concern for the quality of adverse event monitoring or recording. There is also concern that for events noted in audit reports as captured on source documents but not CRFs, these events were not included in the integrated adverse event datasets and may not be correctly coded in disposition and exposure datasets. If you have not already done so, please go through all audit forms and note which subjects (by trial and subject number) had discrepancies between the source document and CRF for reporting of any adverse events (and note if the audit indicates a problem with AE reporting other than this). Provide a listing of these subjects per trial with the adverse event noted and the associated treatment. Cross reference these subject events to the datasets of adverse events, disposition, and exposure and see if these events are included. Provide a table that lists, grouped by trial, each subject in question, the event, whether the AE is in the dataset, and whether the disposition and exposure are optimally coded to reflect the reason for discontinuation. This should be performed for all trials audited. For the pivotal trials, the datasets that are of most importance are the ones submitted as integrated datasets.

A format for your response table is provided below. In this table, “correct” means that the reason is the most appropriate reason for discontinuation, for example, if a subject withdrew consent because of seizure increases, this should be withdrawal due to increase of seizures, not withdrew consent.

Study, site, and subject number	Audit finding and/or event	CRF-is there documentation of event-yes/no	Dataset ADAE.xpt is the event listed in the dataset?	Dataset ADAE.xpt Is the withdrawal /discontinuation reason correct?	Dataset ADEX.xpt is the reason for withdrawal correct?
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2. With regard to the issue of no US data in this application, the initial ISS compares placebo rates from ESL's most common adverse events with the 5 most recently approved AEDs. Although it is unclear how meaningful or valid it is to make such comparison across trials in differing development programs, if such comparison is to be made, to be complete, the reporting rates for SAEs and discontinuations secondary to an AE are needed. Please submit this information for the controlled phases of the phase 3 eslicarbazepine studies as compared to the rates of these events for the last 5 product approvals described in the NDA submission. Also, within the 5 recent approvals, please revise your presentations to show stratification by US and non-US data if possible. We recognize this stratification may not be possible given that the data may not be fully in the public domain. If this is the case, please state such.
3. Inappropriate data pooling-Some data tables (epilepsy, phase 3, laboratory and vital signs) include a treatment week 18 and display the data as placebo-controlled. In study 302 visit 6 (treatment week 18) was open-label. Please verify that the AE tables in the SU do not include the open-label events from study 302 and do not include lead-in, single blind placebo data.
4. Table 9.2-1 in the 120-day Safety Update contains a listing of SAES that occurred between 2-28-08 and 3-30-09. The following is an excerpt duplicated from the listing. Note that initially it would appear the event of "Vomiting" is still blinded. However, a closer look indicates, if the reviewer interprets this correctly, that the event occurred on 2-15-09 and the subject was on 30mg/kg ESL (beginning 12-22-2008 and ongoing).

Study No. Subject No. Case No.	Country	Age (years) Sex	Dose Start Dose Stop	ESL Daily Dose	Event Onset Event Stop	Reported Term Outcome	Preferred Term System Organ Class	Serious	Relationship
2001	Portugal	11	02JUN2008	Blinded	15FEB2009	Vomiting	Vomiting	Hospitalization	Unlikely
2093-305- C193/0003		Female	30OCT2008 27NOV2008 22DEC2008	10 mg/kg 20 mg/kg 30 mg/kg	16FEB2009	Recovered	Gastrointestinal disorders		
			28SEP2008 26NOV2008 21DEC2008 Ongoing						

This presentation is confusing. Please revise the presentation to clearly indicate the treatment group associated with the AE. If an event occurred shortly after a dose adjustment, please include this information. Also, if data is from a controlled trial, include a summary table that compares placebo to drug group rates by dose group as appropriate. If such data presentation is already in the submission, please reference the location(s).

5. In the multi-mod-info-amend.pdf submitted 8-28-09, Tables 3 and 4 show the number and percentage, by treatment group, of non-fatal SAEs and discontinuations secondary to an AE. These tables include phase 1 events. We are not able to locate listings of the events in phase 1 that correlate with these tables. Please reference where we may find such.

If such presentations are not already submitted, please submit listings; one for deaths, one for non-fatal SAEs, one for discontinuations secondary to an AE, and one for all treatment emergent AEs. Present the data in the following way: by the type of event (death, SAE, discontinuation, TEAE), then either pooled for studies for which this is appropriate (for pooled studies, briefly describe the rationale for inclusion/exclusion), or by study. The lists themselves should contain the subject id, the event, and the treatment associated with the event.

6. For phase 1 studies, laboratory parameters and vital signs, the initial ISS generally reports clinically significant findings as reported by the investigators or findings that were considered adverse events (for example, Table 11.2.1.5-1 and Table 11.2.1.5-2). For the phase 1 studies, the ISS also provides a listing of CPK elevations if these were reported or called an adverse event (for example, Table 8.6.16-6). Please apply the potentially clinically significant criteria from Tables 1.5.5.9-1, 1.5.5.10-1, and 1.5.5.11-1 of the initial ISS and sodium levels noted on page 62/582 of the initial ISS to the phase 1 data. If the trial was controlled, summarize by treatment group.
7. The phase 2 bipolar clinical laboratory data discussion is focused on adverse reports and clinically significant changes in clinical laboratory evaluations (initial ISS page 424/582). This seems to be the case for EKG and vital sign data. Please apply the potentially clinically significant criteria from Tables 1.5.5.9-1, 1.5.5.10-1, and 1.5.5.11-1 of the initial ISS and sodium levels noted on page 62/582 of the initial ISS to the phase 2 bipolar data. If the trial phase was controlled, summarize by treatment group. If these presentations are already in the initial ISS (or the 120-day Safety Update), please reference the locations.
8. The 120-day safety update did not include a revised or updated table listing all clinical studies. Please submit such a table.
9. Some information within the NDA submission(s) appears to be contradictory. Examples are listed below. Please address these.
 - There are more subject narratives in the ISS narratives for part 1 than subjects described in the corresponding table in the SU.
 - Section 25.1.2.1, "Pooled Phase III Epilepsy Studies (Part 1 of 2093-301, 2093-302, and 2093-303)" of the ISS submitted 3-29-09 contains the narratives of non-fatal SAES that occurred in part 1 of the controlled phase 3 trials. There are narratives labeled as placebo that, based on the dataset ADAE.xpt, were pre-dosing events (4 of the 9 events –subjects 301-175-90419, 301-112-90394, 301-112-90327, and 301-181-90003). Also, subject 301-181-90003 (toxic skin eruption) is not even in the safety population. Although within the text of the narrative, the randomization date is stated, and one can deduce which event was before randomization, the presentation is not optimal. Please submit a listing of subject numbers (and the corresponding event) for events in section 25.1.2.1 that happened pre-randomization (or in an uncontrolled phase of the trial).
 - Tables included in documents in the 8-28-09 submission appear contradictory. Table 2.1.3-1 in the Clinical Summary of Safety submitted on 8-28-09 indicates there were 4 subjects with 4 TE SAEs in the placebo group and 28 subjects with 46 TE SAES in the pooled studies 301-303 part 1. It would appear this table would be comprehensive as the legend indicates the table includes the 59 AEs from part 2 studies that had onset dates in

part 1 and, erroneously, were not included in the initially submitted ISS tables. Also in the 8-28-09 submission, multi-mod-info-amend.pdf, Table 3, "Summary of any non-fatal SAEs in the entire eslicarbazepine acetate development program by study and by Development Phase" indicates there were a total of 2 placebo subjects with 2 SAEs and 67 ESL subjects with 103 SAES in phase 3 epilepsy studies. The 67 ESL patients in Table 3 compared to 28 in Table 2.1.3-1 may be due to counting part 1 and 2 data, however, clearly the placebo SAEs are incorrect in one of these tables.

- Tables included in documents in the 8-28-09 submission appear contradictory. In the document multi-mod-info-amend.pdf, Table 4, "Summary of Discontinuations due to Adverse Events in the Entire Eslicarbazepine Acetate Development Program and by Study within each Development Phase", it appears that in part 1 of studies 301-303, 10 placebo subjects and 98 ESL subjects discontinued secondary to an AE. In the same submission, different document (the 120- day Safety Update), Table 4.1.4.3-1, "Discontinuations of Study Medication Due to TEAEs Reported in $\geq 2\%$ of Subjects in Any Dose Group by Overall Treatment Group for part 1 of the Phase III Studies (2093-301 and 2093-302 Pooled vs 2093-303 (Safety Population)" indicates that there were 15 placebo subjects and 109 ESL subjects who discontinued study medication due to TEAES. Please explain the differences in the tables.
- Tables that appear to conflict- Table 4.5-1 of the initial ISS is titled, "Brief Summary of Subject Disposition for the Phase 1 Healthy Volunteer Studies (Safety Population)" and notes the number of % of discontinuations secondary to an AE. Table 4 of the multi-mod-info-amend.pdf submitted 8-28-09 is titled, "Summary of Discontinuations due to Adverse Events in the Entire Eslicarbazepine Acetate Development Program and by Study within each Development Phase". Study 115 is in Table 4.5-1 and is not in Table 4. In Table 4.5-1, studies 123 and 126 are not included, yet they are in Table 4. For study 117, in Table 4.5-1, there are 0 discontinuations secondary to an adverse event. In Table 4, for study 117, there is one discontinuation secondary to an adverse event. Also, Table 4 has "0" in the placebo group for study 116. The study report for 116 indicates there was one discontinuation in the placebo group. The details indicate that one subject had events on both placebo and ESL that continued from placebo.

10. We note at the clinicaltrials.gov website, that a phase 3 trial of eslicarbazepine for POS started in December of 2008 ("Efficacy and Safety of Eslicarbazepine Acetate (BIA1-093) as Adjunctive Therapy for Refractory Partial Seizures"). Please reference where we may find information about this trial in your NDA submission(s).
11. Page 37/582 of the initial ISS notes that part 3 study 301 was completed after the ISS cut-off date and not included in the ISS. The 120-day Safety Update, section 9 includes information on deaths and SAES between the 2-28-08 cutoff for the ISS and the 3-30-09 cutoff for the 120-day Safety Update. We are not able to locate information on discontinuations secondary to an AE for part 3 of study 303 or the other ongoing studies noted in section 9 of the 120-day Safety Update. Please reference where we may find this information or submit the information if it has not been submitted.

Demczar, Dorothy

From: karen.joyce@sepracor.com
Sent: Thursday, January 07, 2010 11:15 AM
To: Demczar, Dorothy
Subject: FW: NDA 22-416 Request from Clarification

Dear Dorothy,

Sepracor is requesting clarification from the Division's January 4, 2010 document detailing the Division's concerns regarding NDA 22416 as follows:

CSS Question 1

There are limitations in the design of pre-clinical abuse studies.

Sepracor Clarification Request

Could the CSS specify which studies they are referring to and provide further detail regarding the design issues that prevent a full assessment of the abuse potential of eslicarbazepine acetate?

Clinical Question 6

For phase 1 studies, laboratory parameters and vital signs, the initial ISS generally reports clinically significant findings as reported by the investigators or findings that were considered adverse events (for example, Table 11.2.1.5-1 and Table 11.2.1.5-2). For the phase 1 studies, the ISS also provides a listing of CPK elevations if these were reported or called an adverse event (for example, Table 8.6.16-6). Please apply the potentially clinically significant criteria from Tables 1.5.5.9-1, 1.5.5.10-1, and 1.5.5.11-1 of the initial ISS and sodium levels noted on page 62/582 of the initial ISS to the phase 1 data. If the trial was controlled, summarize by treatment group.

The Division has requested an analysis of potentially clinically significant (PCS) laboratory and vital sign and ECG data as well as a categorical sodium analysis for all of the Phase I clinical trials. A full evaluation of PCS endpoints were already presented in the NDA for the more robust dataset from the Phase III studies, and revealed no unanticipated findings. Since all of the Phase I studies involved a very short duration of exposure (many involved single doses of eslicarbazepine acetate) and employed relatively limited laboratory measurements, Sepracor proposes that we evaluate a limited number of relevant analytes for PCS criteria in these Phase I studies. We propose to perform a PCS analyses on the following laboratory analytes;

- Sodium
- AST
- ALT
- CPK
- Leukocytes
- Platelets

Further, since a thorough QT study was performed (Study 2093-116) as well as a full analysis of ECG data from the Phase III studies, we do not believe that PCS analysis of ECG or vital sign data from the Phase I studies will be revealing of any systemic safety issues that may have been missed by the larger adjunctive therapy studies.

3/16/2010

Please note that a full PCS analysis for the Bipolar Disorder studies is being provided in response to Clinical Issue #7, given the higher doses and longer exposures utilized in those studies.

Does the Division agree with this proposal?

Clinical Question 9, Bullet 1

There are more subject narratives in the ISS narratives for Part 1 than subjects described in the corresponding table in the SU?

Would the Division please provide the Safety Update Table # and identify which ISS narratives (deaths, SAEs, or discons due to AE) that are in question.

Please do not hesitate to contact me if you have any questions.

Kind regards,

Karen

Karen Joyce

Director, Regulatory Affairs

Sepracor, Inc.

Improving Health Through Innovation™

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3/16/2010

From: Demczar, Dorothy
Sent: Wednesday, January 13, 2010 11:58 AM
To: 'karen.joyce@sepracor.com'
Subject: Re: NDA 22416 - clarification for questions #6 and #9

Hi Karen,

I am forwarding you the clinical team's response (below) to your email of January 7, 2010, requesting clarification from the Division's January 4, 2010 document which detailed the Division's concerns regarding NDA 22416:

Clinical Question #6

FDA: For phase 1 studies, laboratory parameters and vital signs, the initial ISS generally reports clinically significant findings as reported by the investigators or findings

that were considered adverse events (for example, Table 11.2.1.5-1 and Table 11.2.1.5-2). For the phase 1 studies, the ISS also provides a listing of CPK

elevations if these were reported or called an adverse event (for example, Table 8.6.16-6). Please apply the potentially clinically significant criteria from Tables

1.5.5.9-1, 1.5.5.10-1, and 1.5.5.11-1 of the initial ISS and sodium levels noted on page 62/582 of the initial ISS to the phase 1 data. If the trial was controlled,

summarize by treatment group.

Sponsor: The Division has requested an analysis of potentially clinically significant (PCS) laboratory and vital sign and ECG data as well as a categorical sodium analysis for all of the Phase I clinical trials. A full evaluation of PCS endpoints were already presented in the NDA for the more robust dataset from the Phase III studies, and revealed no unanticipated findings. Since all of the Phase I studies involved a very short duration of exposure (many involved single doses of eslicarbazepine acetate) and employed relatively limited laboratory measurements, Sepracor proposes that we evaluate a limited number of relevant analytes for PCS criteria in these Phase I studies. We propose to perform a PCS analyses on the following laboratory analytes;

- Sodium
- AST
- ALT
- CPK
- Leukocytes
- Platelets

Further, since a thorough QT study was performed (Study 2093-116) as well as a full analysis of ECG data from the Phase III studies, we do not believe that PCS analysis of ECG or vital sign data from the Phase I studies will be revealing of any systemic safety issues that may have been missed by the larger adjunctive therapy studies.

Please note that a full PCS analysis for the Bipolar Disorder studies is being provided in response to Clinical Issue #7, given the higher doses and longer exposures utilized in those studies.

Does the Division agree with this proposal?

FDA Clarification: Lab proposal: OK

EKG and Vital Sign: In phase 1 studies, for any episodes of syncope or pre-syncope, please describe drug received and whether there were accompanying VS or EKG procedures performed. If so, please comment on whether there was evidence of orthostatic hypotension or an EKG finding. If the syncope or pre-syncope was in the context of a blood draw, please just state that as the case.

Clinical Question #9, Bullet 1

FDA: There are more subject narratives in the ISS narratives for Part 1 than subjects described in the corresponding table in the SU?

Sponsor: Would the Division please provide the Safety Update Table # and identify which ISS narratives (deaths, SAEs, or discons due to AE) that are in question.

FDA clarification: Subject narratives in the ISS for part 1 are in sections 25.1.1.1, 25.1.2.1, and 25.1.3.1. Tables in the SU that display SAEs and discontinuations, respectively, are Tables 4.1.4.2-1 and 4.1.4.3-2. Table 4.1.4.2-1 of the SU indicates there were 4 placebo subjects in the pooled 301 and 302 study data with at least 1 SAE. In the ISS section 25.1.2.1, there are more than 4 placebo narratives for study 301 alone. Please compare the numbers of subject narratives in the ISS to the numbers of subjects noted in the tables referenced. Any differences should be noted. If a narrative is missing, this should be supplied. On the other hand, if a narrative is included from an event that occurred in the single-blind placebo phase or pre-dosing, please note the event and the subject number.

Please feel free to contact me if you need any further clarification.

Thanks,
Dorothy

Dorothy Demczar, PharmD
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Silver Spring, MD 20993
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From: Demczar, Dorothy
Sent: Wednesday, January 13, 2010 6:50 PM
To: 'karen.joyce@sepracor.com'
Subject: NDA 22416 - Clarification for Question #1

Hi Karen,

I am forwarding you the the CSS response (below) to your email of January 7, 2010, requesting clarification from the Division's January 4, 2010 document which detailed the Division's concerns regarding NDA 22416:

CSS Question #1

FDA: There are limitations in the design of pre-clinical abuse studies. These studies do not provide enough data to fully assess the abuse potential of eslicarbazepine acetate.

Sponsor: Could the CSS specify which studies they are referring to and provide further detail regarding the design issues that prevent a full assessment of the abuse potential of eslicarbazepine acetate?

FDA Clarification (CSS response):

Eslicarbazepine acetate has anxiolytic, sedative, and muscle relaxant properties, impairs memory and coordination, and produces physical dependence, as evidenced by the occurrence of withdrawal symptoms upon abrupt withdrawal. This particular profile resembles sedative-hypnotic drugs and in particular benzodiazepines, that are currently scheduled in the Controlled Substance Act.

Many of the preclinical abuse potential studies have limitations in design and do not provide enough data to fully assess the abuse potential of eslicarbazepine acetate:

1. The receptor binding studies do not provide K_i parameters for GABA_A receptors for α_1 , α_2 , α_3 , α_4 , α_5 , and α_6 subunits and TBOB site (chloride channel).
2. The majority of functional studies evaluating drug effects on motor performance and behavior were conducted in rats, a species exhibiting very different metabolism of the drug than humans.
3. Study # 093-873 evaluating effects of the drug on cognition in mice does not provide relevant plasma levels of the drug to enable comparison with human doses and to evaluate adequacy of the doses used.
4. The toxicity studies in rats (#093-809) and beagle dogs (# 093-817), which evaluated withdrawal symptoms, were performed in species having very different metabolism of the drug than humans.
5. The discrimination study in monkeys is invalid due to methodological defects that result in data that is not generalizable to humans.

The design of the study, in particular the choice of the training drug, timing of drug administration, and different route of drugs administration raises concerns. Midazolam is an ultra short-acting benzodiazepine, which in humans has T_{max} of $\sim 0.51 \pm 0.18$ h and half-life of $\sim 3.2 \pm 1$ h after subcutaneous injection. The sponsor did

not provide matching values in monkeys. However, after oral administration in cynomolgus monkeys Tmax was ~ 0.5-3 h.

Eslicarbazepine plasma concentrations following oral dose of SEP-0002093 in the 2 separate monkeys used for evaluation of PK parameters in this experiment had plasma peak values in range of 1h to 24 hours. Because of the individual variability noted, peak plasma values for eslicarbazepine can not be predicted for the four monkeys used in this time dependent drug discrimination paradigm; this fact is of particular concern because it invalidates the study.

CSS remains concerned as previously stated about the quality and validity of the clinical data.

Thanks,
Dorothy

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Demczar, Dorothy

From: Demczar, Dorothy
Sent: Thursday, January 21, 2010 12:55 PM
To: 'karen.joyce@sepracor.com'
Subject: NDA 22416 - Clinical- Request for Information

Follow Up Flag: Follow up
Flag Status: Red

Hi Karen,

I am forwarding a request from the clinical team to you regarding NDA 22416 (eslicarbazepine).

"The 120-day safety update includes information from 15 trials that were either ongoing or completed but not reported. Death and non-fatal SAEs are stated to be reported between the ISS cut-off date and the SU cut-off date. First, please clarify if deaths and non-fatal events up to the cut-off date of the ISS were also included or whether this is not applicable due to trial start dates. If events up to the ISS cut-off were not included, revise the listings of these events accordingly, per trial. Also, please note which trials are clinically completed and which are not. For trials that are clinically completed, please include the date of completion. Please send a listing of discontinuations secondary to an adverse event for these 15 trials, by trial and by treatment assignment (dose group of eslicarbazepine, placebo, or blinded). In order to facilitate review of your NDA, please submit as soon as possible."

Thanks,
Dorothy

Dorothy Demczar, PharmD
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Demczar, Dorothy

From: Demczar, Dorothy
Sent: Friday, January 29, 2010 12:32 PM
To: 'amy.laforte@sepracor.com'
Subject: RE: NDA 22-416 - Division response to clinical question
Follow Up Flag: Follow up
Flag Status: Red

Hello Amy,

I have the following response for you, from the medical reviewer, to your question:

The reviewer would prefer one comprehensive list of all referenced events that occurred up to the cutoff-date of the SU for these 15 trials. An accompanying dataset might facilitate review. The dataset does not need to have the notation of which trials are complete clinically, which are not, and the date of clinical completion that is requested for the listing. The listing should be by "class" of event (death, non-fatal SAE, discontinuation secondary to an AE), then by trial, then by treatment associated. Include notation of which trials are complete clinically, which are not, and the date of clinical completion, as applicable.

thanks,
Dorothy

Dorothy Demczar, PharmD
Regulatory Project Manager
Division of Neurology Products
Phone: (301) 796-2263

From: amy.laforte@sepracor.com [mailto:amy.laforte@sepracor.com]
Sent: Wednesday, January 27, 2010 4:00 PM
To: Demczar, Dorothy
Subject: FW: NDA 22-416 - Excel Spreadsheet for Serial #0024 and Clarification re 1/21/10 request for info

Hi Dorothy,

Please find attached the Excel spreadsheet supporting Serial # 0024, response to Question 1 of FDA's January 4, 2010 request for information. This spreadsheet is identical to the table-1-1-spreadsheet.pdf located in Module 1.11, but provides additional flexibility for the reviewers in the Excel format.

We are also in the process of responding to the remaining questions of January 4 (Clinical Q6 & Q7 and CSS), January 21 (Clinical), and January 25 (REMS in WORD). We did have a quick question on the January 21 request:

"The 120-day safety update includes information from 15 trials that were either ongoing or completed but not reported. Death and non-fatal SAEs are stated to be reported between the ISS cut-off date and the SU cut-off date. First, please clarify if deaths and non-fatal events up to the cut-off date of the ISS were also included or whether this is not applicable due to trial start dates. If events up to the ISS cut-off were not included, revise the listings of these events accordingly, per trial. Also, please note which trials are clinically completed and which are not. For trials that are clinically completed, please include the date of completion. Please send a listing of discontinuations secondary to an adverse event for these 15 trials, by trial and by treatment assignment (dose group of eslicarbazepine, placebo, or blinded). In order to facilitate review of your NDA, please submit as soon as possible"

We have confirmed that additional events in some of the ongoing studies that occurred prior to the ISS cut-off date were not

3/16/2010

included in the 120-day safety update nor the response to the January 4 questions just submitted in Serial 0024.

Would the reviewer prefer to be provided with one comprehensive list of all events (including events both prior to the ISS cut-off and between the ISS and SU cut-off or a supplemental list identifying only those events not reported in our response to the January 4 questions (i.e. prior to the ISS cut-off)?

Thanks,
Amy

Amy J. LaForte, Ph.D.
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Demczar, Dorothy

From: Demczar, Dorothy
Sent: Friday, February 19, 2010 6:43 AM
To: 'karen.joyce@sepracor.com'
Cc: 'amy.laforte@sepracor.com'
Subject: NDA 22416 - Non-clinical request for information

Follow Up Flag: Follow up
Flag Status: Red

Hello Karen,

I have a request for information from our nonclinical group for eslicarbazepine that I am forwarding to Sepracor. I am copying Amy on this since I've been communicating with her recently and I'm not sure if you are in the office today.

In your 26 week rat study (Study #093-810), you demonstrate that plasma oxcarbazepine concentrations measured at 26 weeks are substantially lower (2.2-4.8 fold in males; 2.8-11.2 fold in females) than the plasma concentrations observed in rats given identical doses of eslicarbazepine acetate in your 3 month (Study #093-809) and 4 week (Study #093-808) rat studies. These lower oxcarbazepine plasma concentrations occur in the absence of a substantial difference in plasma concentrations of BIA 2-005 across the three rat studies. Please provide an explanation for the substantially lower oxcarbazepine plasma concentrations in the 26 week rat study.

Thanks,
Dorothy

Dorothy Demczar, BS, PharmD
*Regulatory Project Manager
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Demczar, Dorothy

From: Demczar, Dorothy
Sent: Tuesday, February 23, 2010 6:46 PM
To: 'karen.joyce@sepracor.com'
Subject: NDA 22416 (Eslicarbazepine) - Nonclinical Request for Information

Hi Karen,

I have another request for information from the nonclinical team for Sepracor:

"In the final report for the pre- and post-natal development study in mouse (#093-839), the data provided in Table 26 (page 92 of 343) appear to be for "dydrogesterone", not BIA 2-093. Please provide a corrected table and confirm that these are the only affected data. "

Thanks,
Dorothy

Dorothy Demczar, BS, PharmD
*Regulatory Project Manager
Food and Drug Administration
Division of Neurology Products
Bldg. 22, Rm. 4211
10903 New Hampshire Ave
Silver Spring, MD 20993
Phone: (301) 796-2263
Fax: (301) 796-9842
Email: Dorothy.Demczar@fda.hhs.gov*

This e-mail message is intended for the exclusive use of the recipient(s) named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Dorothy.Demczar@fda.hhs.gov.

Demczar, Dorothy

From: Demczar, Dorothy
Sent: Thursday, March 04, 2010 7:01 AM
To: 'amy.laforte@sepracor.com'
Cc: 'karen.joyce@sepracor.com'
Subject: RE: NDA 22-416 - Notification of Preliminary findings from Study BIA-2093-124

Thanks Amy. I have forwarded your email to the team.

Dorothy

Dorothy Demczar, BS, PharmD
Regulatory Project Manager
Division of Neurology Products
Phone: (301) 796-2263

From: amy.laforte@sepracor.com [mailto:amy.laforte@sepracor.com]
Sent: Wednesday, March 03, 2010 4:32 PM
To: Demczar, Dorothy
Cc: karen.joyce@sepracor.com
Subject: NDA 22-416 - Notification of Preliminary findings from Study BIA-2093-124

Dear Dorothy,

Recognizing that the review team may be nearing the completion of their review, we would like to notify you of preliminary findings from a recently completed study that may require a change to the proposed labeling for SEP-0002093 (eslicarbazepine acetate). As the result of an EMEA post-market commitment, our partner Bial-Portela & Ca (Bial) conducted Study BIA-2093-124 to evaluate the effect of repeated administration of eslicarbazepine acetate on the pharmacokinetics of simvastatin, a substrate of CYP3A4. This was a single-center, 2-way cross-over, randomized, open-label study in which healthy subjects were administered 80 mg simvastatin, either alone or after 14 days of pretreatment with 800 mg eslicarbazepine acetate once daily. This study was noted in the 120 day safety update, but had not yet enrolled any subjects as of March 30, 2009.

This study was recently completed and approximately 2 weeks ago, we were notified by Bial that the preliminary findings indicate two unexpected results. We have reviewed a draft unaudited clinical summary report and accompanying audited pharmacokinetic report. As a result, we believe the results warrant notification to the Division and, in one case, may affect statements in the proposed labeling for safe use of the product.

1. Preliminary pharmacokinetic results demonstrate that concomitant administration of 800 mg SEP-0002093 decreased the systemic exposure of simvastatin by approximately 50%. As a result of this finding, Sepracor believes a modification to the proposed labeling is warranted to inform prescribers of the potential need to adjust the dose of concomitant simvastatin and other CYP3A4 substrates.
2. Preliminary safety results demonstrate that mild to moderate cutaneous eruptions occurred in 7 out of the 30 included subjects, all during the SEP-0002093 period. None were serious. Relationship to study drug was considered as possible in 5 cases, unlikely in 1 case, and not related in another case. In this case, we note that the proposed labeling already includes a warning regarding serious dermatological reactions in section 5.2 and rash is included in the adverse event table describing the results of the Phase 3 studies in section 6.1. Therefore, we do not believe further modification of the labeling is warranted with regard to this finding.

3/23/2010

We are currently preparing an amendment to the NDA to include revised proposed labeling and available summary reports. If you have any questions, we are available for a teleconference at your convenience.

Best regards,
Amy

Amy J. LaForte, Ph.D.
Vice President, Regulatory Affairs
Sepracor Inc.
84 Waterford Drive
Marlborough, MA 01752
(508) 787-4025
amy.laforte@sepracor.com

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3/23/2010

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22416	ORIG-1	SEPRACOR INC	SEP-0002093 ESLICARBAZEPINE ACETATE

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/s/

DOROTHY J DEMCZAR

03/24/2010

E-mailed Requests for Information and other Sponsor communication

MEMORANDUM OF TELEPHONE CONVERSATION

Date: July 22, 2009

Drug: NDA 22416 - Stedesa (eslicarbazepine)

Conversation Between:

FDA:

Norm Hershkowitz, MD, Clinical Team Leader; Teresa Podruchny, MD, Medical Officer;
Tony El Hage, PhD, DSI Inspector; Dorothy Demczar, PharmD, Regulatory PM

Sponsor: Sepracor attendees:

Stewart Mueller Senior Vice President, Regulatory Affairs and Quality Assurance

Amy LaForte, PhD Executive Director, Regulatory Affairs

Karen Joyce Associate Director, Regulatory Affairs

Jahnvi Kharidia, PhD Director, Clinical Pharmacology

Lisa Organisak, PharmD Senior Program Director

In a 7-7-09 email from the sponsor to the Division, the sponsor reported “systematic errors” in the population PK datasets of the three phase 3, epilepsy trials with regard to dosing history, demographics, and derived variables indicating the treatment dose amount and the time in study.

A teleconference was held on 7-22-09 with the sponsor in order to obtain additional details and to inquire whether such errors may have been more systematic and impacted clinical efficacy and safety datasets. The sponsor stated that this data set was different from the clinical data set because the population PK data utilizes NONMEM. The original SAS datasets were used to create the NONMEM data set. (b) (4)

(b) (4) They created their own NONMEM, which was different from the vendor ((b) (4)) that created the original NONMEM data sets for the NDA submission. The sponsor conveyed that they believe the problems are limited to this one vendor in (b) (4) ((b) (4)) who apparently manually entered data and was off by a row resulting in a “frameshift” type of error.

FDA also asked whether the efficacy studies had been audited. The sponsor stated these were audited in the previous year, that there were not problems, and re-iterated that problems were limited only to the SAS to NONMEM conversion by the vendor in (b) (4) Revised module 2/datasets are to be submitted by the end of July.

Subsequent to the teleconference, FDA sent the following email comment to the sponsor.

"At the teleconference of 7-22-09 regarding the cause of the errors in the PK datasets, our understanding is that you believe the problem was specific to data processed by a vendor in (b) (4) (b) (4) and that this problem is not more systemic and does not impact efficacy and safety datasets. Please confirm that the vendor in (b) (4) that you believe is responsible for the error(s) was not involved in the data collection or construction of any other datasets in any other studies. If this is not the case, please advise and indicate which studies and datasets were handled by this vendor. Thank you."

Teresa Podruchny, MD
Medical Officer
DNP, HFD-120

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-22416	----- ORIG-1	----- SEPRACOR INC	----- SEP-0002093 ESLICARBAZEPINE ACETATE

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/s/

DOROTHY J DEMCZAR
03/24/2010



NDA 022416

PDUFA GOAL DATE EXTENSION

Sepracor Inc.
Attention: Karen Joyce
Associate Director Regulatory Affairs
84 Waterford Drive
Marlborough, MA 01752

Dear Ms. Joyce:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Stedesa (eslicarbazepine acetate) 400 mg, 600 mg and 800 mg tablets.

On November 25, 2009, we received your November 24, 2009, major amendment (solicited) to this application that contained a response to our Biostatistics Information Request. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is April 30, 2009.

In addition, we are establishing a new timeline for communication of feedback on proposed labeling and postmarketing commitments in accordance with the "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES - FISCAL YEARS 2008 THROUGH 2012." If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by March 31, 2010.

If you have any questions, call Dorothy Demczar, PharmD, Regulatory Project Manager, at (301) 796-2263.

Sincerely yours,

{See appended electronic signature page}

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22416	ORIG-1	SEPRACOR INC	SEP-0002093 ESLICARBAZEPINE ACETATE

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/s/

RUSSELL G KATZ
12/04/2009



NDA 022416

INFORMATION REQUEST

Sepracor Inc.
Attention: Karen Joyce
Associate Director Regulatory Affairs
84 Waterford Drive
Marlborough, MA 01752

Dear Ms. Joyce:

Please refer to your New Drug Application (NDA) submitted March 29, 2009, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Stedesa (eslicarbazepine acetate) 400mg, 600mg and 800mg tablets.

We also refer to your March 29, 2009 NDA submission, containing a Risk Evaluation and Mitigation Plan.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for eslicarbazepine acetate to ensure that the benefits of the drug outweigh the increased risk of suicidal thoughts and behavior.

Your proposed REMS must include the following:

Medication Guide: As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that eslicarbazepine acetate poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of eslicarbazepine acetate. FDA has determined that eslicarbazepine acetate is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risk could affect patients' decisions to use, or continue to use eslicarbazepine acetate. FDA has also determined that eslicarbazepine acetate is a product for which patient labeling could help prevent serious adverse events.

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed eslicarbazepine acetate.

Timetable for Submission of Assessments: The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than by 18 months, 3 years, and in the 7th year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Your proposed REMS submission should include two parts: a “proposed REMS” and a “REMS supporting document.” Attached is a template for the proposed REMS that you should complete with concise, specific information (see Appendix A). Once FDA finds the content of the REMS acceptable and determines that the application can be approved, we will include this document and the Medication Guide as attachments to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

The REMS supporting document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

Your assessment of the REMS should include an evaluation of:

- a. Patients’ understanding of the serious risks of eslicarbazepine acetate
- b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
- c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

Before we can continue our evaluation of this NDA you will need to submit the proposed REMS. The proposed Risk Evaluation and Mitigation Plan that you have submitted does not contain the REMS elements that we are requiring and therefore is not sufficient.

Under 21 CFR 208.24(d), you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided. You should submit marked up carton and container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide. We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

- “Dispense the enclosed Medication Guide to each patient.” or
- “Dispense the accompanying Medication Guide to each patient.”

Prominently identify the proposed REMS submission with the following wording in bold capital letters at the top of the first page of the submission:

NDA 22-416 PROPOSED REMS

Prominently identify subsequent submissions related to the proposed REMS with the following wording in bold capital letters at the top of the first page of the submission:

NDA 22-416 PROPOSED REMS-AMENDMENT

If you do not submit electronically, please send 5 copies of your REMS-related submissions.

If you have any questions, call Dorothy Demczar, Pharm.D., Regulatory Project Manager, at (301) 796-2263

Sincerely,

{See appended electronic signature page}

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

Enclosure: Appendices A and B

APPENDIX A: MEDICATION GUIDE REMS TEMPLATE

Application number TRADE NAME (DRUG NAME)

Class of Product as per label

Applicant name

Address

Contact Information

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

List the goals and objectives of the REMS.

II. REMS ELEMENTS:

A. Medication Guide

If a Medication Guide is included in the proposed REMS, include the following:

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

B. Timetable for Submission of Assessments

For products approved under an NDA or BLA, specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments shall be no less frequent than by 18 months, 3 years, and in the 7th year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

APPENDIX B:
REMS SUPPORTING DOCUMENT TEMPLATE
MEDICATION GUIDE REMS

This REMS Supporting Document should include the following listed sections 1 through 6. Include in section 4 the reason that the Medication Guide proposed to be included in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Table of Contents
2. Background
3. Goals
4. Supporting Information on Proposed REMS Elements
 - a. Medication Guide
 - b. Timetable for Submission of Assessments of the REMS (for products approved under an NDA or BLA)
5. REMS Assessment Plan (for products approved under an NDA or BLA)
6. Other Relevant Information

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-22416	----- ORIG-1	----- SEPRACOR INC	----- SEP-0002093 ESLICARBAZEPINE ACETATE

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/s/

RUSSELL G KATZ
11/04/2009



NDA 22-416

INFORMATION REQUEST

Sepracor Inc.
Attention: Karen Joyce
Associate Director Regulatory Affairs
84 Waterford Drive
Marlborough, MA 01752

Dear Ms. Joyce:

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

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

•



If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22416	ORIG-1	SEPRACOR INC	SEP-0002093 ESLICARBAZEPINE ACETATE

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/s/

MARTHA R HEIMANN
10/28/2009
Signed for Ramesh Sood

Executive CAC

Date of Meeting: October 6, 2009

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
William Taylor, Ph.D., DSPTP, Alternate Member
Lois Freed, Ph.D., DNP, Supervisor
Christopher D. Toscano, Ph.D., DABT, DNP, Presenting Reviewer

Author of Draft: Christopher D. Toscano, Ph.D., DABT

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

NDA # 22-416

Drug Name: STEDESA (Eslicarbazepine acetate, BIA 2-093)

Sponsor: Sepracor, Inc.

Background: Eslicarbazepine acetate (BIA 2-093) is a prodrug that is hydrolyzed *in vivo* to the major active metabolite, S-licarbazepine (BIA 2-194), and two minor metabolites, R-licarbazepine (BIA 2-195) and oxcarbazepine (OXC). BIA 2-093 and its metabolites are antagonists of inactivated voltage-gated sodium channels and voltage-gated calcium channels. The proposed use of STEDESA is as an adjunctive treatment of partial-onset seizures in adults with epilepsy.

Rat Carcinogenicity Study:

The requirement for a rat carcinogenicity study was waived by the division on 7/20/2007. This decision was based on marked differences in *in vivo* metabolism data between rat and human; the rat predominantly metabolizes both BIA 2-093 and BIA 2-194 to OXC, which is a minor metabolite in humans.

Mouse Carcinogenicity Study:

CrI:CD-1 (ICR) BR VAF/Plus mice were administered BIA 2-093 at doses of 0, 100, 250, and 600 mg/kg/day by oral gavage in 0.5% hydroxypropylmethyl cellulose for 104 weeks. The high dose (HD) group was administered 250 mg/kg/day BIA 2-093 for the first week of the study and then administered 600 mg/kg/day for weeks 2-104. The dose escalation in the high dose group was performed to minimize the severe clinical signs associated with the initial administration of high doses of BIA 2-093, and was agreed upon by the ExecCAC (8/28/2003). After consulting with DNP on 7/8/2005, the Sponsor euthanized all surviving males one week before the planned terminus of the study due to the small number of surviving control animals (11 males at the beginning of week 104). All dose groups consisted of >10 animals/group at termination of the study. A majority of

the early decedents were euthanized *in extremis* due to the presentation of severe clinical signs during the study.

Mid dose males, high dose males, and high dose females exhibited statistically significant increases in the incidence of hepatic adenomas and hepatocellular carcinomas. Accompanying the hepatocellular neoplasms were dose-dependent increases in the incidence of hepatic centrilobular hypertrophy and chronic hepatitis.

Executive CAC Recommendations and Conclusions:

- The Committee concluded that the 2-year mouse carcinogenicity study was adequate and that the incidences of hepatic adenomas and hepatocellular carcinomas in males at the mid and high dose and in females at the high dose were drug related.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc: \
/Division File, DNP
Freed/Supervisor, DNP
Toscano/Reviewer, DNP
Demczar/RPM, DNP
/ASeifried, OND IO

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22416	ORIG-1	SEPRACOR INC	SEP-0002093 ESLICARBAZEPINE ACETATE

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/s/

DOROTHY J DEMCZAR
10/07/2009

DAVID JACOBSON KRAM
10/07/2009



NDA 22-416

INFORMATION REQUEST

Sepracor Inc.
Attention: Karen Joyce
Associate Director Regulatory Affairs
84 Waterford Drive
Marlborough, MA 01752

Dear Ms. Joyce:

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

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

1. With respect to all containers and closures (bottles, caps and blister packaging material) to be used in drug product packaging, provide data using the applicable USP testing (e.g. USP <661> and USP <671>) to assure suitability of the packaging.
2. Provide data to justify the use of a paddle speed of 100 rpm over the use of (b) (4) paddle speed in your dissolution method PT-PTDPE9 with respect to maintaining good discriminatory power. We are looking for evidence of the minimum paddle speed that will provide suitable dissolution characteristics in the formulation (FP) proposed for marketing.
3. Revise the dissolution limit from (b) (4) (Q) in 45 minutes to (b) (4) (Q) in 45 minutes.
4. Justify not having an upper limit on the hardness criteria for the drug product specifications or provide an appropriate upper limit.
5. (b) (4)
6. Provide representative data for the subdivision of the 600mg and 800mg tablets (e.g. weight as described for divisibility in the *Monograph on Dosage Forms: Tablets of the Ph. Eur.*). Also provide comparison dissolution data for the broken tablets versus full tablets. Provide friability data for the broken tablets.

7. [REDACTED] (b) (4)
8. Provide samples of each tablet strength for visual inspection.
9. Provide stability data for the configuration of 60-count, 85cc bottle for the 600mg strength. [REDACTED] (b) (4)

[REDACTED] See ICH Guidance Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Product (e.g. II.C.1.b. Container Closure Sizes and/or Fills (2.3.1.2) - ... if a bracketing design is considered where both container size and fill vary, it should not be assumed that the largest and smallest containers represent the extremes of all packaging configurations. Care should be taken to select the extremes by comparing the various characteristics of the container closure system that may affect product stability. These characteristics include container wall thickness, closure geometry, surface area to volume ratio, headspace to volume ratio, water vapor permeation rate or oxygen permeation rate per dosage unit or unit fill volume, as appropriate.)

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

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

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/s/

RAMESH K SOOD
08/31/2009



NDA 22-416

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Sepracor, Inc.
84 Waterford Drive
Marlborough, Massachusetts 01752-7010

ATTENTION: Karen Joyce
Associate Director, Regulatory Affairs

Please refer to your New Drug Application (NDA) dated March 29, 2009, received March 30, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for eslicarbazepine acetate tablets, 400 mg, 600 mg, and 800 mg.

We also refer to your April 15, 2009, correspondence, received April 15, 2009, requesting review of your proposed proprietary name, Stedesa. We have completed our review of the proposed proprietary name, Stedesa and have concluded that it is acceptable.

The proposed proprietary name, Stedesa, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your April 15, 2009 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, call Laurie Kelley, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5068. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Dorothy Demczar, at (301) 796-2263.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

Carol Holquist
7/10/2009 03:04:56 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 022416

Sepracor Inc.
Attention: Karen Joyce
Associate Director Regulatory Affairs
84 Waterford Drive
Marlborough, MA 01752

Dear Ms. Joyce:

Please refer to your new drug application (NDA) dated March 29, 2009, received March 30, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Stedesa (eslicarbazepine acetate) 400 mg, 600 mg and 800 mg tablets.

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 January 30, 2010.

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 December 31, 2009.

During our filing review of your application, we have identified the following potential review issues:

Clinical

1. Table 3.1-2 in the ISS provides exposure in strata for dose and duration. Based on our preliminary review, exposure to support the expected usual dose of 800 mg appears borderline, in terms of 6 month ICH numbers. Whether this exposure is adequate will be a matter of detailed review of your data.

2. Moreover, in view of the data integrity problems identified for study 303, an additional issue is the acceptability of the contribution of safety data in study 303. We also note that there may not be adequate support for 1200 mg dosing.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

Clinical

1. Provide the total number of non-fatal SAEs in the entire development program of Eslicarbazepine Acetate. Then provide the number by phase (phase 1, 2, 3) and per study. Please provide a similar list for the discontinuations secondary to an adverse event. If this information is in the submission already, please reference the document and page numbers.
2. Datasets for some of the safety data do not contain a variable that identifies what treatment the subject was on at the time of the event. If there is another dataset with this information, other than an ISS dataset, please provide a reference. Otherwise, please submit new datasets with a variable that allows for identification of the treatment the patient was taking at the time of the event.
 - a. For study 301 part 1, the datasets `adversed.xpt`, `adverse.xpt`, and `sae.xpt` and the lab and EKG datasets do not appear to allow one to identify the treatment group.
 - b. For study 301 part 2, the study started at 800 mg, but patients could titrate up or down in 400 mg intervals to dose between 400 mg and 1200 mg. The datasets of adverse events, labs, and EKG findings do not have treatment group information.
 - c. The datasets of adverse events, laboratory data, and EKG data for studies 201, 202, and 203 do not have a variable to allow for identification of the treatment group the patient was on at the time of the data collection.
3. The clinical overview document states that your view is that study 303 is not “sufficiently compliant” to be formally relied upon for a conclusion of safety and efficacy, but that the study can be supportive. On June 3, 2009, in advance of the teleconference we had with you to discuss this on June 4, 2009, you submitted a document detailing problems found at the Mexican sites. Please submit this document formally to the NDA with the cover letter noting that the document is identical to the emailed version of June 3, 2009. As per the teleconference discussion, please send the following:
 - a. A copy of the CRO site initiation and monitoring reports as well as the Sponsor audit reports; both Bial and your audit reports.
 - b. A document detailing each study (and site) and who monitored at primary and secondary levels of monitoring. Later this was noted to be in the NDA submission and the request withdrawn. However, upon re-evaluation of the submission, it appears

- Sepracor did not audit any of the phase 1 studies, the pediatric epilepsy study, or the bipolar studies. Please confirm or provide the information from those audits, as per item 3a in this list.
- c. An analysis of the issues of data integrity in the complete research program. The analysis should include a discussion of differences in findings of audits between auditors and address why the study conduct and data collection at the Mexican sites was apparently so unstructured. You should specifically address, and provide adequate support, as to why you consider the problem isolated to the Mexican sites.
 - d. A description of the missing adverse events in study 303, sites 702 and 703 and any other AEs from this study of which we are not aware, if applicable.
 - e. Provide an ISS like report that includes re-analyses comparing study 303 data to combined data from studies 301 and 302 for outliers, central tendency, SAEs, and discontinuations secondary to adverse events. Also, please include the exposure information you provided verbally in the teleconference of the numbers exposed for 6 months and 1 year if all study data for 303 are dropped. Additionally, please note the dose as well as duration. It was agreed in the teleconference that these re-analyses and all safety data for the 120-day update would be submitted by the end of August.
4. Study reports 301 and 302 have sections (for example, the investigators' curriculum vitae) that are not searchable. Please note, for each study report and for the ISS and ISE, the page numbers of sections that are not searchable. If all pages in a study report or ISS/ISE are searchable, please state so.
 5. Table 2 of the financial disclosure document (financial-cert.pdf) indicates you were unable to obtain disclosure information for a Principal Investigator (PI) and a sub-investigator of this PI in study 302 (Prof. Dr. Perju-Dumbrava Lacramioara (Principal Investigator) (b) (6) (sub-investigator for Dr. Perju-Dumbrava Lacramioara). Please explain why you were not able to obtain this information. Also, through comparison of the lists of investigators found in the document, tabular-listing.pdf, with the information in the document, financial-cert.pdf, there appear to be other investigators missing information: Study 301, (b) (6)
(b) (6)
Study 302, (b) (6)
(b) (6). Please address this issue.
 6. Submit a pediatric development plan for the pediatric age groups not covered by the partial waiver request. The pediatric drug development plan must address the indication proposed in this application.

Chemistry, Manufacturing and Control

1. With respect to product labeling and nomenclature, clarify whether the name eslicarbazepine acetate has been submitted to, and accepted by, the United States

Adopted Names (USAN) Council. If not, you will need to apply for designation of eslicarbazepine acetate as the USAN.

2. To assist in our review, please provide copies of the drug product stability data tables in Adobe (pdf) or Microsoft Excel (xls) format.

Clinical Pharmacology

1. Assay validation report for lamotrigine (Study 119) and topiramate (Study 120) could not be located. Please provide the location in the EDR or submit the report if not provided in the original submission.
2. Assay validation for other AEDs evaluated in the population analysis should also be submitted.
3. The population PK/PD datasets appear to be misplaced for the PK/PD study report (Pooled population PK/PD analysis of eslicarbazepine acetate in patients with epilepsy: SCO/BIA-2093-301, (b) (4) BIA-2093-302 and (b) (4) BIA-2093-303. Document No: EMFFR2007/13/00 ESLEPI32) and, are instead, located in the folder of emffr2007-09-01. Please generate a separate PK/PD folder to store the datasets or create a proper hyperlink to locate the datasets.

Controlled Substance

1. Pharmacokinetic and Pharmacodynamic Section
 - a. An additional GABA_A binding study previously requested by CSS is not present and is needed.
 - b. In the receptor binding study, some receptor data are missing: dopamine D5 (related to cocaine, heroine abuse), adrenergic receptors alpha 1 and beta (present in cortex, hippocampus), muscarinic M2 (present in basal forebrain, thalamus), M3 (present in cortex, hippocampus, thalamus), nicotinic receptor (related to PCP abuse; units not listed either), histamine H2 (present in basal ganglia, amygdala, cortex).
 - c. In the receptor binding study Ki values are not present. As you agreed in the communication from November 13, 2008 (Memorandum of Meeting Minutes), these data will be provided after submission of the NDA. The Ki values for the following receptors need to be provided: all GABA-ergic, serotonergic, dopaminergic and adenosine.
2. Animal Abuse Potential Studies Section
 - a. Discrimination Study in rhesus monkeys requested by CSS is not present and is needed for the abuse potential assessment. As you agreed in the communication from November 13, 2008 (Memorandum of Meeting Minutes), these data will be provided during the NDA review.
 - b. Self-administration study in appropriate species is not present and is requested. (You refer to two published discrimination studies in rats with carbamazepine versus chlordiazepoxide or diazepam and one self-administration study in monkeys with oxcarbazepine). The self-administration study in appropriate species was requested by

CSS in the communication from November 13, 2008 (Memorandum of Meeting Minutes).

3. Clinical Studies

- a. There is no cumulative table of Adverse Events and Adverse Events related to abuse potential summarizing all studies. During the drug development process, multiple MedDRA versions (from 4 to 10) were used. We remain concerned that many adverse events related to abuse potential were not captured (or were collected inconsistently at the various research sites) during these studies. Describe training provided on MedDRA at all sites to demonstrate their ability to assess the terms related to abuse and report them. Provide the methodology used for translating all of the different versions of MedDRA into the most recent version contained in the submission and demonstrate that the applicable terms were handled consistently in the different MedDRA versions.
- b. Provide a tabulation of patients who were discontinued or dropped for reasons related to potential abuse and diversion. Provide case report forms for each of these patients. This request relates to specific terms that should be included in your search and include: abuse, misuse, overdose, and noncompliance to drug dosing, missing or lost drug or drug not accounted for, and/or aberrant behaviors. In addition, all reports of discontinuation or drop outs due to administrative reasons or unknown should include detailed explanations.

4. Submit an updated scheduling proposal, as appropriate, based on the requested information.

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

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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver of pediatric studies in patients 0 to 1 month of age for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We also acknowledge receipt of your request for a partial deferral of pediatric studies in patients 1 month up to 17 years of age for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, call Dorothy Demczar, Pharm.D., Regulatory Project Manager, at (301) 796-2263.

Sincerely,

{See appended electronic signature page}

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

Russell Katz
6/12/2009 02:39:57 PM



NDA 22-416

NDA ACKNOWLEDGMENT

Sepracor
Attention: Karen Joyce
Associate Director Regulatory Affairs
84 Waterford Drive
Marlborough, MA 01752

Dear Ms. Joyce:

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

Name of Drug Product: SEP-0002093 (eslicarbazepine acetate) 400, 600 and 800 mg tablets

Date of Application: March 29, 2009

Date of Receipt: March 30, 2009

Our Reference Number: NDA 22-416

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 May 29, 2009 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/oc/datacouncil/spl.html>. 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.

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
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, call Dorothy Demczar, PharmD, Regulatory Project Manager, at (301) 796-2263.

Sincerely,

{See appended electronic signature page}

Dorothy Demczar, PharmD
Regulatory Project Manager
Division of Neurology
Office of Drug Evaluation 1
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/

Dorothy Demczar
5/8/2009 03:31:23 PM