

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**202834Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 202834

SUPPL #

HFD # 120

Trade Name Fycompa

Generic Name perampanel

Applicant Name Eisai, Inc.

Approval Date, If Known October 22, 2012

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES  NO

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

505(b)(1)

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

YES  NO

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

N/A

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:

N/A

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

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



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

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

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

YES  NO

If yes, explain:

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Name of person completing form: Stephanie N. Parncutt, MHA  
Title: Regulatory Health Project Manager  
Date: October 2012

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

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

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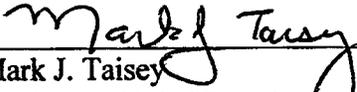
/s/

-----  
STEPHANIE N PARNCUTT  
10/23/2012

RUSSELL G KATZ  
10/28/2012

**DEBARMENT CERTIFICATION**

Eisai 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 NDA 202834 for perampanel tablets.

  
\_\_\_\_\_  
Mark J. Taisey  
President, Global Regulatory Affairs CFU  
Eisai Inc.

28 Apr 2011  
Date

# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION<sup>1</sup>

NDA # 202834 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Fycompa Established/Proper Name: perampanel Dosage Form: Tablets		Applicant: Eisai, Inc. Agent for Applicant (if applicable): Heather A. Bradley, MPH
RPM: Stephanie N. Parcutt, MHA		Division: Division of Neurology Products
<p><b><u>NDA and NDA Efficacy Supplements:</u></b></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><b><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></b></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><b><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input type="checkbox"/> No changes   <input type="checkbox"/> Updated   Date of check:</p> <p><b>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.</b></p>
❖ Actions		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>October 22, 2012</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input type="checkbox"/> None   RTF on 7/21/11

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.

<sup>2</sup> 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 <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a>). If not submitted, explain _____</p>	<p><input type="checkbox"/> Received</p>
<p>❖ Application Characteristics<sup>3</sup></p> <p>Review priority: <input checked="" type="checkbox"/> Standard <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 <span style="margin-left: 200px;">BLAs: Subpart E</span>  <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <span style="margin-left: 100px;"><input type="checkbox"/> Accelerated approval (21 CFR 601.41)</span>  <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <span style="margin-left: 100px;"><input type="checkbox"/> Restricted distribution (21 CFR 601.42)</span>                  Subpart I <span style="margin-left: 200px;">Subpart H</span>  <input type="checkbox"/> Approval based on animal studies <span style="margin-left: 100px;"><input type="checkbox"/> Approval based on animal studies</span></p> <p><input type="checkbox"/> Submitted in response to a PMR <span style="margin-left: 200px;">REMS: <input type="checkbox"/> MedGuide</span>  <input type="checkbox"/> Submitted in response to a PMC <span style="margin-left: 100px;"><input type="checkbox"/> Communication Plan</span>  <input type="checkbox"/> Submitted in response to a Pediatric Written Request <span style="margin-left: 100px;"><input type="checkbox"/> ETASU</span>  <span style="margin-left: 300px;"><input checked="" type="checkbox"/> MedGuide w/o REMS</span>  <span style="margin-left: 300px;"><input checked="" type="checkbox"/> REMS not required</span></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>	
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> <li>• Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<ul style="list-style-type: none"> <li>• Press Office notified of action (by OEP)</li> </ul>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<ul style="list-style-type: none"> <li>• Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<p><input type="checkbox"/> None  <input checked="" type="checkbox"/> HHS Press Release  <input type="checkbox"/> FDA Talk Paper  <input type="checkbox"/> CDER Q&amp;As  <input type="checkbox"/> Other</p>

<sup>3</sup> 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"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>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></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(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></li> </ul>	
<ul style="list-style-type: none"> <li>(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></li> </ul>	
<ul style="list-style-type: none"> <li>(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></li> </ul>	
<ul style="list-style-type: none"> <li>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></li> </ul>	<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"> <li>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.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>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.</li> </ul>	
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> 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).</li> </ul>	
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> 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></li> </ul>	

- [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?

(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)?

*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?

(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)?

*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>	
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**CONTENTS OF ACTION PACKAGE**

❖ Copy of this Action Package Checklist <sup>4</sup>	Included
<b>Officer/Employee List [TAB T]</b>	
❖ 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> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
<b>Action Letters [TAB U]</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Approval 10/22/2012 Refuse to File 7/21/2011
<b>Labeling [TAB V]</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	December 22, 2011
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	May 25, 2011
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	Potiga (ezogabine) last approved label March 19, 2012

<sup>4</sup> Fill in blanks with dates of reviews, letters, etc.

<p>❖ 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>)</p>	<p><input checked="" type="checkbox"/> Medication Guide  <input type="checkbox"/> Patient Package Insert  <input type="checkbox"/> Instructions for Use  <input type="checkbox"/> Device Labeling  <input type="checkbox"/> None</p>
<ul style="list-style-type: none"> <li>• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	<p>See December 22, 2011 label</p>
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<p>See May 25, 2011 label</p>
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	<p>See Potiga (ezogabine) label</p>
<p>❖ Labels (<b>full color</b> carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)</p>	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	<p>July 2, 2012</p>
<p>❖ Proprietary Name</p> <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> <li>• <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></li> </ul>	<p>Proprietary Name Granted Letter April 11, 2012</p> <p>Proprietary Name Review April 11, 2012 and August 13, 2012</p>
<p>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</p>	<p><input checked="" type="checkbox"/> RPM <b>April 10, 2012</b>  <input checked="" type="checkbox"/> DMEPA <b>June 19, 2012;</b>  <b>October 9, 2012; October 18, 2012</b>  <input checked="" type="checkbox"/> DMPP/PLT (DRISK) <b>October 3, 2012</b>  <input checked="" type="checkbox"/> ODPD (DDMAC) <b>October 18, 2012; October 22, 2012</b>  <input checked="" type="checkbox"/> SEALD <b>October 22, 2012</b>  <input checked="" type="checkbox"/> CSS (See CSS Review)</p>
<p><b>Administrative / Regulatory Documents [TAB W]</b></p>	

<ul style="list-style-type: none"> <li>❖ Administrative Reviews (e.g., RPM Filing Review<sup>5</sup>/Memo of Filing Meeting) (indicate date of each review)</li> <li>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</li> <li>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (indicate date)</li> </ul>	<p>CMC Filing Review <b>June 20, 2011</b>                  PharmTox Filing Review <b>July 15, 2011</b>                  Clinical Safety Filing Review <b>August 3, 2011</b>                  RPM Filing Review <b>December 28, 2011</b>                  Clinical Pharmacology Filing Review <b>December 30, 2011</b>                  PharmTox Filing Review <b>January 10, 2012</b>                  Clinical Safety Filing Review <b>February 7, 2012</b>                  RPM Filing Review <b>March 6, 2012</b></p> <p><input checked="" type="checkbox"/> Not a (b)(2)  <input checked="" type="checkbox"/> Not a (b)(2)</p>
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (signed by Division Director)</li> </ul>	<p><input checked="" type="checkbox"/> Included</p>
<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents  <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></li> </ul>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p>
<ul style="list-style-type: none"> <li>• This application is on the AIP                         <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (indicate date)</li> <li>○ If yes, OC clearance for approval (indicate date of clearance communication)</li> </ul> </li> </ul>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p><input type="checkbox"/> Not an AP action</p>
<ul style="list-style-type: none"> <li>❖ Pediatrics (approvals only)                         <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>August 29, 2012</u>                                  If PeRC review not necessary, explain: <u>N/A</u></li> <li>• Pediatric Page/Record (approvals only, must be reviewed by PERC before finalized)</li> </ul> </li> </ul>	<p><input checked="" type="checkbox"/> Included</p>
<ul style="list-style-type: none"> <li>❖ 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)</li> </ul>	<p><input checked="" type="checkbox"/> Verified, statement is acceptable</p>
<ul style="list-style-type: none"> <li>❖ Outgoing communications (letters, including response to FD RR (do not include previous action letters in this tab), emails, faxes, telecons)</li> </ul>	<p>NDA Acknowledgement <b>July 12, 2011</b>                  Mtg. Request Granted <b>August 25, 2011</b>                  Ack. Resubmission Following RTF <b>January 3, 2012</b>                  Information Requests (4): <b>January 26, 2012</b>                  Change of Applicant Name/Address: <b>February 14, 2012</b>                  Methods Validation Request : <b>February 17, 2012</b>                  Information Request: <b>March 1, 2012</b></p>

<sup>5</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

	<p>Filing Issues Identified: <b>March 2, 2012</b>                  Methods Validation Received: <b>March 23, 2012</b>                  Information Requests (4): <b>April 10, 2012</b>                  Information Request: <b>April 16, 2012</b>                  Information Requests (2): <b>May 15, 2012</b>                  CMC Information Request: <b>June 7, 2012</b>                  Information Request: <b>June 14, 2012</b>                  Information Requests (2): <b>June 19, 2012</b>                  Information Requests (2): <b>June 26, 2012</b>                  Labeling PMR/PMC Discussion Comments: <b>June 26, 2012</b>                  Information Request: <b>July 2, 2012</b>                  Information Requests (3): <b>July 9, 2012</b>                  Information Requests (2): <b>July 31, 2012</b>                  Information Request: <b>August 20, 2012</b>                  Information Request: <b>September 4, 2012</b>                  Information Requests (2): <b>September 13, 2012</b>                  DSI Letter : <b>October 1, 2012</b>                  Information Request: <b>October 11, 2012</b>                  Methods Validation Request : <b>October 12, 2012</b>                  DSI Letter : <b>October 18, 2012</b></p>
<p>❖ Internal memoranda, telecons, etc.</p>	<p>Biostatistic IV Consult: <b>June 6, 2011</b>                  CSS Consult: <b>June 6, 2011</b>                  PMHS Consult: <b>June 6, 2011</b>                  QT-IRT Consult: <b>July 7, 2011</b>                  DDMAC Consult: <b>July 14, 2011</b>                  Biostatistic IV Consult: <b>December 28, 2011</b>                  CSS Consult: <b>December 28, 2011</b>                  PMHS Consult: <b>December 28, 2011</b>                  DDMAC Consult: <b>December 28, 2011</b>                  PLT Consult: <b>January 3, 2012</b>                  Methods Validation Consult: <b>February 9, 2012</b>                  DSI Consult: <b>March 5, 2012</b>                  DSI Memo: <b>March 6, 2012</b>                  DSI Consult: <b>April 18, 2012</b>                  Methods Validation Consult: <b>April</b></p>

	<b>27, 2012</b> QT-IRT Consult: <b>June 11, 2012</b> ONDQA Tcon: <b>August 9, 2012</b> ONDQA Memo: <b>August 28, 2012</b>
❖ Minutes of Meetings	
• Regulatory Briefing ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg
• Pre-NDA/BLA meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg
• EOP2 meeting ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> December 5, 2007
• Other milestone meetings (e.g., EOP2a, CMC pilots) ( <i>indicate dates of mtgs</i> )	RTF Mtg: <b>September 26, 2011</b>
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	N/A
• 48-hour alert or minutes, if available ( <i>do not include transcript</i> )	N/A
<b>Decisional and Summary Memos [TAB X]</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> <b>October 22, 2012</b>
Division Director Summary Review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> <b>October 22, 2012</b>
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> <b>October 22, 2012</b>
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> <b>October 22, 2012 (9 PMR's)</b>
<b>Clinical Information<sup>6</sup> [TAB Y]</b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	Clinical Safety <b>October 1, 2012</b>
• Clinical review(s) ( <i>indicate date for each review</i> )	Clinical Safety <b>August 22, 2012</b> Clinical: <b>October 19, 2012</b>
• 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 Cross-Discipline Team Leader Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> PEDS Review <b>August 1, 2011; October 22, 2012</b> <input checked="" type="checkbox"/> QT/IRT Review <b>December 6, 2011</b> <input checked="" type="checkbox"/> QT/IRT Review <b>July 27, 2012</b>
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> CSS Review <b>April 20, 2012</b> <input checked="" type="checkbox"/> CSS Review <b>August 30, 2012</b> <input checked="" type="checkbox"/> CSS Stat Review <b>September 17, 2012</b>

<sup>6</sup> Filing reviews should be filed with the discipline reviews.

❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>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>)</li> </ul>	None None <input checked="" type="checkbox"/> DRISK Review <b>October 3, 2012</b>
❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input checked="" type="checkbox"/> DSI Letters – See Outgoing Communications <input checked="" type="checkbox"/> DSI Review <b>September 19, 2012</b>
<b>Clinical Microbiology</b> <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
<b>Biostatistics [TAB Z]</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> See Biometrics Review
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> See Biometrics Review
Statistical Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> Biometrics Review <b>August 30, 2012</b>
<b>Clinical Pharmacology [TAB A]</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> October 19, 2012
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> See October 22, 2012 Review
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> December 30, 2011; October 22, 2012
❖ DSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of DSI letters</i> )	<input checked="" type="checkbox"/> DSI Review March 6, 2012 <input checked="" type="checkbox"/> DSI Review August 29, 2012
<b>Nonclinical [TAB B]</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> October 18, 2012
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> August 29, 2012
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> August 22, 2012
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> October 24, 2012
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> IND December 18, 2003; NDA July 5, 2012 Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary ( <i>include copies of DSI letters</i> )	<input checked="" type="checkbox"/> None requested

<b>Product Quality [TAB C]</b>		<input type="checkbox"/> None
❖ <b>Product Quality Discipline Reviews</b>		
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/>	October 11, 2012
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/>	None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/>	August 16, 2012; August 22, 2012
❖ <b>Microbiology Reviews</b>		
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/>	Not needed
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		
❖ <b>Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i></b>		
	<input checked="" type="checkbox"/>	None
❖ <b>Environmental Assessment (check one) (original and supplemental applications)</b>		
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>		Review Date August 16, 2012
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>		
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>		
❖ <b>Facilities Review/Inspection</b>		
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(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<sup>7</sup>)</i>		Date completed: October 10, 2012 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>		<input type="checkbox"/> Completed <input checked="" type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

<sup>7</sup> 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.



NDA 202834

**REQUEST FOR METHODS  
VALIDATION MATERIALS**

Eisai, Inc.  
Attention: Heather A. Bradley, MPH  
Senior Manager, Regulatory Affairs  
100 Tice Boulevard  
Woodcliff Lake, NJ 07667

Dear Ms. Bradley:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Fycompa (perampanel tablets) 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg tablets.

We will be performing methods validation studies on Fycompa (perampanel tablets) 2 mg and 12 mg tablets, as described in NDA 202834.

In order to perform the necessary testing, we request the following sample materials and equipments:

**Method Current Version**

Residual elements drug substance

**Samples and Reference Standards**

2 g Perampanel drug substance

Please include the MSDS and the Certificates of Analysis for the sample.

Forward these materials via express or overnight mail to:

Food and Drug Administration  
Attn: Sean Ryan  
District Office and Lab – Kansas City  
11510 W. 80<sup>th</sup> Street – Lab  
Lenexa, KS 66214

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Michael L. Trehy  
MVP coordinator  
Division of Pharmaceutical Analysis, HFD-920  
Office of Testing and Research  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MICHAEL L TREHY  
10/12/2012

**From:** [Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)  
**To:** [Parncutt\\_Stephanie](mailto:Parncutt_Stephanie)  
**Subject:** Re: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets  
**Date:** Thursday, October 11, 2012 8:27:51 AM

---

Received, thanks.

Heather A. Bradley, MPH  
Associate Director, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677  
Tel: 201-949-4691  
Cell: (b) (6)  
Fax: 201-949-4595  
[heather\\_bradley@eisai.com](mailto:heather_bradley@eisai.com)

**From:** "Parncutt, Stephanie" <Stephanie.Parncutt@fda.hhs.gov>  
**To:** "Heather\_Bradley@Eisai.com" <Heather\_Bradley@Eisai.com>  
**Date:** 10/10/2012 06:03 PM  
**Subject:** FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

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Attached is a request from the Division of Medication Error Prevention and Analysis related to their ongoing review of the FYCOMPA application (N 202-834). Please submit your response to this request in electronic archival format as an amendment to the above NDA. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

[\\* Please see the comments below from the Division of Medication Error Prevention and Analysis:](#)

#### **A. Container Labels and Professional Sample Blister Pack and Carton Labeling**

1. The proprietary name is presented in two different font colors "Fyc" in red and "compa" in green. Consequently, the use of two colors highlights and may bring prominence to only a portion of the name. Additionally, the use of two colors in the proprietary name incorporates similar principles of TallMan lettering which is typically reserved for differentiating known look-alike established name pairs or in rare circumstances proprietary name pairs to help reduce the risk of name confusion resulting in medication error. Since Fycompa is not a name that has been involved in name confusion, the differentiating color of the "Fyc" portion and the "compa" portion is inappropriately applied. Therefore, the name should be presented with the use of one unique color, preferably not one of the colors utilized for strength differentiation.

2. In the proprietary name, the bottom of the letter "c" is extended with the use of a sweeping

graphic line that intersects the letter “o” and sweeps above the letters that follow. The graphic line represents intervening matter that decreases the readability of the proprietary name. Remove this sweeping graphic line from the proprietary name.

3. The “Rx Only” statement is too prominent. Debold the “Rx Only” statement.
4. The (b) (4) symbol is too prominent. Decrease the size of the (b) (4) symbol.

## **B. Professional Sample Blister Pack**

We find the original layout of the tablets in a straight line to be less confusing and less error-prone as compared to the circular layout of the tablets in the revised blister pack. We recommend the use of the original layout. However, if that is not feasible, we provide the following recommendations for the revised presentation.

1. Revise the statement (b) (4) to read “Take one tablet orally once daily at bedtime” for increased clarity.
2. The light green font used for the days of the week lack sufficient contrast against the green background. For days 1 through 7 font color, consider using the same light orange color that used for the 2 mg strength. For days 8 through 14 font color, consider using the same dark orange color that is used for the 4 mg strength. This may help to improve contrast and further help to differentiate the Week 1 and Week 2 regimens.
3. Add the instructions for removing the tablets from the blister pack to the left inside panel in order to have the instructions where they are more readily seen.
4. The 2-D artwork shows brackets around the tablets. Please clarify whether or not these represent actual physical barriers on the blister pack.

Please respond to this request ASAP; if you have any questions, please contact me to discuss.

-----  
Stephanie N. Parcutt, 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.parcutt@fda.hhs.gov](mailto:stephanie.parcutt@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 [stephanie.parcutt@fda.hhs.gov](mailto:stephanie.parcutt@fda.hhs.gov).

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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STEPHANIE N PARNCUTT  
10/11/2012

**From:** [Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)  
**To:** [Parncutt\\_Stephanie](mailto:Parncutt_Stephanie)  
**Subject:** RE: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets  
**Date:** Thursday, September 06, 2012 10:37:43 AM

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Hi Stephanie,  
Confirming receipt, thanks.

Heather A. Bradley, MPH  
Associate Director, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677  
Tel: 201-949-4691  
Cell: (b) (6)  
Fax: 201-949-4595  
[heather\\_bradley@eisai.com](mailto:heather_bradley@eisai.com)

From: "Parncutt, Stephanie" <Stephanie.Parncutt@fda.hhs.gov>  
To: "Heather\_Bradley@Eisai.com" <Heather\_Bradley@Eisai.com>  
Date: 09/05/2012 03:59 PM  
Subject: RE: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

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[Heather,](#)

[Please see Clinical Pharmacology's additional requests:](#)

- 1. Please clarify whether internal standard was used in the bioanalytical method which was used to analyze carbamazepine and 10,11-epoxide carbamazepine plasma concentrations for your study E2007-E044-006.**
- 2. Please provide the bioanalytical report for measurements of 6- $\beta$ -hydroxycortisol and cortisol in urine samples collected for study E2007-E044-006.**

[Please confirm receipt. Thank you,](#)

[Stephanie](#)

---

**From:** [Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com) [[mailto:Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)]  
**Sent:** Wednesday, September 05, 2012 11:35 AM  
**To:** Parncutt, Stephanie  
**Subject:** RE: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

Dear Stephanie,  
In response to the Clinical Pharmacology Information request received on 31 Aug, attached are the

requested bioanalytical report and figures that have been re-created for improved readability. I will submit an amendment with archive copies of both.

Regards,  
Heather

Heather A. Bradley, MPH  
Associate Director, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677  
Tel: 201-949-4691  
Cell: (b) (6)  
Fax: 201-949-4595  
heather\_bradley@eisai.com

From: "Parncutt, Stephanie" <Stephanie.Parncutt@fda.hhs.gov>  
To: "Heather\_Bradley@Eisai.com" <Heather\_Bradley@Eisai.com>  
Date: 08/31/2012 01:19 PM  
Subject: RE: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

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Heather,

Please see Clinical Pharmacology's additional requests:

**1. Please provide bioanalytical report for (b) (4) bioanalytical method no: 004/003 which you used to analyze carbamazepine and its metabolite for your study E2007-044-006. If you already submitted the report, please provide the location.**

**2. The figures on page 240-243 of study report of E2007-044-002 (total page 4390) were not readable. Please upload the correct figures.**

Please confirm receipt. Thank you,

Stephanie

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**From:** Heather\_Bradley@Eisai.com [[mailto:Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)]  
**Sent:** Tuesday, August 28, 2012 4:05 PM  
**To:** Parncutt, Stephanie  
**Subject:** Re: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

Received, thank you.

Heather A. Bradley, MPH

Associate Director, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677  
Tel: 201-949-4691  
Cell: (b) (6)  
Fax: 201-949-4595

heather\_bradley@eisai.com

From: "Parncutt, Stephanie" <Stephanie.Parncutt@fda.hhs.gov>  
To: "Heather\_Bradley@Eisai.com" <Heather\_Bradley@Eisai.com>  
Date: 08/28/2012 03:53 PM  
Subject: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

---

Attached is a request from the Clinical Pharmacology team related to their ongoing review of the FYCOMPA application (N 202-834). Please submit your response to this request in electronic archival format as an amendment to the above NDA. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

\* [Please see the comments below from the Clinical Pharmacology team reviewer:](#)

**You only provided partial validation report for bioanalytical assay (b) (4) 101-001/101-001MU used to analyze urine samples. Though you provided some information in summary of biopharmaceutical studies and analytical methods such as accuracy and precision, you need to provide the validation report containing results in detail.**

Please respond to this request within 7 to 10 business days; if you are unable to meet this timeframe, please contact me to discuss.

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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-----  
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/s/  
-----

STEPHANIE N PARNCUTT  
09/13/2012

**From:** [Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)  
**To:** [Parncutt\\_Stephanie](mailto:Parncutt_Stephanie)  
**Subject:** Re: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets  
**Date:** Tuesday, September 04, 2012 11:07:00 AM

---

Hi Stephanie,

Received, thank you. The provided attachment makes reference to the fact that labeling revisions, presumably by disciplines other than CMC are underway. Can you confirm that is the case? In the filing communication letter it states that we should receive the label by September 22nd. Is that still the target date? Is there any indication that the review clock will be extended based on the requests and responses we've provided to date? Any information you can share would be appreciated.

Regards,  
Heather

Heather A. Bradley, MPH  
Associate Director, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677  
Tel: 201-949-4691  
Cell: (b) (6)  
Fax: 201-949-4595  
[heather\\_bradley@eisai.com](mailto:heather_bradley@eisai.com)

**From:** "Parncutt, Stephanie" <[Stephanie.Parncutt@fda.hhs.gov](mailto:Stephanie.Parncutt@fda.hhs.gov)>  
**To:** "Heather\_Bradley@Eisai.com" <[Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)>  
**Date:** 09/04/2012 10:31 AM  
**Subject:** FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

---

Attached is a request from the Chemistry, Manufacturing, and Controls team related to their ongoing review of the FYCOMPA application (N 202-834). Please submit your response to this request in electronic archival format as an amendment to the above NDA. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

[\\* Please see the attachment below from the Chemistry, Manufacturing and Controls team reviewer:](#)

Please respond to this request within 7 to 10 business days; if you are unable to meet this timeframe, please contact me to discuss.

Thank you,

~~~~~  
[Stephanie N. Parncutt, MHA](mailto:Stephanie.N.Parncutt@FDA)  
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](mailto:stephanie.parncutt@fda.hhs.gov)

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[attachment "(8-30-12)List of changes to SPL text.doc" deleted by Heather Bradley/RIG/EisaiInc]

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*Please refer to Module 1.14.1.3 entitled “Draft Labeling Text”, from your December 22, 2012 submission. Please also refer to the Proposed Labeling Text (SPL). Please note, we are currently working on the Package Insert (PI) language and such language is not part of this request. Our Chemistry, Manufacturing and Control team has included the following list of changes to be made in the Proposed Labeling text (SPL) by Eisai, Inc.*

## **2 mg Tablets**

### Inactive ingredients:

[Ferric oxide \(Yellow\)](#) - should be added

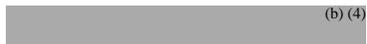
 <sup>(b) (4)</sup> - should be removed from the list

### Size of tablets

6.6 mm instead of  <sup>(b) (4)</sup>

## **4 mg Tablets**

### Inactive ingredients:

 <sup>(b) (4)</sup> - should be removed from the list

## **6 mg Tablets**

### Inactive ingredients:

[Microcrystalline cellulose](#) - should be added to the list

 <sup>(b) (4)</sup> - should be removed from the list

## **8 mg Tablets**

### Inactive ingredients:

[Microcrystalline cellulose](#) - should be added to the list

[Ferric oxide \(Black\)](#) - should be added

 <sup>(b) (4)</sup> - should be removed from the list

## **10 mg Tablets**

### Inactive ingredients:

[Microcrystalline cellulose](#) - should be added to the list

[Ferric oxide \(Yellow\)](#) - should be added

 <sup>(b) (4)</sup> - should be removed from the list

## **12 mg Tablets**

Inactive ingredients:

[Microcrystalline cellulose](#) – should be added to the list

 - should be removed from the list

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/s/  
-----

STEPHANIE N PARNCUTT  
09/13/2012

**From:** [Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)  
**To:** [Parncutt\\_Stephanie](mailto:Parncutt_Stephanie)  
**Subject:** RE: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets  
**Date:** Monday, September 03, 2012 3:19:38 PM

---

Hi Stephanie,  
Receipt confirmed, thanks.

Heather A. Bradley, MPH  
Associate Director, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677  
Tel: 201-949-4691  
Cell: (b) (6)  
Fax: 201-949-4595  
[heather\\_bradley@eisai.com](mailto:heather_bradley@eisai.com)

From: "Parncutt, Stephanie" <Stephanie.Parncutt@fda.hhs.gov>  
To: "Heather\_Bradley@Eisai.com" <Heather\_Bradley@Eisai.com>  
Date: 08/31/2012 01:19 PM  
Subject: RE: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

---

[Heather,](#)

[Please see Clinical Pharmacology's additional requests:](#)

**1. Please provide bioanalytical report for (b) (4) bioanalytical method no: 004/003 which you used to analyze carbamazepine and its metabolite for your study E2007-044-006. If you already submitted the report, please provide the location.**

**2. The figures on page 240-243 of study report of E2007-044-002 (total page 4390) were not readable. Please upload the correct figures.**

[Please confirm receipt. Thank you,](#)

[Stephanie](#)

---

**From:** [Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com) [[mailto:Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)]  
**Sent:** Tuesday, August 28, 2012 4:05 PM  
**To:** Parncutt, Stephanie  
**Subject:** Re: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

Received, thank you.

Heather A. Bradley, MPH  
Associate Director, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677  
Tel: 201-949-4691  
Cell: (b) (6)  
Fax: 201-949-4595  
heather\_bradley@eisai.com

From: "Parncutt, Stephanie" <Stephanie.Parncutt@fda.hhs.gov>  
To: "Heather\_Bradley@Eisai.com" <Heather\_Bradley@Eisai.com>  
Date: 08/28/2012 03:53 PM  
Subject: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

---

Attached is a request from the Clinical Pharmacology team related to their ongoing review of the FYCOMPA application (N 202-834). Please submit your response to this request in electronic archival format as an amendment to the above NDA. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

\* [Please see the comments below from the Clinical Pharmacology team reviewer:](#)

**You only provided partial validation report for bioanalytical assay (b) (4) 101-001/101-001MU used to analyze urine samples. Though you provided some information in summary of biopharmaceutical studies and analytical methods such as accuracy and precision, you need to provide the validation report containing results in detail.**

Please respond to this request within 7 to 10 business days; if you are unable to meet this timeframe, please contact me to discuss.

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/  
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STEPHANIE N PARNCUTT  
09/04/2012

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** August 9, 2012  
**TIME:** 9:00AM- 10:00PM (EST)  
**LOCATION:** TCON/CDER WO 2560  
**APPLICATION:** NDA 202834  
**DRUG NAME:** FYCOMPA (PERAMPANEL), Tablet  
**TYPE OF MEETING:** FDA initiated TCON  
**MEETING CHAIR:** Angelica Dorantes, ONDQA Biopharmaceutics Leader  
**MEETING RECORDER:** Jewell Martin, Regulatory Health Project Manager  
**MEETING PURPOSE:** The purpose of the TCON was to discuss IR sent on June 7, 2012 and the Eisai response received on July 6, 2012.

**FDA Attendees:**

Tien Mien Chen, PhD, ONDQA Biopharmaceutics Reviewer  
Lyudmila Soldatova, PhD, ONDQA CMC Reviewer  
Angelica Dorantes, PhD, ONDQA Biopharmaceutics Team Lead  
Martha R Heimann, PhD, ONDQA CMC Lead  
Jewell Martin, MA, MBA, PMP, ONDQA Regulatory Health Project Manager

**EISAI Inc. Attendees:**

Robert Clark, US Regulatory Affairs - CMC  
Jim Ferry, US Clinical Pharmacology  
David Solomon, Global Fycompa Regulatory Affairs Leader (UK)  
Hugh DeLargy, Regulatory Affairs - CMC (UK)  
Yoshifumi Uemoto, Fycompa Pharmaceutical Science and Technology Team Leader  
Hiroshi Omae, Fycompa PST Team Member  
Nobuya Suzuki, Fycompa PST Team Member

**Meeting notes:**

Discussion of IR sent on June 7, 2012, Eisai response received on July 6, 2012:

**Question 13**

*The proposed dissolution acceptance criterion of (b) (4) is not supported by the provided dissolution data. The dissolution data for: 1) each of the 2, 4, 6, and 12 mg strengths used in the PK (bio-batches) and/or clinical studies, and 2) the stability batches for the 6, 8 and 10 mg strengths, support a dissolution acceptance criterion of  $Q = (b) (4)$  at 15 min for your product at release and during the stability testing. Therefore, revise the drug product specification to include a  $Q = (b) (4)$  at 15 minutes and provide the updated specifications table. Additionally, provide the dissolution data for the 15-minute time point for the registration batches currently under the stability program (each strength).*

- The applicant mentioned that based on the dissolution results, their proposed sampling time at (b) (4) value is an appropriate dissolution criterion for the evaluation of the quality of their product.

- The Agency responded that the provided dissolution data for each strength of their product (bottle and blisters) clearly supported a dissolution acceptance criterion of Q <sup>(b) (4)</sup> at 15min. There is only one individual point not meeting Q <sup>(b) (4)</sup> at 15 min. The applicant believes that the one data point is an anomaly.
- The Agency clarified that the setting of the dissolution acceptance criterion is always based on mean data and it must be recognized that some batches may require Stage 2 and, occasionally, Stage 3 testing.
- The applicant agreed and accepted the Agency's recommendation of Q <sup>(b) (4)</sup> at 15min for the dissolution test of their product.
- The Agency requested the submission of the updated specifications table for the drug product with the revised dissolution acceptance criterion in the module 3.2.P.5.1, and an updated module 3.2.P.8.1.3.
- The applicant will update the specifications as requested and submit an amendment to NDA.

**Question 3:**

*Revise the acceptance criterion for individual unspecified related substances to NMT <sup>(b) (4)</sup> in the specifications for all dosage strengths. This acceptance criterion should be set at the identification threshold for such impurities based on the maximum daily intake in accordance with ICH Q3B(R2) requirements.*

- The Agency requested that the applicant revise the acceptance criterion for individual unspecified related substances to NMT <sup>(b) (4)</sup> in the specifications for stability studies for all dosage strengths, in Section 3.2.P.8.1.3. ( Analytical Tests and Acceptance criteria for Perampanel Tablets, 2, 4, 6,8, 10, and 12mg for Stability Studies, Table 3.2.P.8.1-30 and Table 3.2.P.8.1-31).

**Question 12:**

*Provide a representative packaging batch records including the packaging batch record for blister card of the Starter Kit.*

- The Agency requested the applicant replace the Master Lot packaging record for Banzel 400mg (Rufinamide) Tablets in 120 cc bottles, which is not relevant to Perampanel tablets, with the executed packaging batch record for Perampanel tablets used for stability studies that are packaged in the bottles and blisters (representative batch record).
  - The applicant does not have executed records for commercial batch records at this time. There are no Starter Kit executed batch records because the kits have not been produced commercially either.
  - The Agency clarified that they want 1 example of bottle executed packaging batch records and 1 example of blister executed packaging batch records for drug product batches used for stability studies. The Agency stated that it was up to the applicant to determine which strength and which bottle count to provide.

- The applicant stated that current batch records are in Japanese and that it would take at least 2 weeks for the information to be translated.
- The Agency requested that the applicant provide all other information discussed as soon as possible and submit the batch records in a separate amendment when the translated version becomes available.
  - The applicant agreed to provide dissolution information by next week and the translated batch record within 2 weeks.

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/s/  
-----

JEWELL D MARTIN  
08/09/2012

ANGELICA DORANTES  
08/09/2012

**From:** [Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)  
**To:** [Parncutt\\_Stephanie](mailto:Parncutt_Stephanie)  
**Subject:** RE: Responses to CSS Requests of 27 Jul and 2 Aug Re: FW: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets  
**Date:** Tuesday, August 07, 2012 4:37:11 PM

---

Receipt confirmed, thanks.

Heather A. Bradley, MPH  
Associate Director, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677  
Tel: 201-949-4691  
Cell: (b) (6)  
Fax: 201-949-4595  
[heather\\_bradley@eisai.com](mailto:heather_bradley@eisai.com)

From: "Parncutt, Stephanie" <Stephanie.Parncutt@fda.hhs.gov>  
To: "Heather\_Bradley@Eisai.com" <Heather\_Bradley@Eisai.com>  
Date: 08/07/2012 03:57 PM  
Subject: RE: Responses to CSS Requests of 27 Jul and 2 Aug Re: FW: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

---

Heather,

Please see the following response/request from CSS:



Please confirm receipt.

Stephanie

---

**From:** Heather\_Bradley@Eisai.com [[mailto:Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)]  
**Sent:** Friday, August 03, 2012 10:47 AM  
**To:** Parncutt, Stephanie  
**Subject:** Responses to CSS Requests of 27 Jul and 2 Aug Re: FW: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

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

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/s/  
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STEPHANIE N PARNCUTT  
08/20/2012

**From:** [Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)  
**To:** [Parncutt\\_Stephanie](mailto:Parncutt_Stephanie)  
**Subject:** Re: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets  
**Date:** Monday, July 30, 2012 12:14:29 PM

---

Received, thank you.

Heather A. Bradley, MPH  
 Associate Director, Global Regulatory Affairs

Eisai Inc.  
 155 Tice Boulevard  
 Woodcliff Lake, NJ 07677  
 Tel: 201-949-4691  
 Cell: (b) (6)  
 Fax: 201-949-4595  
[heather\\_bradley@eisai.com](mailto:heather_bradley@eisai.com)

**From:** "Parncutt, Stephanie" <Stephanie.Parncutt@fda.hhs.gov>  
**To:** "Heather\_Bradley@Eisai.com" <Heather\_Bradley@Eisai.com>  
**Date:** 07/30/2012 12:05 PM  
**Subject:** FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

---

Attached is a request from the Clinical Safety team related to their ongoing review of the FYCOMPA application (N 202-834). Please submit your response to this request in electronic archival format as an amendment to the above NDA. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

**\* [Please see the comments below from the Clinical Safety team reviewer:](#)**

**1) We have noted that the shift results for the urine parameters, pH and specific gravity, were provided in the most recent Safety Information Amendment. Please provide the shift results from normal to abnormal for all of the urine parameters measured in the epilepsy Phase 3 DB studies (urine ketones, leukocytes, protein, glucose, microscopy).**

Please complete the following table:

**Subjects (baseline BP ≤140/90) who developed SBP>140 mmHg or DBP>90 mmHg for at least 2 consecutive visits, Epilepsy Phase 3 DB Pool (randomized dose groups)**

|                |                         |
|----------------|-------------------------|
| <b>Placebo</b> | <b>Perampanel n (%)</b> |
| <b>n (%)</b>   |                         |

|                                                   |    | 2 mg | 4 mg | 8 mg | 12 mg | Total |
|---------------------------------------------------|----|------|------|------|-------|-------|
| <b>n with SBP≤140 and DBP≤90 mmHg at baseline</b> | n= | n=   | n=   | n=   | n=    | n=    |
| Cumulative incidence (%) Weeks 0-6                |    |      |      |      |       |       |

|                                             |  |  |  |  |  |  |
|---------------------------------------------|--|--|--|--|--|--|
| Cumulative incidence (%) Weeks 0-12         |  |  |  |  |  |  |
| Cumulative incidence (%) in Phase 3 DB Pool |  |  |  |  |  |  |

Please respond to this request by COB August 1, 2012; if you are unable to meet this timeframe, please contact me to discuss.

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](mailto:stephanie.parncutt@fda.hhs.gov)

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/s/  
-----

STEPHANIE N PARNCUTT  
07/31/2012

**From:** [Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)  
**To:** [Parncutt\\_Stephanie](mailto:Parncutt_Stephanie)  
**Subject:** RE: Fycompa NDA 202834 Submissions Update  
**Date:** Friday, July 27, 2012 1:52:12 PM

---

Hi Stephanie,  
I received both new requests today.

Regards,  
Heather

Heather A. Bradley, MPH  
Associate Director, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677  
Tel: 201-949-4691  
Cell: (b) (6)  
Fax: 201-949-4595  
[heather\\_bradley@eisai.com](mailto:heather_bradley@eisai.com)

**From:** "Parncutt, Stephanie" <[Stephanie.Parncutt@fda.hhs.gov](mailto:Stephanie.Parncutt@fda.hhs.gov)>  
**To:** "Heather\_Bradley@Eisai.com" <[Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)>  
**Date:** 07/27/2012 01:25 PM  
**Subject:** RE: Fycompa NDA 202834 Submissions Update

---

[Heather,](#)

I'll be sending you two more Information Requests shortly, that I just received. Please confirm upon receipt.

[Stephanie](#)

---

**From:** [Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com) [[mailto:Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)]  
**Sent:** Friday, July 27, 2012 10:24 AM  
**To:** Parncutt, Stephanie  
**Subject:** Fycompa NDA 202834 Submissions Update

Dear Stephanie,  
Please be informed that a response to the 2 Jul 2012 Clinical Safety Information Request was submitted this morning as s0037.

Also attached is a pre-publication copy of s0038, a response to the 23 Jul 2012 Clinical Safety Information Request. Sequence 0038 will be submitted through the electronic gateway on Monday, Jul 30.

Pending your confirmation that our existing pediatric deferral certification statement submitted in s0018 on 21 Mar 2012 is acceptable (see e-mail from 24 Jul 2012), this will bring us current with no outstanding open requests. Please confirm.

Thanks and regards,  
Heather

Heather A. Bradley, MPH  
Associate Director, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677  
Tel: 201-949-4691  
Cell: (b) (6)  
Fax: 201-949-4595

heather\_bradley@eisai.com

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**From:** Parncutt, Stephanie  
**To:** ["Heather\\_Bradley@Eisai.com"](mailto:Heather_Bradley@Eisai.com)  
**Subject:** FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets  
**Date:** Friday, July 27, 2012 1:37:00 PM

---

Attached is a request from the CSS team related to their ongoing review of the FYCOMPA application (N 202-834). Please submit your response to this request in electronic archival format as an amendment to the above NDA. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

[\\* Please see the comments below from the CSS reviewer:](#)

1. **Revise Table 1: Add two columns "treatment name" and "sequence number" in Table 1 "Summary of Reasons for Missed Assessments in Study E2007-A001-024".**
2. **Provide the same information as Table 1 for the Run-in Period for both completers (n=34) and non-completers (n=6) only.**

Please respond to this request within 7 to 10 business days; if you are unable to meet this timeframe, please contact me to discuss.

Thank you,

~~~~~  
Stephanie N. Parncutt  
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](mailto:stephanie.parncutt@fda.hhs.gov)

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**From:** Parncutt, Stephanie  
**To:** "[Heather Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)"  
**Subject:** FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets  
**Date:** Friday, July 27, 2012 1:31:00 PM

---

Attached is a request from the Clinical Safety team related to their ongoing review of the FYCOMPA application (N 202-834). Please submit your response to this request in electronic archival format as an amendment to the above NDA. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

[\\* Please see the comments below from the Clinical Safety team reviewer:](#)

**1) Narratives for the following 3 subjects who were incarcerated: 305-5185-5022, 306-1801-6010, 227-13141019. Please provide detailed information regarding the events leading up to the incarceration, the specific crime that led to the incarceration, and prior history of incarcerations.**

**1) Narratives for the 3 subjects with ligament rupture: 306-2455-6004, 306-2457-6006, 218-2021-1003. We have noted that some of these subjects have narrative that were submitted in the NDA. However, the narratives do not include information regarding the ligament rupture. Please provide information regarding the events surrounding the ligament ruptures: traumatic vs spontaneous, specific ligament involved, perampanel dose, Study #, and Study Day.**

Please respond to this request by COB July 31, 2012; if you are unable to meet this timeframe, please contact me to discuss.

Thank you,

-----  
Stephanie N. Parncutt  
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  
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-----  
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/s/  
-----

STEPHANIE N PARNCUTT  
07/31/2012

**From:** [Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)  
**To:** [Parncutt\\_Stephanie](mailto:Parncutt_Stephanie)  
**Subject:** RE: NDA 202834/Fycompa (perampanel) Tablets submitio update  
**Date:** Thursday, July 05, 2012 8:28:45 PM

---

Hi Stephanie,  
Received, thank you.

Heather A. Bradley, MPH  
Associate Director, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677  
Tel: 201-949-4691  
Cell: (b) (6)  
Fax: 201-949-4595  
[heather\\_bradley@eisai.com](mailto:heather_bradley@eisai.com)

**From:** "Parncutt, Stephanie" <[Stephanie.Parncutt@fda.hhs.gov](mailto:Stephanie.Parncutt@fda.hhs.gov)>  
**To:** "Heather\_Bradley@Eisai.com" <[Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)>  
**Date:** 07/05/2012 07:38 PM  
**Subject:** RE: NDA 202834/Fycompa (perampanel) Tablets submitio update

---

[Heather,](#)

[Thank you for the submission update, I will inform the team.](#)

[I also have an additional Information Request from our Clinical Safety Team:](#)

**Please submit the following narratives by COB on July 13, 2012:**

- 1) Subject 17 in Study 002 (erythema multiforme)**
- 2) Narratives for the subjects in the nonepilepsy studies with the PTs angioedema (n=2) and bronchospasm (n=3).**

[Please confirm receipt.](#)

[Thank you,](#)

[Stephanie](#)

---

**From:** [Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com) [[mailto:Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)]  
**Sent:** Thursday, July 05, 2012 3:21 PM  
**To:** Parncutt, Stephanie

**Subject:** NDA 202834/Fycompa (perampanel) Tablets submitio update

Hi Stephanie,

Please note that sequence 0033 was submitted through the gateway today, and contains our response to Question 4 of the June 13 Clinical Safety Information Request.

In addition, I have the following updates for other pending requests:

- June 21 Clin Safety Request: s0034 will be submitted by Wed July 11
- June 29 CSS Request: s0035 will be submitted by Fri Jul 13
- Jul 3 Clin Pharm Request: s0036 will be submitted by the requested deadline, i.e. by Fri Jul 13 (may be combined with s0035 if feasible)
- Jul 2 Clin Safety Request: we will need additional time to prepare this response, likely s0037 week of July 16

Please let me know if you need additional information.

Regards,  
Heather

Heather A. Bradley, MPH  
Associate Director, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677  
Tel: 201-949-4691  
Cell: (b) (6)  
Fax: 201-949-4595

heather\_bradley@eisai.com

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/s/  
-----

STEPHANIE N PARNCUTT  
07/09/2012

**From:** [Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)  
**To:** [Parncutt\\_Stephanie](mailto:Parncutt_Stephanie)  
**Subject:** Re: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets  
**Date:** Tuesday, July 03, 2012 4:41:07 PM

---

Hi Stephanie,  
Confirming receipt. thanks.

Heather A. Bradley, MPH  
Associate Director, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677  
Tel: 201-949-4691  
Cell: (b) (6)  
Fax: 201-949-4595  
[heather\\_bradley@eisai.com](mailto:heather_bradley@eisai.com)

**From:** "Parncutt, Stephanie" <Stephanie.Parncutt@fda.hhs.gov>  
**To:** "'Heather\_Bradley@Eisai.com'" <Heather\_Bradley@Eisai.com>  
**Date:** 07/03/2012 02:07 PM  
**Subject:** FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

---

Attached is a request from the Clinical Pharmacology team related to their ongoing review of the FYCOMPA application (N 202-834). Please submit your response to this request in electronic archival format as an amendment to the above NDA. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

\* [Please see the comments below from the Clinical Pharmacology team reviewer:](#)

**The drug-drug interaction study for ketoconazole and perampanel is under review. We noticed you conducted physiological-based pharmacokinetic (PBPK) modeling to investigate the effects of CYP3A4 inhibitor/inducer on perampanel. Please provide information on the use of PBPK modeling and simulation, including modeling and simulation report and executable model files. Please also provide simulation results of the effect of ketoconazole on steady-state PK of perampanel.**

Please respond to this request within 7 to 10 business days; if you are unable to meet this timeframe, please contact me to discuss.

Thank you,

~~~~~  
[Stephanie N. Parncutt](mailto:Stephanie.N.Parncutt)  
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](mailto:stephanie.parncutt@fda.hhs.gov)

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/s/  
-----

STEPHANIE N PARNCUTT  
07/09/2012

**From:** [Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)  
**To:** [Parncutt\\_Stephanie](mailto:Parncutt_Stephanie)  
**Subject:** Re: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets  
**Date:** Monday, July 02, 2012 1:00:57 PM

---

Dear Stephanie,  
Confirming receipt. Given the other pending responses (Clin Safety Jun 21 and CSS Jun 29), and the July 4th holiday this week, generating a response for submission by July 9th for this new request will be difficult. I will provide an update on timing once we meet and assess the programming needs of the requested tables.

Thanks,  
Heather

Heather A. Bradley, MPH  
Associate Director, Global Regulatory Affairs

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Fax: 201-949-4595  
[heather\\_bradley@eisai.com](mailto:heather_bradley@eisai.com)

From: "Parncutt, Stephanie" <[Stephanie.Parncutt@fda.hhs.gov](mailto:Stephanie.Parncutt@fda.hhs.gov)>  
To: "'Heather\_Bradley@Eisai.com'" <[Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)>  
Date: 07/02/2012 12:34 PM  
Subject: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

---

Attached is a request from the Clinical Safety team related to their ongoing review of the FYCOMPA application (N 202-834). Please submit your response to this request in electronic archival format as an amendment to the above NDA. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

**\* [Please see the comments below from the Clinical Safety team reviewer:](#)**

- 1) Please provide the narrative with vital sign and ECG results for subject 206-0016-0075 with the AE coded as ventricular arrhythmia.
  - 2) Please provide the narrative for the 2 subjects with AE coded as cyanosis in the Phase 1 studies.
  - 3) Please provide the unique subject ID of the patient who discontinued due to the TEAE blood sodium decreased in the epilepsy all treated pool.
  - 4) Please provide the information for the tables in the attached document.
- Please respond to this request by COB July 9, 2012; if you are unable to meet this timeframe, please contact me to discuss.

Thank you,

~~~~~

Stephanie N. Parncutt  
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](mailto:stephanie.parncutt@fda.hhs.gov)

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[attachment "(7-2-12)Table shells for FDA request.doc" deleted by Heather Bradley/RIG/EisaiInc]

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/s/  
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STEPHANIE N PARNCUTT  
07/09/2012

**From:** [Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)  
**To:** [Parncutt\\_Stephanie](mailto:Parncutt_Stephanie)  
**Subject:** Re: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets  
**Date:** Friday, June 29, 2012 1:11:45 PM

---

Hi Stephanie,  
Confirming receipt.

Are there any other review disciplines working on information requests, possibly waiting for sign-off after the mid-cycle review?

Thanks,  
Heather

Heather A. Bradley, MPH  
Associate Director, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677  
Tel: 201-949-4691  
Cell: (b) (6)  
Fax: 201-949-4595  
[heather\\_bradley@eisai.com](mailto:heather_bradley@eisai.com)

From: "Parncutt, Stephanie" <Stephanie.Parncutt@fda.hhs.gov>  
To: "'Heather\_Bradley@Eisai.com'" <Heather\_Bradley@Eisai.com>  
Date: 06/29/2012 12:03 PM  
Subject: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

---

Attached is a request from the CSS team related to their ongoing review of the FYCOMPA application (N 202-834). Please submit your response to this request in electronic archival format as an amendment to the above NDA. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

\* [Please see the comments below from the CSS reviewer:](#)

(b) (4)



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

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/s/  
-----

STEPHANIE N PARNCUTT  
07/02/2012

**From:** [Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)  
**To:** [Parncutt\\_Stephanie](mailto:Parncutt_Stephanie)  
**Subject:** Re: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets  
**Date:** Monday, June 25, 2012 12:16:13 PM

---

Hi Stephanie,  
Confirming receipt.

Thanks,  
Heather

Heather A. Bradley, MPH  
Associate Director, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677  
Tel: 201-949-4691  
Cell: (b) (6)  
Fax: 201-949-4595  
[heather\\_bradley@eisai.com](mailto:heather_bradley@eisai.com)

From: "Parncutt, Stephanie" <Stephanie.Parncutt@fda.hhs.gov>  
To: "'Heather\_Bradley@Eisai.com'" <Heather\_Bradley@Eisai.com>  
Date: 06/25/2012 11:51 AM  
Subject: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

---

Attached is a request from the Division of Medication Error Prevention and Analysis related to their ongoing review of the FYCOMPA application (N 202-834). Please submit your response to this request in electronic archival format as an amendment to the above NDA. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

[\\* Please see the comments below from the Division of Medication Error Prevention and Analysis:](#)

**A. Container Labels (2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg)**

1. All of the labels contain a green color block at the top of the label which increases the look-alike similarity between the different strengths. Delete the green color block from the labels in order to improve strength differentiation.
2. The established name does not appear to be at least ½ the height of the proprietary name. Ensure the established name is printed in letters that are at least ½ the height of the letters comprising the proprietary name [21 CFR 201.10(g)(2)].
3. The (b) (4) symbol appears in the middle of the principal display panel (PDP) and is too

close to the established name. Relocate the (b) (4) symbol so that it appears further away from the proprietary name and established name.

4. The oval color block surrounding the statement of strength has a yellowish green border which increases the look-alike similarity between the different strengths. Delete the yellowish green border.

5. The statement of strength is located above the product identifying information. This is not the customary location and may hinder a provider's ability to quickly and easily identify this information on the label. Relocate the statement of strength to a position below the established name and dosage form as follows:

Proprietary Name  
Established Name  
Strength

To accomplish this move, reposition the proprietary name, established name, and dosage form higher on the PDP.

6. We note the statement of strength is backed by an oval color block that matches the corresponding tablet color. However, the 8 mg strength is difficult to read because it appears in a white font on a light purple background which does not provide sufficient color contrast. Consider using a black font for the 8 mg statement of strength or increasing the saturation of the light purple background in order to improve contrast.

7. The net quantity statement is backed by a color block which increases the prominence of the statement. Additionally, the net quantity statement is in the middle of the principal display panel and is too prominent in this location. Remove the color block and relocate the net quantity statement to the upper right corner or lower right corner of the PDP, away from the statement of strength.

8. The medication guide statement is on the left side panel and lacks prominence in that location. Additionally, it is not optimally worded. Relocate the Medication Guide statement to the bottom section of the PDP. In order to accomplish this move, relocate the "Manufactured by" statement, "Marketed by" statement, as well as the "Esai" logo to the bottom of the left side panel. We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton.

- a. "Attention Pharmacist: Dispense the enclosed Medication Guide to each patient." or
- b. "Attention Pharmacist: Dispense the accompanying Medication Guide to each patient."

9. The "Esai" logo is too prominent. Decrease the size of the "Esai" logo.

10. The NDC numbers only contain the first five numbers (i.e., 62856-XXX-XX) and are, therefore, not complete. Include the entire NDC number on all labels.

## **B. Professional Sample Blister Pack**

### **1. Outside Folder Card**

- a. The regimens for Week 1 and Week 2 are not well separated from one another. Use a

heavy bold line, bar or other means to separate Week 1 from Week 2.

b. See Comment A.3 above.

c. The net quantity statement can be improved for clarity. Revise the net quantity statement to read: “This package contains: Seven 2 mg tablets and seven 4 mg tablets”.

d. The “Esai” logo is too prominent. Decrease the size of the “Esai” logo.

e. The Agency does not consider starter packs to be drug samples; therefore, the use of the term (b)(4) on drug sample labeling is inappropriate and should not be used. Delete the statement (b)(4) per 21 CFR 203.38 (c) and 64 FR 67720 at 67741.

## 2. Inside Folder Card

a. The proprietary name and established name are not on the portion of the blister pack that contains the tablets. Place the proprietary name and established name on the right inside panel in order that the product identifying information will be on the portion of the blister that contains the tablets in case the two sides get separated.

b. There are no instructions that state how the tablets should be removed from the blister pack. Provide brief instructions for removing the tablets from the blister pack.

c. On the right inside panel, the statement of strength is not preceded by the statement “Each tablet contains”. This statement may help to prevent patients from confusing an entire week’s worth of tablets as a 2 mg or 4 mg dose. Therefore, revise the statements of strength to read: “Each tablet contains 2 mg” and “Each tablet contains 4 mg”.

d. See Comment B.1.a. above.

e. See Comment A.3 above.

## C. Professional Sample Blister Pack Carton

We note there are some slight differences in information layout between the professional sample blister pack carton electronic submission and the mock-up mailed to the Agency. The following comments are based on the electronic submission dated January 17, 2012.

1. The net quantity statement is on the back panel. Relocate the net quantity statement to the PDP.

2. The net quantity statement is not optimally worded. See Comment B.1.c. above.

## D. Insert Labeling

The dangerous symbol “/” is used when expressing the daily dose (e.g., 4 mg/day) in Dosage and Administration, Section 2.1 *Partial-Onset Seizures*. Replace the symbol “/” with the word “per” when referring to the total daily dose (e.g., 4 mg per day).

Please respond to this request within 7 to 10 business days; if you are unable to meet this timeframe, please contact me to discuss.

Thank you,

~~~~~

Stephanie N. Parncutt  
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](mailto:stephanie.parncutt@fda.hhs.gov)

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/s/  
-----

STEPHANIE N PARNCUTT  
06/26/2012

**From:** [Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)  
**To:** [Parncutt, Stephanie](mailto:Parncutt, Stephanie)  
**Subject:** RE: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets  
**Date:** Thursday, June 21, 2012 12:40:32 PM  
**Attachments:** [req-def-ped-stud.pdf](#)

---

Hi Stephanie,  
Confirming e-mail and attachment.

In turn, I can also confirm that we have delivered two submissions via the electronic gateway today, June 21:

- sequence 0029 provides our partial responses to the June 13-18 clinical requests (to be continued with a response to Q4 and any additional points from the e-mail below). Sequence 0029 also contains a revised 1.9.2 Request for Deferral of Pediatric Studies as discussed (also attached for quick reference). **Please Note** that sequence 0029 also contains a courtesy copy of an additional NIDA report that should be forwarded to the CSS reviewers
- sequence 0030 provides an official archive copy of information e-mailed to Safety Project Manager Dr. Kelly Summers, regarding an identification of perampanel AED trials related to FDA's verification of the Ryvlin et.al. meta-analysis of SUDEP

Please confirm receipt of this information on s0029 and s0030, and if possible could you confirm if any other review disciplines (aside from CMC and Clin Safety) are generating information requests stemming from the May 22 mid-cycle review meeting?

Thanks and regards,  
Heather

Heather A. Bradley, MPH  
Associate Director, Global Regulatory Affairs

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Woodcliff Lake, NJ 07677  
Tel: 201-949-4691  
Cell: (b) (6)  
Fax: 201-949-4595  
[heather\\_bradley@eisai.com](mailto:heather_bradley@eisai.com)

---

From: "Parncutt, Stephanie" <Stephanie.Parncutt@fda.hhs.gov>  
To: "Heather\_Bradley@Eisai.com" <Heather\_Bradley@Eisai.com>  
Date: 06/21/2012 11:58 AM  
Subject: RE: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

---

[Heather,](#)

[Our Clinical Safety team has provided the following responses and attachment, in response to your](#)

June 15, 2012 email:

1. If after this explanation the reviewer still requests that our SAE narratives be reviewed to identify CIOMS text description terms not in our AE database, we request that the review be limited to the double-blind placebo controlled studies, so as to provide a background against which such events can be analyzed. In addition, we ask that FDA provide a list of terms that we can use for a programmed search relating to "any homicidal or suicidal ideations or who committed any physical assault/abuse or homicide (harmed/injured self or another person in any way". A manual review for any word possibly related to physical harm would be prohibitively time consuming given the number of narratives in our filing and the number of potentially related terms. However, while we may identify terms contained in the CIOMS and not in the AE database, we do not consider it appropriate to overwrite the AE database with these terms since they are not investigator-reported on any study-level source documentation that we can verify. Furthermore, any unlocking of our AE database and re-coding would then impact the numerous other AE tables provided throughout the dossier.

**We have noted your explanation. We no longer request that the SAE narratives be reviewed. However, please confirm that there were no homicides that were committed by a subject while taking perampanel (or within 30 days after drug discontinuation).**

2. Given the description of safety reporting provided above, a review of narratives for TEAEs leading to discontinuation is unlikely to reveal any terms that are not located in the AE database/AE listings already provided since those listings are the only source material used for these narratives. Given this explanation, we propose that a manual review of these narratives for TEAEs leading to discontinuation should not be required.

**This is acceptable.**

3. Likewise for TEAEs (Q8 received Jun 15), there is no additional source data for the AE listings other than the CRFs coded to the AE database so there is no additional content to perform a manual review on.

**Please also provide narratives for the subjects with TEAEs coded to the PTs human bite and physical assault.**

4. Therefore, given our stated reasons against adding additional AE terms post-hoc to the AE database, we plan to provide the requested tables and analyses from Q4 on the existing AE database.

**This is acceptable.**

Please also provide the additional information in the attached word document.

We would like to request that the attachment be completed by COB on June 29, 2012.

Please confirm receipt of this email and it's attachment. Thank you,

Stephanie

---

**From:** Heather\_Bradley@Eisai.com [[mailto:Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)]

**Sent:** Tuesday, June 19, 2012 12:46 PM

**To:** Heather\_Bradley@Eisai.com

**Cc:** Parncutt, Stephanie

**Subject:** RE: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

Dear Stephanie,

Please confirm receipt of the e-mail below from Friday, June 15.

In addition, I have a status update on our response to the June 13-June 18 Clin Safety Requests. We will be submitting a response this week to Questions 1, 2, 3, 6, 7 and 9. The response to Question 4 requires additional time to produce the large volume of tables and publish for submission. The response to questions 5 and 8 are also delayed pending the response to our June 15 e-mail.

Thanks,  
Heather

Heather A. Bradley, MPH  
Associate Director, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677  
Tel: 201-949-4691  
Cell: (b) (6)  
Fax: 201-949-4595  
heather\_bradley@eisai.com

From: Heather Bradley/RIG/EisaiInc  
To: "Parncutt, Stephanie" <Stephanie.Parncutt@fda.hhs.gov>  
Date: 06/15/2012 02:45 PM  
Subject: RE: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

---

Dear Stephanie,

We are assessing the questions received on June 13, 14 and 15 regarding the review of narratives (Q5 and Q7) and TEAE listings (Q8) for additional information/terms that may not have not been coded to the relevant MedDRA PTs and reflected in our AE database. We ask that you share the following preliminary description and questions/comments for clarification with the clinical safety reviewers.

1. Adverse Event → CRF AE page → AE database → AE Listings
2. Adverse Event Leading to Discontinuation → CRF AE Page → AE database → AE Listings  
→ Narrative from Listings only
3. Serious Adverse Event → CRF AE Page → AE database (ongoing reconciliation with SAE database) → AE Listings  
↳ SAE Report sent to PV → Investigator queried for additional information as necessary → SAE database (ongoing reconciliation with AE database) → CIOMS → Final SAE Narrative from Listings and CIOMS

Adverse Events reported by a subject are documented on the study CRF AE page by the investigator. These CRF pages are entered and coded to comprise our AE database which generates AE listings. If an event results in study discontinuation, then the narrative for this event is written from data contained only in the AE listings.

Should an event be assessed by an investigator as a SAE, in addition to the CRF AE page the investigator also completes a SAE form to submit to Eisai Pharmacovigilance for consideration for expedited reporting to health authorities. The investigator may be asked for additional information by

PV to fully understand and document the event and this additional information is used to complete a CIOMS form. However, while Eisai Product Safety may request additional clarifications that result in the investigator changing the verbatim term or adding additional terms, Eisai Product Safety does not add additional event terms on their own. Likewise, a study monitor reviewing CRF pages may notice that there are individual event terms in the source documents and query the investigator whether they should be reported as adverse events, but it is the investigator's determination as to whether a given term is best subsumed under a diagnosis or other event term. For both the clinical trial AE database and the PV SAE database, the investigator verbatim term is coded to the closest MedDRA LLT.

When writing narratives for SAEs (after final AE/SAE database reconciliation and database lock), the source information is both the listings generated from the AE database and the CIOMS form containing free text descriptions from the investigator. That is why narratives may contain information not in the CRF pages or AE database.

Therefore, while it is possible that the SAE narratives contain supporting descriptions of events not captured on CRF pages nor coded in the AE database, it is not standard practice to use that CIOMS description to then add new events to the AE database that were not reported by an investigator on study source documentation (Q5).

Questions/Comments:

1. If after this explanation the reviewer still requests that our SAE narratives be reviewed to identify CIOMS text description terms not in our AE database, we request that the review be limited to the double-blind placebo controlled studies, so as to provide a background against which such events can be analyzed. In addition, we ask that FDA provide a list of terms that we can use for a programmed search relating to "any homicidal or suicidal ideations or who committed any physical assault/abuse or homicide (harmed/injured self or another person in any way". A manual review for any word possibly related to physical harm would be prohibitively time consuming given the number of narratives in our filing and the number of potentially related terms. However, while we may identify terms contained in the CIOMS and not in the AE database, we do not consider it appropriate to overwrite the AE database with these terms since they are not investigator-reported on any study-level source documentation that we can verify. Furthermore, any unlocking of our AE database and re-coding would then impact the numerous other AE tables provided throughout the dossier.
2. Given the description of safety reporting provided above, a review of narratives for TEAEs leading to discontinuation is unlikely to reveal any terms that are not located in the AE database/AE listings already provided since those listings are the only source material used for these narratives. Given this explanation, we propose that a manual review of these narratives for TEAEs leading to discontinuation should not be required.
3. Likewise for TEAEs (Q8 received Jun 15), there is no additional source data for the AE listings other than the CRFs coded to the AE database so there is no additional content to perform a manual review on.
4. Therefore, given our stated reasons against adding additional AE terms post-hoc to the AE database, we plan to provide the requested tables and analyses from Q4 on the existing AE database. We would be happy to have a teleconference with the safety reviewer and the Division to discuss this if needed.

Thanks and regards,  
Heather

Heather A. Bradley, MPH  
Associate Director, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677  
Tel: 201-949-4691

Cell: (b) (6)  
Fax: 201-949-4595  
heather\_bradley@eisai.com

From: "Parncutt, Stephanie" <Stephanie.Parncutt@fda.hhs.gov>  
To: "Heather\_Bradley@Eisai.com" <Heather\_Bradley@Eisai.com>  
Date: 06/15/2012 11:03 AM  
Subject: RE: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

---

Heather,

Again, our Clinical Safety team has an additional Information Request:

**1) In addition to our previous request for a review of all of the SAEs and discontinuation TEAEs (Item #5), please review all of the subjects with TEAEs in the entire safety database (using all sources with information regarding the study subjects in addition to the CRFs) and provide a comprehensive list of the subjects (with hyperlinks to the narratives) with any homicidal or suicidal ideations or who committed any physical assault/abuse, homicide, or suicide attempt (harmed/injured self or another person in any way).**

**In the table listing these subjects, please include columns for treatment group, country/center/subject ID, age/sex/race, maximum dose/last dose, number of days in DB study/OLE study, preferred term, study day AE start/day of death, AE day, relevant medical/psychiatric history, and concomitant medications (at time of AE).**

**Please provide this information by COB on June 22, 2012 for the subjects with TEAEs in the MedDRA SOC Psychiatric disorders or with TEAEs coded to the MedDRA PTs Irritability, Akathisia, Human bite, Physical assault, or Psychomotor hyperactivity.**

**Please provide this information by COB on July 6, 2012 for the remaining subjects.**

Please confirm receipt,

Stephanie

---

**From:** Heather\_Bradley@Eisai.com [[mailto:Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)]  
**Sent:** Thursday, June 14, 2012 2:54 PM  
**To:** Parncutt, Stephanie  
**Subject:** RE: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

Hi Stephanie,  
Confirming receipt.

Thanks,  
Heather

Heather A. Bradley, MPH  
Associate Director, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677  
Tel: 201-949-4691  
Cell: (b) (6)  
Fax: 201-949-4595

heather\_bradley@eisai.com

From: "Parncutt, Stephanie" <Stephanie.Parncutt@fda.hhs.gov>  
To: "Heather\_Bradley@Eisai.com" <Heather\_Bradley@Eisai.com>  
Date: 06/14/2012 02:21 PM  
Subject: RE: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

---

Heather,

In addition, our Clinical Safety team has one more Information Request:

**Please provide the following information by COB on June 21, 2012:**

**1) The narratives provided in the submission contain information that is not documented within the CRFs. For example for subject 304-5118-4002, it is stated in the narrative, that the subject "was admitted to a psychiatric unit for homicidal and suicidal threats." However this information is not documented in the corresponding CRF. Please report the other sources that are used to compile information for the narratives.**

Please confirm receipt,

Stephanie

---

**From:** Heather\_Bradley@Eisai.com [[mailto:Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)]  
**Sent:** Wednesday, June 13, 2012 3:31 PM  
**To:** Parncutt, Stephanie  
**Subject:** Re: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

Hi Stephanie,  
Confirming receipt of this request. We are assessing these, and I will get back to you with any issues regarding the requested June 21 response time.

Can you please have the Clinical Safety Team reviewer confirm for the following sentence at the end of request #5, is that meant to refer to item#4? i.e. reperform the analyses requested in Item #4 after we do the additional search requested in #5?

**"Please reperform the analyses requested in Item 5) above after this additional search is performed."**

Heather A. Bradley, MPH  
Associate Director, Global Regulatory Affairs

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Woodcliff Lake, NJ 07677  
Tel: 201-949-4691  
Cell: (b) (6)  
Fax: 201-949-4595  
heather\_bradley@eisai.com

From: "Parncutt, Stephanie" <Stephanie.Parncutt@fda.hhs.gov>  
To: "'Heather\_Bradley@Eisai.com'" <Heather\_Bradley@Eisai.com>  
Date: 06/13/2012 01:42 PM  
Subject: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

---

Attached is a request from the Clinical Safety team related to their ongoing review of the FYCOMPA application (N 202-834). Please submit your response to this request in electronic archival format as an amendment to the above NDA. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

**\* [Please see the comments below from the Clinical Safety team reviewer:](#)**

**1) For treatment-emergent markedly abnormal laboratory results, please provide markedly abnormal low values for magnesium (by treatment group) for all of the epilepsy and nonepilepsy pools. Please also provide tables with the analysis limited to subjects with normal baseline values.**

**2) For subject 306-4703-6008, the narrative does not include the SAE, Mental Disorder Due to a General Medical Condition. Please send the narrative with this SAE listed and described.**

**3) Please provide narratives for all of the subjects who had treatment-emergent tendon rupture. We have noted that narratives for the 2 SAEs coded to tendon rupture (301-0101-0005 and 301-0128-0005) have already been provided. However, please provide additional information: specifically for subject 301-0128-0005, please provide information regarding the specific tendon that was involved and whether this occurred prior to or after the fall. Please also confirm that the subjects with TEAEs that were coded to PTs related to tendon disorders (tendinitis, tendon injury, and tendon disorder) did not also experience a tendon rupture.**

**4) We have noted that in the 120-Day Safety Update, in Appendix 5, Sections 5 and 6 report the analyses performed for TEAEs of aggressiveness and psychotic disorders, respectively. Each of these analyses included 5 MedDRA preferred terms.**

**We have also noted that in response to our information request, additional searches for TEAEs coded to the 2 MedDRA SMQs Hostility/Aggression and Psychosis/psychotic disorders were performed. However, the Tables provided in this safety information amendment (dated February 6, 2012) combined these 2 SMQs.**

**Please provide separate tables for these 2 SMQs for each pooled group (running separate analyses for only narrow preferred terms and for both narrow and broad preferred terms).**

**Furthermore, please provide similar tables for both SAEs and TEAEs leading to study or study**

drug discontinuation (along with a list of subjects, preferred terms, and hyperlinks to the narratives).

Please also provide Kaplan-Meier estimated rates of the time to first occurrence of these 2 SMQs - in both tabular and graphical formats.

Please also provide analyses of the severity and outcome of these AEs, and the subjects' history of anger/aggression (and other psychiatric disorders) prior to entering the study.

5) We have reviewed the narratives for the SAEs and discontinuation TEAEs coded to the Psychiatric Disorders SOC. Some of these narratives that were coded to the PTs aggression, belligerence, anger also contained information such as "striking his wife," "homicidal and suicidal threats," "physical altercation," "biting her sister's finger" that were not coded to the relevant MedDRA PTs such as physical assault, physical abuse, homicidal ideation, or suicidal ideation. Please review all of the narratives of subjects with SAEs and discontinuation TEAEs in the entire safety database and provide a comprehensive list of the subjects (with hyperlinks to the narratives) with any homicidal or suicidal ideations or who committed any physical assault/abuse or homicide (harmed/injured self or another person in any way).

In the table listing these subjects, please include columns for treatment group, country/center/subject ID, age/sex/race, maximum dose/last dose, number of days in DB study/OLE study, preferred term, study day AE start/day of death, AE day, relevant medical/psychiatric history, and concomitant medications (at time of AE).

Please reperform the analyses requested in Item 5) above after this additional search is performed.

6) In the Effects During Pregnancy section in the 120-Day Safety Update and the ISS, it is reported that there were 14 pregnancies in 13 women enrolled in the epilepsy studies with 1 pregnancy in Study 304, 12 in Study 307, and 1 in Study 207.

However, in Table 20.35 of the Safety Update, a subject from Study 306 is also listed (4805-6005) and there are no subjects listed from Study 304.

Within the ADAE dataset (for the epilepsy studies), there is a subject with the AE term coded to spontaneous abortion in Study 304 (subject 5151-4001) who is not listed in Table 20.35. Also, in the Safety Update (Table 20.5-75.1), there are only 5 subjects listed with the preferred term, abortion induced, in the epilepsy all treated pool (while there are 7 subjects in the epilepsy studies with induced abortions listed as an AE within the narratives provided in Table 20.35). Furthermore, we have found 2 subjects who experienced 2 pregnancies (including subject 306-3956-6001 had a second positive pregnancy test on December 27, 2011 noted within the narrative.)

Please explain the above discrepancies.

Therefore, in the epilepsy studies, for treatment-emergent pregnancies, we have counted a total of 15 pregnancies (13 in Study 307, 1 in Study 304, and 1 in Study 207). [We have noted that subject 306-4805-6005 experienced a pregnancy during the prerandomization phase.]

Additionally, in the nonepilepsy and Phase 1 studies, we have counted a total of 1 pregnancy in perampanel exposed subjects. [We have noted that subject 013-1001-0213 did not receive perampanel.]

Please confirm these totals.

Furthermore, the hyperlink to the narrative for subject 307-3003-6001 did not link to the updated narrative that included information for both of the subject's pregnancies.

Please resubmit Table 20.35 with a comprehensive list of all of the subjects who experienced pregnancy during any of the epilepsy, nonepilepsy, and Phase 1 studies - with the outcome of the pregnancy listed for each pregnancy (and correct hyperlinks to narratives and CRFs).

For subject 306-3956-6001, please provide any additional follow up information regarding the outcome of the subject's pregnancy (positive pregnancy test on December 27, 2011).

For subject 306-2760-6003, please provide autopsy results for the male neonate.

**For the two healthy births, please provide any further information (if available) regarding any congenital malformations.**

Please respond to this request by COB June 21, 2012; if you are unable to meet this timeframe, please contact me to discuss.

Thank you,

-----  
Stephanie N. Parncutt  
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](mailto:stephanie.parncutt@fda.hhs.gov)

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[This e-mail message may contain privileged, confidential and/or proprietary information of Eisai. If you believe that it has been sent to you in error, please contact the sender immediately and delete the message including any attachments, without copying, using, or distributing any of the information contained therein. This e-mail message should not be interpreted to include a digital or electronic signature that can be used to authenticate an agreement, contract or other legal document, nor to reflect an intention to be bound to any legally-binding agreement or contract.]

[This e-mail message may contain privileged, confidential and/or proprietary information of Eisai. If you believe that it has been sent to you in error, please contact the sender immediately and delete the message including any attachments, without copying, using, or distributing any of the information contained therein. This e-mail message should not be interpreted to include a digital or electronic signature that can be used to authenticate an agreement, contract or other legal document, nor to reflect an intention to be bound to any legally-binding agreement or contract.]

[This e-mail message may contain privileged, confidential and/or proprietary information of Eisai. If you believe that it has been sent to you in error, please contact the sender immediately and delete the message including any attachments, without copying, using, or distributing any of the information contained therein. This e-mail message should not be interpreted to include a digital or electronic signature that can be used to authenticate an agreement, contract or other legal document, nor to reflect an intention to be bound to any legally-binding agreement or contract.][attachment "(6-21-12)FDA Safety request.doc" deleted by Heather Bradley/RIG/EisaiInc]

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contained therein. This e-mail message should not be interpreted to include a digital or electronic signature that can be used to authenticate an agreement, contract or other legal document, nor to reflect an intention to be bound to any legally-binding agreement or contract.]

[This e-mail message may contain privileged, confidential and/or proprietary information of Eisai. If you believe that it has been sent to you in error, please contact the sender immediately and delete the message including any attachments, without copying, using, or distributing any of the information contained therein. This e-mail message should not be interpreted to include a digital or electronic signature that can be used to authenticate an agreement, contract or other legal document, nor to reflect an intention to be bound to any legally-binding agreement or contract.]

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

/s/  
-----

STEPHANIE N PARNCUTT  
06/26/2012

**From:** [Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)  
**To:** [Parncutt\\_Stephanie](mailto:Parncutt_Stephanie)  
**Subject:** RE: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets  
**Date:** Wednesday, June 20, 2012 5:24:13 PM

---

Hi Stephanie,  
Yes, I can add the days to the 1.9.2 document that will be submitted tomorrow.

Heather A. Bradley, MPH  
Associate Director, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677  
Tel: 201-949-4691  
Cell: (b) (6)  
Fax: 201-949-4595  
[heather\\_bradley@eisai.com](mailto:heather_bradley@eisai.com)

**From:** "Parncutt, Stephanie" <[Stephanie.Parncutt@fda.hhs.gov](mailto:Stephanie.Parncutt@fda.hhs.gov)>  
**To:** "Heather\_Bradley@Eisai.com" <[Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)>  
**Date:** 06/20/2012 04:39 PM  
**Subject:** RE: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

---

[Heather,](#)

[In your submission, scheduled for tomorrow, please just put the last day of each corresponding month, for the submission dates. This request was made by our PEDS team.](#)

[Stephanie](#)

---

**From:** [Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com) [[mailto:Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)]  
**Sent:** Wednesday, June 20, 2012 2:12 PM  
**To:** Parncutt, Stephanie  
**Subject:** RE: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

Hi Stephanie,  
The May 25, 2011 and Mar 26, 2012 version of 1.9.2 Request for Deferral of Pediatric Studies are the only officially submitted dates as of today, but an updated version will be updated via sequence 0029 which will be submitted tomorrow June 21. I've attached a preview copy of the updated 1.9.2 with the dates I provided via e-mail on April 25, 2012 and again yesterday. The archive eCTD will be updated via sequence 0029 tomorrow with the attached 1.9.2, which now contains protocol submission, study start, study end, and CSR submission dates (see table on page 2). Although it does not have the MM/DD/YYYY format, the month given can be interpreted to mean any day up to the last working day of that month.

If there are further changes needed please let me know, but the attached version is already built into the s0029 submission that will be delivered through the gateway tomorrow so any further changes will require a subsequent update.

Thanks,  
Heather

Heather A. Bradley, MPH  
Associate Director, Global Regulatory Affairs

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155 Tice Boulevard  
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Tel: 201-949-4691  
Cell: (b) (6)  
Fax: 201-949-4595  
[heather\\_bradley@eisai.com](mailto:heather_bradley@eisai.com)

**From:** "Parncutt, Stephanie" <[Stephanie.Parncutt@fda.hhs.gov](mailto:Stephanie.Parncutt@fda.hhs.gov)>  
**To:** "Heather\_Bradley@Eisai.com" <[Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)>  
**Date:** 06/20/2012 01:57 PM  
**Subject:** RE: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

---

[Heather,](#)

[I see the submission of you Request for Deferral of Pediatric Studies in your May 25, 2011 submission as well as the revised version in the March 26, 2012 correspondence. Is there a more recent version? Also, in regards to the dates you listed below, our Pediatric team needs more specific dates in a MM/DD/YYYY format.](#)

Stephanie

---

**From:** Heather\_Bradley@Eisai.com [[mailto:Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)]  
**Sent:** Tuesday, June 19, 2012 3:30 PM  
**To:** Parncutt, Stephanie  
**Subject:** Re: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

Hi Stephanie,  
Below is the e-mail response provided on April 25, 2012 for this request. I may have neglected to then incorporate the e-mail response into an official archive copy. I will add these dates to the 1.9.2 Request for Deferral of Pediatric Studies, which will then contain Protocol submission, Estimated Start, Estimated End and Study Submission dates.

Please let me know if the reviewer requires any additional information.

Regards,  
Heather

----- Forwarded by Heather Bradley/RIG/EisaiInc on 06/19/2012 03:26 PM -----

**From:** Heather Bradley/RIG/EisaiInc  
**To:** "Parncutt, Stephanie" <Stephanie.Parncutt@fda.hhs.gov>  
**Date:** 04/25/2012 03:22 PM  
**Subject:** Re: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

Dear Stephanie,  
As requested by the Maternal Health Reviewer, please find below the anticipated protocol submission date and study submission date for our proposed pediatric studies:

| Study          | Protocol Submission | Study Submission |
|----------------|---------------------|------------------|
| E2007-G000-232 | 1 Nov 2011 (b) (4)  | May 2014         |

(b) (4)

(b) (4)

An official archive copy of this response will be submitted to NDA 202834 as an Information Amendment.

Please let me know if you require any additional information.

Regards,  
Heather

Heather A. Bradley, MPH  
Associate Director, Global Regulatory Affairs

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Heather A. Bradley, MPH  
Associate Director, Global Regulatory Affairs

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Tel: 201-949-4691  
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Fax: 201-949-4595  
heather\_bradley@eisai.com

**From:** "Parncutt, Stephanie" <Stephanie.Parncutt@fda.hhs.gov>  
**To:** "Heather\_Bradley@Eisai.com" <Heather\_Bradley@Eisai.com>  
**Date:** 06/19/2012 02:52 PM  
**Subject:** FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

---

Attached is a request from the PEDS team related to their ongoing review of the FYCOMPA application (N 202-834). Please submit your response to this request in electronic archival format as an amendment to the above NDA. It is acceptable for you to email

your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

\* [Please see the comments below from the PEDS team reviewer:](#)

Please ask the Sponsor to submit a timeline for completion of their pediatric studies for FYCOMPA? We need additional dates other than what they submitted. The timeline should include protocol submission, study completion, and study submission dates (i.e. January 1, 2012).

Please respond to this request ASAP,  
Thank you,

-----  
Stephanie N. Parncutt  
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](mailto:stephanie.parncutt@fda.hhs.gov)

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

STEPHANIE N PARNCUTT  
06/26/2012

**From:** [Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)  
**To:** [Parncutt\\_Stephanie](mailto:Parncutt_Stephanie)  
**Subject:** RE: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets  
**Date:** Monday, June 18, 2012 7:54:22 AM

---

Hi Stephanie,  
Confirming receipt.

Thanks,  
Heather

Heather A. Bradley, MPH  
Associate Director, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677  
Tel: 201-949-4691  
Cell: (b) (6)  
Fax: 201-949-4595  
[heather\\_bradley@eisai.com](mailto:heather_bradley@eisai.com)

**From:** "Parncutt, Stephanie" <Stephanie.Parncutt@fda.hhs.gov>  
**To:** "'Heather\_Bradley@Eisai.com'" <Heather\_Bradley@Eisai.com>  
**Date:** 06/18/2012 01:58 AM  
**Subject:** RE: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

---

[Heather,](#)

[There is an additional Information Request, from our clinical Safety reviewer:](#)

**Just one more request for perampanel by COB June 20, 2012:**

**1) For subject 304-5110-4012, both of the narratives that were submitted in the resubmission and in the 120-day safety update (hyperlinked to the list of subjects with suicidality TEAEs) only contains information regarding DB Study 304 and does not contain information regarding the suicidal ideation that occurred in OLE Study 307. Please submit an updated narrative including information regarding the suicidal ideation.**

[Please confirm receipt,](#)

[Stephanie](#)

---

**From:** Heather\_Bradley@Eisai.com [[mailto:Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)]  
**Sent:** Friday, June 15, 2012 11:38 AM  
**To:** Parncutt, Stephanie  
**Subject:** RE: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

Hi Stephanie,  
Confirming receipt.

Thanks,  
Heather

Heather A. Bradley, MPH  
Associate Director, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
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heather\_bradley@eisai.com

From: "Parncutt, Stephanie" <Stephanie.Parncutt@fda.hhs.gov>  
To: "Heather\_Bradley@Eisai.com" <Heather\_Bradley@Eisai.com>  
Date: 06/15/2012 11:03 AM  
Subject: RE: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

---

Heather,

Again, our Clinical Safety team has an additional Information Request:

**1) In addition to our previous request for a review of all of the SAEs and discontinuation TEAEs (Item #5), please review all of the subjects with TEAEs in the entire safety database (using all sources with information regarding the study subjects in addition to the CRFs) and provide a comprehensive list of the subjects (with hyperlinks to the narratives) with any homicidal or suicidal ideations or who committed any physical assault/abuse, homicide, or suicide attempt (harmed/injured self or another person in any way).**

**In the table listing these subjects, please include columns for treatment group, country/center/subject ID, age/sex/race, maximum dose/last dose, number of days in DB study/OLE study, preferred term, study day AE start/day of death, AE day, relevant medical/psychiatric history, and concomitant medications (at time of AE).**

**Please provide this information by COB on June 22, 2012 for the subjects with TEAEs in the MedDRA SOC Psychiatric disorders or with TEAEs coded to the MedDRA PTs Irritability, Akathisia, Human bite, Physical assault, or Psychomotor hyperactivity.**

**Please provide this information by COB on July 6, 2012 for the remaining subjects.**

Please confirm receipt,

Stephanie

---

**From:** Heather\_Bradley@Eisai.com [[mailto:Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)]  
**Sent:** Thursday, June 14, 2012 2:54 PM  
**To:** Parncutt, Stephanie  
**Subject:** RE: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

Hi Stephanie,  
Confirming receipt.

Thanks,  
Heather

Heather A. Bradley, MPH  
Associate Director, Global Regulatory Affairs

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Date: 06/14/2012 02:21 PM  
Subject: RE: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

---

[Heather,](#)

[In addition, our Clinical Safety team has one more Information Request:](#)

**Please provide the following information by COB on June 21, 2012:**

**1) The narratives provided in the submission contain information that is not documented within the CRFs. For example for subject 304-5118-4002, it is stated in the narrative, that the subject "was admitted to a psychiatric unit for homicidal and suicidal threats." However this information is not documented in the corresponding CRF. Please report the other sources that are used to compile information for the narratives.**

[Please confirm receipt,](#)

[Stephanie](#)

---

**From:** Heather\_Bradley@Eisai.com [[mailto:Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)]  
**Sent:** Wednesday, June 13, 2012 3:31 PM  
**To:** Parncutt, Stephanie  
**Subject:** Re: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

Hi Stephanie,

Confirming receipt of this request. We are assessing these, and I will get back to you with any issues regarding the requested June 21 response time.

Can you please have the Clinical Safety Team reviewer confirm for the following sentence at the end of request #5, is that meant to refer to item#4? i.e. reperform the analyses requested in Item #4 after we do the additional search requested in #5?

**"Please reperform the analyses requested in Item 5) above after this additional search is performed."**

Heather A. Bradley, MPH  
Associate Director, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677  
Tel: 201-949-4691  
Cell: (b) (6)  
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From: "Parncutt, Stephanie" <Stephanie.Parncutt@fda.hhs.gov>  
To: "Heather\_Bradley@Eisai.com" <Heather\_Bradley@Eisai.com>  
Date: 06/13/2012 01:42 PM  
Subject: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

---

Attached is a request from the Clinical Safety team related to their ongoing review of the FYCOMPA application (N 202-834). Please submit your response to this request in electronic archival format as an amendment to the above NDA. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

**\* [Please see the comments below from the Clinical Safety team reviewer:](#)**

- 1) For treatment-emergent markedly abnormal laboratory results, please provide markedly abnormal low values for magnesium (by treatment group) for all of the epilepsy and nonepilepsy pools. Please also provide tables with the analysis limited to subjects with normal baseline values.**
- 2) For subject 306-4703-6008, the narrative does not include the SAE, Mental Disorder Due to a General Medical Condition. Please send the narrative with this SAE listed and described.**
- 3) Please provide narratives for all of the subjects who had treatment-emergent tendon rupture. We have noted that narratives for the 2 SAEs coded to tendon rupture (301-0101-0005 and 301-0128-0005) have already been provided. However, please provide additional information: specifically for subject 301-0128-0005, please provide information regarding the specific tendon that was involved and whether this occurred prior to or after the fall. Please also confirm that the subjects with TEAEs that were coded to PTs related to tendon disorders (tendinitis, tendon injury, and tendon disorder) did not also experience a tendon**

rupture.

4) We have noted that in the 120-Day Safety Update, in Appendix 5, Sections 5 and 6 report the analyses performed for TEAEs of aggressiveness and psychotic disorders, respectively. Each of these analyses included 5 MedDRA preferred terms.

We have also noted that in response to our information request, additional searches for TEAEs coded to the 2 MedDRA SMQs Hostility/Aggression and Psychosis/psychotic disorders were performed. However, the Tables provided in this safety information amendment (dated February 6, 2012) combined these 2 SMQs.

Please provide separate tables for these 2 SMQs for each pooled group (running separate analyses for only narrow preferred terms and for both narrow and broad preferred terms).

Furthermore, please provide similar tables for both SAEs and TEAEs leading to study or study drug discontinuation (along with a list of subjects, preferred terms, and hyperlinks to the narratives).

Please also provide Kaplan-Meier estimated rates of the time to first occurrence of these 2 SMQs - in both tabular and graphical formats.

Please also provide analyses of the severity and outcome of these AEs, and the subjects' history of anger/aggression (and other psychiatric disorders) prior to entering the study.

5) We have reviewed the narratives for the SAEs and discontinuation TEAEs coded to the Psychiatric Disorders SOC. Some of these narratives that were coded to the PTs aggression, belligerence, anger also contained information such as "striking his wife," "homicidal and suicidal threats," "physical altercation," "biting her sister's finger" that were not coded to the relevant MedDRA PTs such as physical assault, physical abuse, homicidal ideation, or suicidal ideation. Please review all of the narratives of subjects with SAEs and discontinuation TEAEs in the entire safety database and provide a comprehensive list of the subjects (with hyperlinks to the narratives) with any homicidal or suicidal ideations or who committed any physical assault/abuse or homicide (harmed/injured self or another person in any way).

In the table listing these subjects, please include columns for treatment group, country/center/subject ID, age/sex/race, maximum dose/last dose, number of days in DB study/OLE study, preferred term, study day AE start/day of death, AE day, relevant medical/psychiatric history, and concomitant medications (at time of AE).

Please reperform the analyses requested in Item 5) above after this additional search is performed.

6) In the Effects During Pregnancy section in the 120-Day Safety Update and the ISS, it is reported that there were 14 pregnancies in 13 women enrolled in the epilepsy studies with 1 pregnancy in Study 304, 12 in Study 307, and 1 in Study 207.

However, in Table 20.35 of the Safety Update, a subject from Study 306 is also listed (4805-6005) and there are no subjects listed from Study 304.

Within the ADAE dataset (for the epilepsy studies), there is a subject with the AE term coded to spontaneous abortion in Study 304 (subject 5151-4001) who is not listed in Table 20.35. Also, in the Safety Update (Table 20.5-75.1), there are only 5 subjects listed with the preferred term, abortion induced, in the epilepsy all treated pool (while there are 7 subjects in the epilepsy studies with induced abortions listed as an AE within the narratives provided in Table 20.35). Furthermore, we have found 2 subjects who experienced 2 pregnancies (including subject 306-3956-6001 had a second positive pregnancy test on December 27, 2011 noted within the narrative.)

Please explain the above discrepancies.

Therefore, in the epilepsy studies, for treatment-emergent pregnancies, we have counted a total of 15 pregnancies (13 in Study 307, 1 in Study 304, and 1 in Study 207). [We have noted that subject 306-4805-6005 experienced a pregnancy during the prerandomization phase.]

Additionally, in the nonepilepsy and Phase 1 studies, we have counted a total of 1 pregnancy in perampanel exposed subjects. [We have noted that subject 013-1001-0213 did not receive

perampanel.]

**Please confirm these totals.**

**Furthermore, the hyperlink to the narrative for subject 307-3003-6001 did not link to the updated narrative that included information for both of the subject's pregnancies.**

**Please resubmit Table 20.35 with a comprehensive list of all of the subjects who experienced pregnancy during any of the epilepsy, nonepilepsy, and Phase 1 studies - with the outcome of the pregnancy listed for each pregnancy (and correct hyperlinks to narratives and CRFs).**

**For subject 306-3956-6001, please provide any additional follow up information regarding the outcome of the subject's pregnancy (positive pregnancy test on December 27, 2011).**

**For subject 306-2760-6003, please provide autopsy results for the male neonate.**

**For the two healthy births, please provide any further information (if available) regarding any congenital malformations.**

Please respond to this request by COB June 21, 2012; if you are unable to meet this timeframe, please contact me to discuss.

Thank you,

-----  
Stephanie N. Parncutt  
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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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STEPHANIE N PARNCUTT  
06/19/2012

**From:** [Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)  
**To:** [Parncutt\\_Stephanie](mailto:Parncutt_Stephanie)  
**Subject:** RE: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets  
**Date:** Friday, June 15, 2012 2:45:56 PM

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Dear Stephanie,

We are assessing the questions received on June 13, 14 and 15 regarding the review of narratives (Q5 and Q7) and TEAE listings (Q8) for additional information/terms that may not have not been coded to the relevant MedDRA PTs and reflected in our AE database. We ask that you share the following preliminary description and questions/comments for clarification with the clinical safety reviewers.

1. Adverse Event → CRF AE page → AE database → AE Listings
2. Adverse Event Leading to Discontinuation → CRF AE Page → AE database → AE Listings  
→ Narrative from Listings only
3. Serious Adverse Event → CRF AE Page → AE database (ongoing reconciliation with SAE database) → AE Listings

↳ SAE Report sent to PV → Investigator queried for additional information as necessary → SAE database (ongoing reconciliation with AE database) → CIOMS → Final SAE Narrative from Listings and CIOMS

Adverse Events reported by a subject are documented on the study CRF AE page by the investigator. These CRF pages are entered and coded to comprise our AE database which generates AE listings. If an event results in study discontinuation, then the narrative for this event is written from data contained only in the AE listings.

Should an event be assessed by an investigator as a SAE, in addition to the CRF AE page the investigator also completes a SAE form to submit to Eisai Pharmacovigilance for consideration for expedited reporting to health authorities. The investigator may be asked for additional information by PV to fully understand and document the event and this additional information is used to complete a CIOMS form. However, while Eisai Product Safety may request additional clarifications that result in the investigator changing the verbatim term or adding additional terms, Eisai Product Safety does not add additional event terms on their own. Likewise, a study monitor reviewing CRF pages may notice that there are individual event terms in the source documents and query the investigator whether they should be reported as adverse events, but it is the investigator's determination as to whether a given term is best subsumed under a diagnosis or other event term. For both the clinical trial AE database and the PV SAE database, the investigator verbatim term is coded to the closest MedDRA LLT.

When writing narratives for SAEs (after final AE/SAE database reconciliation and database lock), the source information is both the listings generated from the AE database and the CIOMS form containing free text descriptions from the investigator. That is why narratives may contain information not in the CRF pages or AE database.

Therefore, while it is possible that the SAE narratives contain supporting descriptions of events not captured on CRF pages nor coded in the AE database, it is not standard practice to use that CIOMS description to then add new events to the AE database that were not reported by an investigator on study source documentation (Q5).

Questions/Comments:

1. If after this explanation the reviewer still requests that our SAE narratives be reviewed to identify

CIOMS text description terms not in our AE database, we request that the review be limited to the double-blind placebo controlled studies, so as to provide a background against which such events can be analyzed. In addition, we ask that FDA provide a list of terms that we can use for a programmed search relating to "any homicidal or suicidal ideations or who committed any physical assault/abuse or homicide (harmed/injured self or another person in any way". A manual review for any word possibly related to physical harm would be prohibitively time consuming given the number of narratives in our filing and the number of potentially related terms. However, while we may identify terms contained in the CIOMS and not in the AE database, we do not consider it appropriate to overwrite the AE database with these terms since they are not investigator-reported on any study-level source documentation that we can verify.

Furthermore, any unlocking of our AE database and re-coding would then impact the numerous other AE tables provided throughout the dossier.

2. Given the description of safety reporting provided above, a review of narratives for TEAEs leading to discontinuation is unlikely to reveal any terms that are not located in the AE database/AE listings already provided since those listings are the only source material used for these narratives. Given this explanation, we propose that a manual review of these narratives for TEAEs leading to discontinuation should not be required.
3. Likewise for TEAEs (Q8 received Jun 15), there is no additional source data for the AE listings other than the CRFs coded to the AE database so there is no additional content to perform a manual review on.
4. Therefore, given our stated reasons against adding additional AE terms post-hoc to the AE database, we plan to provide the requested tables and analyses from Q4 on the existing AE database.
- 5.

We would be happy to have a teleconference with the safety reviewer and the Division to discuss this if needed.

Thanks and regards,  
Heather

Heather A. Bradley, MPH  
Associate Director, Global Regulatory Affairs

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Heather,

Again, our Clinical Safety team has an additional Information Request:

1) In addition to our previous request for a review of all of the SAEs and discontinuation TEAEs (Item #5), please review all of the subjects with TEAEs in the entire safety database (using all sources with information regarding the study subjects in addition to the CRFs) and provide a comprehensive list of the subjects (with hyperlinks to the narratives) with any homicidal or suicidal ideations or who committed any physical assault/abuse, homicide, or suicide attempt (harmed/injured self or another person in any way).

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Please provide this information by COB on July 6, 2012 for the remaining subjects.

Please confirm receipt,

Stephanie

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**From:** Heather\_Bradley@Eisai.com [[mailto:Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)]  
**Sent:** Thursday, June 14, 2012 2:54 PM  
**To:** Parncutt, Stephanie  
**Subject:** RE: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

Hi Stephanie,  
Confirming receipt.

Thanks,  
Heather

Heather A. Bradley, MPH  
Associate Director, Global Regulatory Affairs

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**Please provide the following information by COB on June 21, 2012:**

**1) The narratives provided in the submission contain information that is not documented within the CRFs. For example for subject 304-5118-4002, it is stated in the narrative, that the subject "was admitted to a psychiatric unit for homicidal and suicidal threats." However this information is not documented in the corresponding CRF. Please report the other sources that are used to compile information for the narratives.**

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Stephanie

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**"Please reperform the analyses requested in Item 5) above after this additional search is performed."**

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Associate Director, Global Regulatory Affairs

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Date: 06/13/2012 01:42 PM  
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**[\\* Please see the comments below from the Clinical Safety team reviewer:](#)**

**1) For treatment-emergent markedly abnormal laboratory results, please provide markedly abnormal low values for magnesium (by treatment group) for all of the epilepsy and nonepilepsy pools. Please also provide tables with the analysis limited to subjects with normal baseline values.**

**2) For subject 306-4703-6008, the narrative does not include the SAE, Mental Disorder Due to a General Medical Condition. Please send the narrative with this SAE listed and described.**

**3) Please provide narratives for all of the subjects who had treatment-emergent tendon rupture. We have noted that narratives for the 2 SAEs coded to tendon rupture (301-0101-0005 and 301-0128-0005) have already been provided. However, please provide additional information: specifically for subject 301-0128-0005, please provide information regarding the specific tendon that was involved and whether this occurred prior to or after the fall. Please also confirm that the subjects with TEAEs that were coded to PTs related to tendon disorders (tendinitis, tendon injury, and tendon disorder) did not also experience a tendon rupture.**

**4) We have noted that in the 120-Day Safety Update, in Appendix 5, Sections 5 and 6 report the analyses performed for TEAEs of aggressiveness and psychotic disorders, respectively. Each of these analyses included 5 MedDRA preferred terms.**

**We have also noted that in response to our information request, additional searches for TEAEs coded to the 2 MedDRA SMQs Hostility/Aggression and Psychosis/psychotic disorders were performed. However, the Tables provided in this safety information amendment (dated February 6, 2012) combined these 2 SMQs.**

**Please provide separate tables for these 2 SMQs for each pooled group (running separate analyses for only narrow preferred terms and for both narrow and broad preferred terms).**

**Furthermore, please provide similar tables for both SAEs and TEAEs leading to study or study drug discontinuation (along with a list of subjects, preferred terms, and hyperlinks to the narratives).**

**Please also provide Kaplan-Meier estimated rates of the time to first occurrence of these 2 SMQs - in both tabular and graphical formats.**

**Please also provide analyses of the severity and outcome of these AEs, and the subjects' history of anger/aggression (and other psychiatric disorders) prior to entering the study.**

**5) We have reviewed the narratives for the SAEs and discontinuation TEAEs coded to the Psychiatric Disorders SOC. Some of these narratives that were coded to the PTs aggression, belligerence, anger also contained information such as "striking his wife," "homicidal and suicidal threats," "physical altercation," "biting her sister's finger" that were not coded to the relevant MedDRA PTs such as physical assault, physical abuse, homicidal ideation, or suicidal ideation. Please review all of the narratives of subjects with SAEs and discontinuation TEAEs in the entire safety database and provide a comprehensive list of the subjects (with hyperlinks to the narratives) with any homicidal or suicidal ideations or who committed any physical assault/abuse or homicide (harmed/injured self or another person in any way).**

**In the table listing these subjects, please include columns for treatment group, country/center/subject ID, age/sex/race, maximum dose/last dose, number of days in DB study/OLE study, preferred term, study day AE start/day of death, AE day, relevant**

medical/psychiatric history, and concomitant medications (at time of AE).  
Please reperform the analyses requested in Item 5) above after this additional search is performed.

6) In the Effects During Pregnancy section in the 120-Day Safety Update and the ISS, it is reported that there were 14 pregnancies in 13 women enrolled in the epilepsy studies with 1 pregnancy in Study 304, 12 in Study 307, and 1 in Study 207.

However, in Table 20.35 of the Safety Update, a subject from Study 306 is also listed (4805-6005) and there are no subjects listed from Study 304.

Within the ADAE dataset (for the epilepsy studies), there is a subject with the AE term coded to spontaneous abortion in Study 304 (subject 5151-4001) who is not listed in Table 20.35. Also, in the Safety Update (Table 20.5-75.1), there are only 5 subjects listed with the preferred term, abortion induced, in the epilepsy all treated pool (while there are 7 subjects in the epilepsy studies with induced abortions listed as an AE within the narratives provided in Table 20.35). Furthermore, we have found 2 subjects who experienced 2 pregnancies (including subject 306-3956-6001 had a second positive pregnancy test on December 27, 2011 noted within the narrative.)

Please explain the above discrepancies.

Therefore, in the epilepsy studies, for treatment-emergent pregnancies, we have counted a total of 15 pregnancies (13 in Study 307, 1 in Study 304, and 1 in Study 207). [We have noted that subject 306-4805-6005 experienced a pregnancy during the prerandomization phase.]

Additionally, in the nonepilepsy and Phase 1 studies, we have counted a total of 1 pregnancy in perampanel exposed subjects. [We have noted that subject 013-1001-0213 did not receive perampanel.]

Please confirm these totals.

Furthermore, the hyperlink to the narrative for subject 307-3003-6001 did not link to the updated narrative that included information for both of the subject's pregnancies.

Please resubmit Table 20.35 with a comprehensive list of all of the subjects who experienced pregnancy during any of the epilepsy, nonepilepsy, and Phase 1 studies - with the outcome of the pregnancy listed for each pregnancy (and correct hyperlinks to narratives and CRFs).

For subject 306-3956-6001, please provide any additional follow up information regarding the outcome of the subject's pregnancy (positive pregnancy test on December 27, 2011).

For subject 306-2760-6003, please provide autopsy results for the male neonate.

For the two healthy births, please provide any further information (if available) regarding any congenital malformations.

Please respond to this request by COB June 21, 2012; if you are unable to meet this timeframe, please contact me to discuss.

Thank you,

~~~~~  
Stephanie N. Parncutt  
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](mailto:stephanie.parncutt@fda.hhs.gov)

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/s/  
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STEPHANIE N PARNCUTT  
06/19/2012

**From:** [Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)  
**To:** [Parncutt\\_Stephanie](mailto:Parncutt_Stephanie)  
**Subject:** RE: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets  
**Date:** Thursday, June 14, 2012 2:54:19 PM

---

Hi Stephanie,  
Confirming receipt.

Thanks,  
Heather

Heather A. Bradley, MPH  
Associate Director, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677  
Tel: 201-949-4691  
Cell: (b) (6)  
Fax: 201-949-4595  
[heather\\_bradley@eisai.com](mailto:heather_bradley@eisai.com)

**From:** "Parncutt, Stephanie" <Stephanie.Parncutt@fda.hhs.gov>  
**To:** "'Heather\_Bradley@Eisai.com'" <Heather\_Bradley@Eisai.com>  
**Date:** 06/14/2012 02:21 PM  
**Subject:** RE: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

---

[Heather,](#)

[In addition, our Clinical Safety team has one more Information Request:](#)

**Please provide the following information by COB on June 21, 2012:**

**1) The narratives provided in the submission contain information that is not documented within the CRFs. For example for subject 304-5118-4002, it is stated in the narrative, that the subject "was admitted to a psychiatric unit for homicidal and suicidal threats." However this information is not documented in the corresponding CRF. Please report the other sources that are used to compile information for the narratives.**

[Please confirm receipt,](#)

[Stephanie](#)

---

**From:** [Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com) [[mailto:Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)]  
**Sent:** Wednesday, June 13, 2012 3:31 PM  
**To:** Parncutt, Stephanie  
**Subject:** Re: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

Hi Stephanie,  
Confirming receipt of this request. We are assessing these, and I will get back to you with any issues regarding the requested June 21 response time.

Can you please have the Clinical Safety Team reviewer confirm for the following sentence at the end of request #5, is that meant to refer to item#4? i.e. reperform the analyses requested in Item #4 after we do the additional search requested in #5?

**"Please reperform the analyses requested in Item 5) above after this additional search is performed."**

Heather A. Bradley, MPH  
Associate Director, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677  
Tel: 201-949-4691  
Cell: (b) (6)  
Fax: 201-949-4595  
heather\_bradley@eisai.com

From: "Parncutt, Stephanie" <Stephanie.Parncutt@fda.hhs.gov>  
To: "Heather\_Bradley@Eisai.com" <Heather\_Bradley@Eisai.com>  
Date: 06/13/2012 01:42 PM  
Subject: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

---

Attached is a request from the Clinical Safety team related to their ongoing review of the FYCOMPA application (N 202-834). Please submit your response to this request in electronic archival format as an amendment to the above NDA. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

**\* [Please see the comments below from the Clinical Safety team reviewer:](#)**

- 1) For treatment-emergent markedly abnormal laboratory results, please provide markedly abnormal low values for magnesium (by treatment group) for all of the epilepsy and nonepilepsy pools. Please also provide tables with the analysis limited to subjects with normal baseline values.**
- 2) For subject 306-4703-6008, the narrative does not include the SAE, Mental Disorder Due to a General Medical Condition. Please send the narrative with this SAE listed and described.**
- 3) Please provide narratives for all of the subjects who had treatment-emergent tendon rupture. We have noted that narratives for the 2 SAEs coded to tendon rupture (301-0101-0005 and 301-0128-0005) have already been provided. However, please provide additional information: specifically for subject 301-0128-0005, please provide information regarding the specific tendon that was involved and whether this occurred prior to or after the fall. Please also confirm that the subjects with TEAEs that were coded to PTs related to tendon disorders (tendinitis, tendon injury, and tendon disorder) did not also experience a tendon**

rupture.

4) We have noted that in the 120-Day Safety Update, in Appendix 5, Sections 5 and 6 report the analyses performed for TEAEs of aggressiveness and psychotic disorders, respectively. Each of these analyses included 5 MedDRA preferred terms.

We have also noted that in response to our information request, additional searches for TEAEs coded to the 2 MedDRA SMQs Hostility/Aggression and Psychosis/psychotic disorders were performed. However, the Tables provided in this safety information amendment (dated February 6, 2012) combined these 2 SMQs.

Please provide separate tables for these 2 SMQs for each pooled group (running separate analyses for only narrow preferred terms and for both narrow and broad preferred terms).

Furthermore, please provide similar tables for both SAEs and TEAEs leading to study or study drug discontinuation (along with a list of subjects, preferred terms, and hyperlinks to the narratives).

Please also provide Kaplan-Meier estimated rates of the time to first occurrence of these 2 SMQs - in both tabular and graphical formats.

Please also provide analyses of the severity and outcome of these AEs, and the subjects' history of anger/aggression (and other psychiatric disorders) prior to entering the study.

5) We have reviewed the narratives for the SAEs and discontinuation TEAEs coded to the Psychiatric Disorders SOC. Some of these narratives that were coded to the PTs aggression, belligerence, anger also contained information such as "striking his wife," "homicidal and suicidal threats," "physical altercation," "biting her sister's finger" that were not coded to the relevant MedDRA PTs such as physical assault, physical abuse, homicidal ideation, or suicidal ideation. Please review all of the narratives of subjects with SAEs and discontinuation TEAEs in the entire safety database and provide a comprehensive list of the subjects (with hyperlinks to the narratives) with any homicidal or suicidal ideations or who committed any physical assault/abuse or homicide (harmed/injured self or another person in any way).

In the table listing these subjects, please include columns for treatment group, country/center/subject ID, age/sex/race, maximum dose/last dose, number of days in DB study/OLE study, preferred term, study day AE start/day of death, AE day, relevant medical/psychiatric history, and concomitant medications (at time of AE).

Please reperform the analyses requested in Item 5) above after this additional search is performed.

6) In the Effects During Pregnancy section in the 120-Day Safety Update and the ISS, it is reported that there were 14 pregnancies in 13 women enrolled in the epilepsy studies with 1 pregnancy in Study 304, 12 in Study 307, and 1 in Study 207.

However, in Table 20.35 of the Safety Update, a subject from Study 306 is also listed (4805-6005) and there are no subjects listed from Study 304.

Within the ADAE dataset (for the epilepsy studies), there is a subject with the AE term coded to spontaneous abortion in Study 304 (subject 5151-4001) who is not listed in Table 20.35. Also, in the Safety Update (Table 20.5-75.1), there are only 5 subjects listed with the preferred term, abortion induced, in the epilepsy all treated pool (while there are 7 subjects in the epilepsy studies with induced abortions listed as an AE within the narratives provided in Table 20.35). Furthermore, we have found 2 subjects who experienced 2 pregnancies (including subject 306-3956-6001 had a second positive pregnancy test on December 27, 2011 noted within the narrative.)

Please explain the above discrepancies.

Therefore, in the epilepsy studies, for treatment-emergent pregnancies, we have counted a total of 15 pregnancies (13 in Study 307, 1 in Study 304, and 1 in Study 207). [We have noted that subject 306-4805-6005 experienced a pregnancy during the prerandomization phase.]

Additionally, in the nonepilepsy and Phase 1 studies, we have counted a total of 1 pregnancy in peramp panel exposed subjects. [We have noted that subject 013-1001-0213 did not receive

perampanel.]

**Please confirm these totals.**

**Furthermore, the hyperlink to the narrative for subject 307-3003-6001 did not link to the updated narrative that included information for both of the subject's pregnancies.**

**Please resubmit Table 20.35 with a comprehensive list of all of the subjects who experienced pregnancy during any of the epilepsy, nonepilepsy, and Phase 1 studies - with the outcome of the pregnancy listed for each pregnancy (and correct hyperlinks to narratives and CRFs).**

**For subject 306-3956-6001, please provide any additional follow up information regarding the outcome of the subject's pregnancy (positive pregnancy test on December 27, 2011).**

**For subject 306-2760-6003, please provide autopsy results for the male neonate.**

**For the two healthy births, please provide any further information (if available) regarding any congenital malformations.**

Please respond to this request by COB June 21, 2012; if you are unable to meet this timeframe, please contact me to discuss.

Thank you,

-----  
Stephanie N. Parncutt  
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](mailto:stephanie.parncutt@fda.hhs.gov)

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/s/  
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STEPHANIE N PARNCUTT  
06/14/2012



NDA 202834

**INFORMATION REQUEST**

Eisai, Inc.  
Attention: Heather A. Bradley, MPH  
Associate Director, Regulatory Affairs  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677

Dear Ms. Bradley:

Please refer to your December 22, 2011, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for perampanel film coated tablets, 2mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg.

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

**Drug Substance**

1. Include a test and limit for (b) (4) in the specification for starting material (b) (4).
2. Include a test and acceptance limit for Assay attribute in the specification for intermediate (b) (4).
3. Provide information on the origin of the previous primary reference standard Batch 10091905 that was used for elucidation of structure of perampanel, i.e., what manufacturing process was used for this reference standard.
4. Revise the acceptance criterion for particle size in the drug substance specification to include the (b) (4) particle size distribution as the particle distribution can impact the drug product dissolution and content uniformity.
5. Provide the Limit of Detection and Limit of Quantification for identifying the polymorphic forms other than perampanel  $\frac{3}{4}$  hydrate, for the XRPD method.
6. Provide a statement with citation of the appropriate 21 CFR regulation that the (b) (4), are manufactured from (b) (4).
7. Provide information on the particle size determination for drug substance batches during the stability studies to evaluate any potential agglomeration on storage.
8. Include the accelerated stability testing in the post-approval stability protocol for the first three production batches of drug substance.

9. Include the X-Ray Powder Diffraction test at the test time point of (b) (4), in the proposed Test Schedules for First Three Production Batches and for Annual Production Batches.

### **Drug Product**

1. Demonstrate effect of the particle size distribution on content uniformity of perampanel tablets with Formulation D (6, 8, 10, and 12 mg) since the Proposed Operating Conditions for manufacturing process differ for Formulation C tablets and for Formulation D tablets.
2. Revise the In-process Controls for perampanel 2 mg (b) (4) and 4, 6, 8, 10 and 12 mg (b) (4) to measure the hardness and thickness of the (b) (4) periodically during the (b) (4), and not only at the initial setup of the (b) (4) (refer to Section 3.2.P.3.4 of the NDA submission).
3. Revise the acceptance criterion for individual unspecified related substances to NMT (b) (4) in the specifications for all dosage strengths. This acceptance criterion should be set at the identification threshold for such impurities based on the maximum daily intake in accordance with ICH Q3B(R2) requirements.
4. Include a test in the drug product specification to monitor the polymorphic form of perampanel that has undergone the tablet manufacturing process, or provide justification why such a test is not needed.
5. Include a test in the drug product specification that assures compliance of the perampanel tablets with USP <467> requirements for residual solvents.
6. Include a test and a limit for (b) (4) in the drug product specifications since the polymorphic form of the drug substance (b) (4).
7. Provide the LOD for Related Substances for the analytical method Assay and Related Substances by HPLC for drug product testing.
8. Provide information on the reference standards used for testing of the drug product, i.e. provide a reference to the (b) (4) used to obtain a reference standards for perampanel and related impurities, and Certificates of Analysis for these standards.
9. Provide a comparison of the technical drawing for Starter Kit (blister of 14 tablets) and for the (b) (4) that were used for packaging of the perampanel tablets, 2 mg and 4 mg, for stability studies. In case the product contact surfaces and/or dimensions of the (b) (4) are different in the Starter Kit Blister, provide stability data for drug product packaged in Starter Kit Blister.
10. Provide appropriate CFR citation to confirm that all HDPE bottle components, blister packaging components, and components of the (b) (4) for bulk tablets, that are in contact with the drug product, are safe for use when in contact with the drug.
11. Provide clarification on the stability protocols/testing intervals in the Section 3.2.P.8.1.2 Stability Protocols as follows:
  - a) Table 3.2.P.8.1-10: Do you propose testing (Test A) at 6-month and 9-month time points of long-term testing for 2 mg batch 800854A, and for 4 mg batches P5X004ZZA and P5X005ZZA?

- b) Table 3.2.P.8.1-21: Do you propose testing (Test A) at 6-month time point of long-term testing for 6 mg batch W061007, 8 mg batch W061015, 10 mg batch W061020, and 12 mg batches W061025 and W061033?
  - c) Table 3.2.P.8.1-23: Do you propose testing (Test A) at 6-month time point of long-term testing for 8 mg batch W061016, 10 mg batch W061021, and 12 mg batch W061034?
  - d) Table 3.2.P.8.1-25: Do you propose testing (Test A) at 6-month time point of long-term testing for 6 mg batch W061009, 8 mg batch W061017, 10 mg batch W061022, and 12 mg batches W061027 and W061035?
12. Provide a representative packaging batch records including the packaging batch record for blister card of the Starter Kit.
13. The proposed dissolution acceptance criterion of (b) (4) is not supported by the provided dissolution data. The dissolution data for: 1) each of the 2, 4, 6, and 12 mg strengths used in the PK (bio-batches) and/or clinical studies, and 2) the stability batches for 6, 8 and 10 mg strengths, support a dissolution acceptance criterion of Q (b) (4) at 15 min for your product at release and during the stability testing. Therefore, revise the drug product specification to include a Q (b) (4) at 15 minutes and provide updated specification. Additionally, provide the dissolution data for the 15-minute time point for the registration batches currently under the stability program (each strength).

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/  
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RAMESH K SOOD  
06/07/2012

## REQUEST FOR CONSULTATION

TO (Office/Division): **OND /Div Cardiology and Renal Products IRT-QT**  
Attn: **Devi Kozeli (WO22/Room 4183)**

FROM (Name, Office/Division, and Phone Number of Requestor): **Sally Yasuda, MS, PharmD, Safety Team Leader, Division of Neurology Products**

DATE <b>June 6, 2012</b>	IND NO.	NDA NO. <b>202834</b>	TYPE OF DOCUMENT <b>Cardiac Safety Report</b>	DATE OF DOCUMENT <b>04/20/2012</b>
NAME OF DRUG <b>FYCOMPA (perapanel) Tablets</b>		PRIORITY CONSIDERATION <b>Standard</b>	CLASSIFICATION OF DRUG <b>Partial onset-seizures</b>	DESIRED COMPLETION DATE <b>July 13, 2012</b>

NAME OF FIRM: **Eisai, Inc.**

### REASON FOR REQUEST

#### I. GENERAL

- |   |  |  |
|---|--|--|
| <input type="checkbox"/> NEW PROTOCOL<br><input checked="" type="checkbox"/> PROGRESS REPORT<br><input type="checkbox"/> NEW CORRESPONDENCE<br><input type="checkbox"/> DRUG ADVERTISING<br><input type="checkbox"/> ADVERSE REACTION REPORT<br><input type="checkbox"/> MANUFACTURING CHANGE / ADDITION<br><input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE-NDA MEETING<br><input type="checkbox"/> END-OF-PHASE 2a MEETING<br><input type="checkbox"/> END-OF-PHASE 2 MEETING<br><input type="checkbox"/> RESUBMISSION<br><input checked="" type="checkbox"/> SAFETY / EFFICACY<br><input type="checkbox"/> PAPER NDA<br><input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER<br><input type="checkbox"/> FINAL PRINTED LABELING<br><input type="checkbox"/> LABELING REVISION<br><input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE<br><input type="checkbox"/> FORMULATIVE REVIEW<br><input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
|---|--|--|

#### II. BIOMETRICS

- |   |  |
|---|--|
| <input type="checkbox"/> PRIORITY P NDA REVIEW<br><input type="checkbox"/> END-OF-PHASE 2 MEETING<br><input type="checkbox"/> CONTROLLED STUDIES<br><input type="checkbox"/> PROTOCOL REVIEW<br><input type="checkbox"/> OTHER (SPECIFY BELOW): | <input type="checkbox"/> CHEMISTRY REVIEW<br><input type="checkbox"/> PHARMACOLOGY<br><input type="checkbox"/> BIOPHARMACEUTICS<br><input type="checkbox"/> OTHER (SPECIFY BELOW): |
|---|--|

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION<br><input type="checkbox"/> BIOAVAILABILITY STUDIES<br><input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE<br><input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS<br><input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|--|--|

#### IV. DRUG SAFETY

- |   |   |
|---|---|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL<br><input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES<br><input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)<br><input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY<br><input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE<br><input type="checkbox"/> POISON RISK ANALYSIS |
|---|---|

#### V. SCIENTIFIC INVESTIGATIONS

- |  |                                      |
|--|--------------------------------------|
| <input checked="" type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|--|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** NDA 202834 was resubmitted on December 22, 2011 and provides for treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older. This is a NME. The resubmission has a PDUFA goal date of 10-22-12. Please review and comment on the Cardiac Safety Report contained in the 120-Day Safety Update Report (within Appendix 4) submitted in the Clincial/Safety Update on April 20, 2102 (Module 5.3.5.3.28). The entire submission may be accessed at :\\CDSESUB1\EVSPROD\NDA202834\202834.ENX. This Cardiac Safety Report reviewed OLE Study 228 which revealed after 12 months of treatment a mean change from baseline of QTcF of 12.6 msec (median 15.0) in the highest dose group (>8-12 mg/day). The Sponsor's report concludes that this QT signal was not caused by perampanel treatment. Please review this study in the context of the other ECG data and comment on the Sponsor's conclusion. We have noted the FDA IRT's review of the TQT study (Study 013) that reported that no significant QTc prolongation effect of perampanel (6 mg and 12 mg) was detected. Please contact Dr. Mary Doi (mary.doi@fda.hhs.gov) if you have any questions.

<p>SIGNATURE OF REQUESTOR Stephanie Parncutt, Regulatory Project Manager, DNP Food and Drug Administration Phone: 301-796-4098 Email: stephanie.parncutt@fda.hhs.gov</p>	<p>METHOD OF DELIVERY (Check one) <input type="checkbox"/> DFS      <input checked="" type="checkbox"/> EMAIL      <input type="checkbox"/> MAIL      <input type="checkbox"/> HAND</p>
<p>PRINTED NAME AND SIGNATURE OF RECEIVER</p>	<p>PRINTED NAME AND SIGNATURE OF DELIVERER</p>

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/s/  
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STEPHANIE N PARNCUTT  
06/11/2012

**From:** [Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)  
**To:** [Parncutt\\_Stephanie](mailto:Parncutt_Stephanie)  
**Subject:** RE: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets  
**Date:** Tuesday, May 15, 2012 1:58:46 PM

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Hi Stephanie,  
Sorry, yes it was received. I'll get back to you if we have any issues with the timeline.

Thanks,  
Heather

Heather A. Bradley, MPH  
Associate Director, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677  
Tel: 201-949-4691  
Cell: (b) (6)  
Fax: 201-949-4595  
[heather\\_bradley@eisai.com](mailto:heather_bradley@eisai.com)

From: "Parncutt, Stephanie" <[Stephanie.Parncutt@fda.hhs.gov](mailto:Stephanie.Parncutt@fda.hhs.gov)>  
To: "Parncutt, Stephanie" <[Stephanie.Parncutt@fda.hhs.gov](mailto:Stephanie.Parncutt@fda.hhs.gov)>, "[Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)" <[Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)>  
Date: 05/15/2012 01:48 PM  
Subject: RE: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

---

[Heather,](#)

[Can you please confirm receipt of this second IR?](#)

[Stephanie](#)

---

**From:** Parncutt, Stephanie  
**Sent:** Friday, May 11, 2012 1:48 PM  
**To:** 'Heather\_Bradley@Eisai.com'  
**Subject:** FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

Attached is a request from the Clinical Safety team related to their ongoing review of the FYCOMPA application (N 202-834). Please submit your response to this request in electronic archival format as an amendment to the above NDA. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

[\\* Please see the comments below from the Clinical Safety team reviewer:](#)

**1) Please resend the dataset SUPPYP for Study e2007-g000-304. It cannot be opened with SAS.**

2) For the ADAE datasets provided in the NDA and in the 120-day Safety Update, the full MedDRA hierarchy is not included. Specifically, the High Level Group Terms (HLGT) are not included. Please resubmit the ADAE (epilepsy, nonepilepsy, and Phase 1) datasets with a column for MedDRA HLGT. Also, please confirm that the SOCs included in the ADAE datasets are primary SOCs. If so, please also include a column with secondary SOCs.

3) In the NDA and in the 120-day Safety Update, the section Adverse Events of Particular Interest: Falls, the number of falls (SAEs) occurring with concurrent seizures is reported. Please describe how this information was obtained (narrative, CRF, versus verbatim term). It is reported in the 120-day Safety Update (page 96), there were 136 subjects with 226 falls. Please stratify these falls by whether or not they occurred with concurrent seizures. Specifically, please identify and report the falls that occurred as a result of a seizure (by unique subject ID and study day #). Please also identify and report all of the injuries (in the Accidents and Injury SMQ) that occurred as a result of a seizure (by unique subject ID and study day #).

Please respond to this request by COB May 21, 2012 (Item #3 can be provided by May 25, 2012); if you are unable to meet this timeframe, please contact me to discuss.

Thank you,

~~~~~  
Stephanie N. Parncutt  
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](mailto:stephanie.parncutt@fda.hhs.gov)

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/s/  
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STEPHANIE N PARNCUTT  
05/15/2012

**From:** [Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)  
**To:** [Parncutt\\_Stephanie](mailto:Parncutt_Stephanie)  
**Subject:** Re: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets  
**Date:** Tuesday, May 08, 2012 2:42:13 PM

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Dear Stephanie,  
Confirming receipt. I'll let you know if we have any questions.

On another note, we are approaching the 5 month point of the application's review. I'm curious to know if there will be any opportunity to receive an update on the status of the overall review after your mid-cycle review meeting (i.e. if there is an anticipated extension of the review clock, when we will begin label negotiations, the status of the scheduling recommendation, etc.). I'd appreciate anything you can share about this process.

Regards,  
Heather

Heather A. Bradley, MPH  
Associate Director, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677  
Tel: 201-949-4691  
Cell: (b) (6)  
Fax: 201-949-4595  
[heather\\_bradley@eisai.com](mailto:heather_bradley@eisai.com)

**From:** "Parncutt, Stephanie" <[Stephanie.Parncutt@fda.hhs.gov](mailto:Stephanie.Parncutt@fda.hhs.gov)>  
**To:** "'Heather\_Bradley@Eisai.com'" <[Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)>  
**Date:** 05/08/2012 02:15 PM  
**Subject:** FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

---

Attached is a request from the Clinical Safety team related to their ongoing review of the FYCOMPA application (N 202-834). Please submit your response to this request in electronic archival format as an amendment to the above NDA. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

\* [Please see the comments below from the Clinical Safety team reviewer:](#)

**1) Thank you for providing datasets in the 120-day Safety Update on 4/20/12. The split lab datasets (adlb01-Epilepsy through adlb07-Epilepsy) have different dataset labels. However, these 7 datasets have the same dataset name. Please resubmit the laboratory datasets for the epilepsy studies with unique dataset names.**

**2) There is an Epoch column for the datasets. Please explain why Study 231 is listed as CORE within that column?**

3) In the 120-day Safety Update, Table 20.8-44.1 lists the TEAEs leading to discontinuation by SOC, PT and Modal Dose of Perampanel for the Epilepsy All Treated Pool. Within the SOC, Pregnancy, Puerperium and Perinatal Conditions, there are no subjects listed with the PT pregnancy. However, in the ISS, Appendix B, Table 20.8-3, there is one subject listed with the PT pregnancy. Please explain this discrepancy. Please verify that all of the subjects listed in the ISS are included in the 120-day Safety Update.

4) For treatment-emergent markedly abnormal laboratory results, please provide markedly abnormal high values for creatine kinase and LDH (by treatment group) for the all treated epilepsy pool (including the data from the 120-day Safety Update). Please also provide these values when the analysis was limited to subjects with normal baseline values.

Please respond to this request by COB May 14, 2012; if you are unable to meet this timeframe, please contact me to discuss.

Thank you,

-----  
Stephanie N. Parncutt  
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](mailto:stephanie.parncutt@fda.hhs.gov)

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/s/  
-----

STEPHANIE N PARNCUTT  
05/15/2012

**From:** [Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)  
**To:** [Parncutt\\_Stephanie](mailto:Parncutt_Stephanie)  
**Subject:** Re: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets  
**Date:** Monday, April 16, 2012 12:57:04 PM

---

Hi Stephanie,  
Confirming receipt of this request. I will get back to you if we have questions or if we cannot respond by EOB April 20th. Please note that the 4-month safety update will also be submitted this week.

Heather A. Bradley, MPH  
Associate Director, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677  
Tel: 201-949-4691  
Cell: (b) (6)  
Fax: 201-949-4595  
[heather\\_bradley@eisai.com](mailto:heather_bradley@eisai.com)

**From:** "Parncutt, Stephanie" <Stephanie.Parncutt@fda.hhs.gov>  
**To:** "Heather\_Bradley@Eisai.com" <Heather\_Bradley@Eisai.com>  
**Date:** 04/16/2012 12:24 PM  
**Subject:** FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

---

Attached is a request from the Clinical Safety team related to their ongoing review of the FYCOMPA application (N 202-834). Please submit your response to this request in electronic archival format as an amendment to the above NDA. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

**[\\* Please see the comments below from the Clinical Safety team reviewer:](#)**

**Please provide the following information:**

**1) Additional analyses of weight and appetite was provided for the epilepsy population in the ISS (Section 9.1.1.4). However, these analyses were not provided for the nonepilepsy population. Please provide these analyses for the nonepilepsy population.**

**2) On page 483 of the ISS, in the second to last sentence of the second paragraph, the hyperlink to 2.7.4, Table 32 connects to a table of extent of exposure and not to a display of ADRs by SOC and preferred term. Please provide the correct table.**

**3) For treatment-emergent markedly abnormal laboratory results, please provide markedly abnormal high values for creatine kinase and LDH (by treatment group) for all of the epilepsy and nonepilepsy pools. Please also provide tables when the analysis was limited to subjects with normal baseline values.**

**4) For orthostatic changes in blood pressure and pulse, (Sections 9.1.1.5, 9.1.2.5, and 9.1.3), the**

values are reported for abnormal vital sign changes from supine to standing. Tables 20.12-27, 20.12-61, 22.6-7, and 22.6-8 report the number of subjects who had abnormal changes in systolic blood pressure, diastolic blood pressure, and pulse. Please provide information (in tables) for subjects who had decreases in blood pressure and increases in pulse, concurrently. Specifically, please report the number of subjects who had both a systolic blood pressure decrement  $\geq 20$  mmHg (or decrement  $\geq 40$  mmHg) and pulse increment  $\geq 15$  bpm (or increment  $\geq 30$  bpm).

**5) Analysis of subjects who fit the search criteria for DRESS. Please see attached search criteria.**

Please respond to this request by COB April 20, 2012; if you are unable to meet this timeframe, please contact me to discuss.

Thank you,

~~~~~  
Stephanie N. Parncutt  
Regulatory Project Manager  
Division of Neurology Products  
Center for Drug Evaluation and Research, FDA  
10903 New Hampshire Avenue; WO22 Rm. 4355  
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[attachment "UPDATED MedDRA terms for identification of DRESS 041612.doc" deleted by Heather Bradley/RIG/EisaiInc]

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## Updated List of MedDRA. Search terms for identification of DRESS<sup>1</sup>

### *Modified RegiSCAR criteria for DRESS<sup>2</sup>*

Reaction suspected to be drug related with
1. Acute skin rash
2. Involvement of at least one internal organ
3. Enlarged lymph nodes of at least two sites
4. One of the following blood count abnormalities (as reference you should use the limits provided by the lab that has done the analysis)
- lymphocytes above or below the lab limits
- eosinophils above the lab limits (in % or absolute count)
- platelets below the lab limits
5. Fever above 38°C
(At least 3 of these criteria should be present for HSS/DRESS)

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

<sup>1</sup> MedDRA version 13.1. Some PT may be mentioned in more than one SOC.

<sup>2</sup> There should be certain temporal proximity for the onset of these AE (within 1 month of each other).

Eosinophilia  
Febrile neutropenia  
Granulocytopenia  
Hemolytic anemia  
Hemolysis  
Hypereosinophilic syndrome  
Leukemoid reaction  
Leukopenia  
Lymphocytosis  
Lymphopenia  
Leukocytoclastic vasculitis  
Lymphadenitis  
Lymphadenopathy  
Lymphoma  
Monocytosis  
Mononucleosis  
Neutropenia  
Pancytopenia  
Platelet disorder  
Platelet toxicity  
Splentitis  
Splénomegaly  
Splénosis  
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  
Polyarthritis  
Tendonitis

Tenosynovitis  
Synovitis  
Any PT under the MedDRA Connective tissue disorder HLGTT.

#### 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 HLGTT

#### 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/  
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STEPHANIE N PARNCUTT  
04/16/2012



NDA 202834

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07667

ATTENTION: Heather A. Bradley, MPH  
Associate Director, Regulatory Affairs

Dear Ms. Bradley:

Please refer to your New Drug Application (NDA) dated and received May 25, 2011 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for perampanel tablets, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg.

Please also refer to your resubmission dated and received December 22, 2011. We also refer to your correspondence dated and received January 17, 2012, requesting review of your proposed proprietary name, Fycompa.

We have completed our review of the proposed proprietary name Fycompa, and have concluded that it is acceptable. If **any** of the proposed product characteristics as stated in your January 17, 2012 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

The proposed proprietary name, Fycompa 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 you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Laurie Kelley, Safety 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, Stephanie Parncutt at (301) 796-4098.

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/  
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LAURIE A KELLEY  
04/11/2012

CAROL A HOLQUIST  
04/11/2012

# REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW

**To be completed for all new NDAs, new BLAs, Efficacy Supplements, and PLR Conversion Supplements**

**Application:** NDA 202834

**Name of Drug:** FYCOMPA (perampanel) Tablets 2mg, 4mg, 6mg, 8mg, 10mg, 12mg

**Applicant:** Eisai, Inc.

**Submission Date:** December 22, 2011

**Receipt Date:** December 22, 2011

## Background and Summary Description

Perampanel is a proposed first-in-class antagonist of the AMPA glutamate receptor on post-synaptic neurons. AMPA antagonists could potentially reduce excessive excitatory activity and excitotoxicity, and thus exhibit anticonvulsant and potentially antiepileptogenic effects. . The sponsor proposes the following indication for perampanel: “for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older.” The sponsor proposes a recommended starting dose of 2 mg orally once daily before bedtime and recommends titration depending on response and tolerability to a maximum dose of 12 mg once a day.

## Review

The submitted labeling was reviewed in accordance with the labeling requirements listed in the “Selected Requirements for Prescribing Information (SRPI)” section of this review. Labeling deficiencies are identified in this section with an “X” in the checkbox next to the labeling requirement.

In addition, the following labeling issues were identified:

1. Recommend that the first Warning and Precaution in the Highlights “Suicidal Behavior and Ideation” include ways to mitigate or monitor this adverse reaction.
2. Recommend that Section 2.3 of “Patients with Renal Impairment” in the Full Prescribing Information be removed because according to the 2010 *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format*

Guidance, “If there is ... no specific recommendation about dosage adjustment” in patients with renal insufficiency “that information should ordinarily not be included in the Dosage and Administration section.”

3. For the Patient Counseling Information section, use command language. For example, instead of stating “Patients should be counseled about ...” state “Counsel patients about ...”
4. The words (b) (4) should be removed from the Prescribing Information (b) (4)
5. For the Patient Counseling Information section, add verbiage on counseling patients on the risk of withdrawal seizures and that FYCOMPIA is a controlled substance that can be misused and abused.

### **Conclusions/Recommendations**

All labeling deficiencies identified in the SRPI section of this review and identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to resubmit labeling that addresses all identified labeling deficiencies by April 5, 2012. The resubmitted labeling will be used for further labeling discussions.

Stephanie N. Parcutt	1/5/12
Regulatory Project Manager	Date
Robbin Nighswander	3/5/12
Chief, Project Management Staff	Date

# Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. Only identified deficiencies are marked below.

## Highlights (HL)

- **General comments**

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- There is no redundancy of information.

Reviewer Comment: The dosing information about patients with hepatic impairment is redundant.

- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.) **(Not Applicable)**
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are presented in the following order:

• <b>Highlights Limitation Statement</b> (required statement)
• <b>Drug names, dosage form, route of administration, and controlled substance symbol, if applicable</b> (required information)
• <b>Initial U.S. Approval</b> (required information)
• <b>Boxed Warning</b> (if applicable)
• <b>Recent Major Changes</b> (for a supplement)
• <b>Indications and Usage</b> (required information)
• <b>Dosage and Administration</b> (required information)
• <b>Dosage Forms and Strengths</b> (required information)
• <b>Contraindications</b> (required heading - if no contraindications are known, it must state "None")
• <b>Warnings and Precautions</b> (required information)

• <b>Adverse Reactions</b> (required AR contact reporting statement)
• <b>Drug Interactions</b> (optional heading)
• <b>Use in Specific Populations</b> (optional heading)
• <b>Patient Counseling Information Statement</b> (required statement)
• <b>Revision Date</b> (required information)

- **Highlights Limitation Statement**

- Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

- **Product Title**

- Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

Reviewer Comment: Recommend that the words “for oral use” be added after the dosage form and the controlled substance symbol be added at the end of the sentence.

- **Initial U.S. Approval**

- The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning (Not Applicable)**

- All text in the boxed warning is **bolded**.
- Summary of the warning must not exceed a length of 20 lines.
- Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
- Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC) (Not Applicable)**

- Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
- The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) ~ 2/2010.”
- For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.

- A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
- Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) ~ removal 2/2010.”

- **Indications and Usage**

- If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product] is a (name of class) indicated for (indication(s)).” Identify the established pharmacologic class for the drug at:  
<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

Reviewer Comment: Add the established pharmacologic class “antiepileptic druge (AED).”

- **Contraindications**

- This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- All contraindications listed in the FPI must also be listed in HL.
- List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction. **(Not Applicable)**
- For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI. **(Not Applicable)**

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

- Must include the verbatim statement: “See 17 for Patient Counseling Information” or if the product has FDA-approved patient labeling: “See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”).”

- **Revision Date**

- A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

## Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read: **(Not Applicable)**
  - 8.1 Pregnancy
  - 8.3 Nursing Mothers (not 8.2)
  - 8.4 Pediatric Use (not 8.3)
  - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the Full Prescribing Information are not listed.” **(Not Applicable)**

## Full Prescribing Information (FPI)

- **General Format**

- A horizontal line must separate the TOC and FPI.
- The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
- The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning (Not Applicable)**
  - Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
  - Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).
  
- **Contraindications (Not Applicable)**
  - For Pregnancy Category X drugs, list pregnancy as a contraindication.
  
- **Adverse Reactions**
  - Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.  For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:
    - “Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”
  - For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:
    - “The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.” **(Not Applicable)**
  
- **Use in Specific Populations**
  - Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.
  
- **Patient Counseling Information**
  - This section is required and cannot be omitted.
  - Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:
    - “See FDA-approved patient labeling (Medication Guide)”

- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Reviewer’s Comments: Amend statement from [see Medication Guide] to “See FDA-approved patient labeling (Medication Guide).”

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/s/  
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STEPHANIE N PARNCUTT  
04/10/2012

**From:** [Martin\\_Rabe@eisai.com](mailto:Martin_Rabe@eisai.com)  
**To:** [Parncutt\\_Stephanie](mailto:Parncutt_Stephanie)  
**Cc:** ["Heather\\_Bradley@Eisai.com"](mailto:Heather_Bradley@Eisai.com)  
**Subject:** Re: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets  
**Date:** Tuesday, April 03, 2012 12:18:18 PM

---

Dear Stephanie,

I just wanted to acknowledge receipt of your request and we should be able to respond in the 7-10 days time period.

Best Regards,  
Martin

\*\*\*\*\*

Martin P. Rabe, MSc  
Senior Director, Global Regulatory Affairs  
Head of Neuroscience

Eisai, Inc  
155 Tice Blvd, Woodcliff Lake, NJ 07677  
Direct: 201 949 4379 | Fax: 201 949 4595 | Mobile: (b) (6)  
[martin\\_rabe@eisai.com](mailto:martin_rabe@eisai.com)

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From: "Parncutt, Stephanie" <Stephanie.Parncutt@fda.hhs.gov>  
To: "Heather\_Bradley@Eisai.com" <Heather\_Bradley@Eisai.com>  
Cc: "martin\_rabe@eisai.com" <martin\_rabe@eisai.com>  
Date: 04/03/2012 11:49 AM  
Subject: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

---

Below is a request from the Nonclinical team related to their ongoing review of the FYCOMPA application (N 202-834). Please submit your response to this request in electronic archival format as an amendment to the above NDA. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

[\\* Please see the comment below from the Nonclinical reviewer:](#)

**In the Drug Substance Impurities document (Section 3.2.S.3.2) for NDA 202-834, you state that (b) (4) one of the starting materials for perampanel, was found to be positive by the Ames test” (page 7). You also state that “As a result of the DEREK**

**(Deductive Estimation of Risk from Existing Knowledge software) assessment (*in silico* assessment), there were no genotoxic impurities with the exception of [REDACTED] (b) (4) (page 20). The study reports supporting these statements cannot be located. We request that you either provide the location of these study reports in your application or submit the study reports for these and any other genotoxicity assessments that you have performed on the specified and unspecified impurities detailed in Section 3.2.S.3.2.**

Please respond to this request within 7-10 days; if you are unable to meet this timeframe, please contact me to discuss.

Thank you,

~~~~~

Stephanie N. Parncutt  
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

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email: [stephanie.parncutt@fda.hhs.gov](mailto:stephanie.parncutt@fda.hhs.gov)

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STEPHANIE N PARNCUTT  
04/10/2012



NDA 202834

**METHODS VALIDATION  
MATERIALS RECEIVED**

Eisai, Inc.  
Attention: Heather A. Bradley, MPH  
Senior Manager, Regulatory Affairs  
100 Tice Boulevard  
Woodcliff Lake, NJ 07667

Dear Ms. Bradley:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Fycompa (perampanel tablets) 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg tablets and to our February 17, 2012, letter requesting sample materials for methods validation testing.

We acknowledge receipt on March 23, 2012, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Michael L. Trehy  
MVP Coordinator  
Division of Pharmaceutical Analysis, HFD-920  
Office of Testing and Research  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

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/s/  
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MICHAEL L TREHY  
03/23/2012

## Parncutt, Stephanie

---

**To:** Parncutt, Stephanie; 'Heather\_Bradley@Eisai.com'  
**Subject:** RE: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

**From:** Heather\_Bradley@Eisai.com [[mailto:Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)]  
**Sent:** Thursday, March 22, 2012 10:46 AM  
**To:** Parncutt, Stephanie  
**Subject:** RE: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

Dear Stephanie,

Below please find an update on several recent Information Requests:

- responses to requests in the Day 74 Filing Communication Letter (dated 2 Mar 2012, received 5 Mar 2012) were submitted via the gateway as s0018 yesterday, 21 Mar.
- responses to the 19 Mar Information Request will be submitted tomorrow as s0019. This response will address all items with the exception of Request #6. For this request to explain discrepancies between ISS Section 2 (Disposition) and Section 7.4 (AEs Leading to Discontinuation), we will need additional time to provide a subject-by-subject explanation for the discrepancies in Phase 2 and 3 populations. Tomorrow's s0019 submission will contain a partial response to Item #6 with a subject-by-subject explanation for the 11 discrepancies in the Phase 1 population. We expect to have further information to submit next week.
- I can confirm receipt of the 21 Mar Information Request from CSS. We are assessing the comments and I will get back to you if we are not able to respond in 7-10 days.

Please let me know if you need any additional information.

Regards,  
Heather

Heather A. Bradley, MPH  
Associate Director, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677  
Tel: 201-949-4691  
Cell: (b) (6)  
Fax: 201-949-4595  
heather\_bradley@eisai.com

---

**From:** Parncutt, Stephanie  
**Sent:** Wednesday, March 21, 2012 4:47 PM  
**To:** 'Heather\_Bradley@Eisai.com'  
**Subject:** FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

Attached is a request from the CSS team related to their ongoing review of the FYCOMPA application (N 202-834). Please submit your response to this request in electronic archival format as an

amendment to the above NDA. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

\* Please see the comments below from the CSS team reviewer:

(b) (4)

Please respond to this request in 7-10 days; if you are unable to meet this timeframe, please contact me to discuss.

Thank you,

~~~~~  
Stephanie N. Parncutt  
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

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STEPHANIE N PARNCUTT  
04/10/2012

**From:** [Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)  
**To:** [Parncutt\\_Stephanie](mailto:Parncutt_Stephanie)  
**Subject:** Re: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets  
**Date:** Tuesday, March 20, 2012 12:02:56 PM

---

Hi Stephanie,  
I'd like to confirm receipt of this information request. We are assessing the comments, and I will get back to you if we will need an extension beyond this Friday, March 23 to submit our response.

Please note that we have responses to the items in the Day 74 letter ready for submission tomorrow, March 21. This will be s0018 to the NDA. The items in this latest information request will be submitted in a subsequent submission, s0019.

Regards,  
Heather

Heather A. Bradley, MPH  
Associate Director, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677  
Tel: 201-949-4691  
Cell: (b) (6)  
Fax: 201-949-4595  
[heather\\_bradley@eisai.com](mailto:heather_bradley@eisai.com)

**From:** "Parncutt, Stephanie" <[Stephanie.Parncutt@fda.hhs.gov](mailto:Stephanie.Parncutt@fda.hhs.gov)>  
**To:** "Heather\_Bradley@Eisai.com" <[Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)>  
**Date:** 03/19/2012 05:04 PM  
**Subject:** FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

---

Attached is a request from the Clinical Safety team related to their ongoing review of the FYCOMPA application (N 202-834). Please submit your response to this request in electronic archival format as an amendment to the above NDA. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

\* [Please see the comments below from the Clinical Safety team reviewer:](#)

**Please provide the following information by COB on March 23, 2012:**

**1) For all deaths in the open-label extension studies in both the epilepsy and nonepilepsy studies, please provide the case report forms for the double-blind portions of the studies.**

**2) For the subject 0009-0176 (the subject who died in OLE Study 207), portions of the seizure diary are missing from the case report form. Please provide the subject's seizure diary for the following dates: 5/20/08 - 8/18/08 and after 11/11/08.**

**3) Please also provide a list (along with the CRFs) of all deaths that occurred in the epilepsy**

studies up to 60 days after the last dose of treatment.

4) Please provide tables of Demography and Baseline Characteristics by Modal Dose of Perampanel for the following pools: Epilepsy Phase 3 Double-blind pool, Epilepsy Phase 2 Double-blind pool, Parkinson's Disease Double-blind pool, Neuropathic pain Double-blind pool, and Nonepilepsy Double-blind pool.

5) For Tables 4 and 5 of the ISS, please explain the discrepancy between the number of total patients in the perampanel groups in Studies 206 and 208. In Table 4, the total number of perampanel subjects equals 139 from Study 206 (n=101) and Study 208 (n=38). However, according to Table 5, the total number of perampanel subjects equals 150 from Study 206 (n=46, did not enroll in OLE), Study 208 (n=9, did not enroll in OLE), and Study 206/208/207 (n=95, DB perampanel).

6) Please explain the discrepancy between the number of subjects who discontinued due to AE (in the Disposition Section 2 of the ISS) and the number of subjects who had TEAEs leading to treatment discontinuation (in Section 7.4 of the ISS).

- Phase 1 trials: 46 subjects (perampanel group) discontinued due to AE (from Disposition) versus 35 in Section 7.4
- Epilepsy DB trials (phase 3 and 2):
  - 100 subjects (perampanel) discontinued (Disposition) versus 106 in Section 7.4
  - 22 subjects (placebo) discontinued (disposition) versus 25 in Section 7.4
- Epilepsy All treated pool: 243 subjects discontinued (Disposition) versus 283 in Section 7.4
- Nonepilepsy DB pool:
  - 308 subjects (perampanel) discontinued (Disposition) versus 314 in Section 7.4
  - 105 subjects (placebo) discontinued (disposition) versus in 106 Section 7.4
- Nonepilepsy all treated pool: 503 subjects discontinued (Disposition) versus 546 in Section 7.4

7) In Table 116 of the ISS, the numbers reported in the 3 columns, number of days in DB study/OL study, study day AE start/day of death, and day of death from last dose, are not consistent with the narratives (which are also inconsistent with the CRFs). For example, for subject 0122-0004 (study 204/205) in the narrative it is reported that the subject took his last dose of study drug on Study Day 813 (b) (6) and died 15 days later on Study Day 828 (b) (6). However, in the CRF, the date of last dose of study medication is reported as (b) (6) (and the date of death as (b) (6)). And in Table 116, the number of days in OL study is reported as 365 and the day of death from last dose as 463.

Please provide a new Table 116 with the accurate number of study days for every subject for the 3 columns listed above.

8) For subject #013-1001-0303, the only lab values that are reported on (b) (6) are ALT and AST. Typically a hepatic panel includes a measurement of ALT and AST along with alkaline phosphatase, bilirubin, and albumin. Please investigate whether there were any other liver enzyme results that were obtained on that same day. If the other results were obtained, please report them. If the other results were not obtained, please explain why they were not obtained.

Please respond to this request by COB March 23, 2012; if you are unable to meet this timeframe, please contact me to discuss.

Thank you,

~~~~~  
Stephanie N. Parncutt  
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](mailto:stephanie.parncutt@fda.hhs.gov)

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/s/  
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STEPHANIE N PARNCUTT  
04/10/2012



NDA 202834

**FILING COMMUNICATION**

Eisai, Inc.  
Attention: Heather A Bradley, MPH  
Senior Manager, Regulatory Affairs  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677

Dear Ms. Bradley:

Please refer to your New Drug Application (NDA) dated December 22, 2012, received December 22, 2012, submitted of the Federal Food, Drug, and Cosmetic Act, for FYCOMPA (perampanel) Tablets 2mg, 4mg, 6mg, 8mg, 10mg, 12mg.

We also refer to your amendments dated January 17, 2012.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is October 22, 2012.

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, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September 22, 2012.

During our filing review of your application, we identified the following potential review issues:

**Nonclinical**

1. The Pathology Report for the carcinogenicity study in mouse (study B-4955) contains handwritten comments in the margins of the report. The Pathology Report will need to be amended to incorporate the handwritten comments, with explanations for the changes,

and signed and dated by the Study Pathologist. The Study Director will also need to sign and date the amended study report, which is to be submitted as an amendment to the NDA.

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. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

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

Under **Highlights (HL)** section of Labeling

1. Recommend that the first Warning and Precaution in the Highlights “Suicidal Behavior and Ideation” include ways to mitigate or monitor this adverse reaction.
2. Recommend that Section 2.3 of “Patients with Renal Impairment” in the Full Prescribing Information be removed because according to the 2010 *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* Guidance, “If there is ... no specific recommendation about dosage adjustment” in patients with renal insufficiency “that information should ordinarily not be included in the Dosage and Administration section.”
3. For the Patient Counseling Information section, use command language. For example, instead of stating “Patients should be counseled about ...” state “Counsel patients about ...”
4. The words (b)(4) should be removed from the Prescribing Information (b)(4)
5. For the Patient Counseling Information section, add verbiage on counseling patients on the risk of withdrawal seizures and that FYCOMPIA is a controlled substance that can be misused and abused.
6. The dosing information about patients with hepatic impairment is redundant.
7. Additional important information on section headings are presented in their respective order:

|                                                                                                                                  |
|----------------------------------------------------------------------------------------------------------------------------------|
| • <b>Highlights Limitation Statement</b> (required statement)                                                                    |
| • <b>Drug names, dosage form, route of administration, and controlled substance symbol, if applicable</b> (required information) |
| • <b>Initial U.S. Approval</b> (required information)                                                                            |
| • <b>Boxed Warning</b> (if applicable)                                                                                           |
| • <b>Recent Major Changes</b> (for a supplement)                                                                                 |
| • <b>Indications and Usage</b> (required information)                                                                            |
| • <b>Dosage and Administration</b> (required information)                                                                        |
| • <b>Dosage Forms and Strengths</b> (required information)                                                                       |
| • <b>Contraindications</b> (required heading – if no contraindications are known, it must state “None”)                          |
| • <b>Warnings and Precautions</b> (required information)                                                                         |
| • <b>Adverse Reactions</b> (required AR contact reporting statement)                                                             |

|                                                                        |
|------------------------------------------------------------------------|
| • <b>Drug Interactions</b> (optional heading)                          |
| • <b>Use in Specific Populations</b> (optional heading)                |
| • <b>Patient Counseling Information Statement</b> (required statement) |
| • <b>Revision Date</b> (required information)                          |

8. The Product Title must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol. We recommend that the words “for oral use” be added after the dosage form and the controlled substance symbol be added at the end of the sentence.
9. Under Indications and Usage, if a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)].” Identify the established pharmacologic class for the drug at: <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

Under **Full Prescribing Information (FPI)** section of Labeling

10. Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.
11. For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions: “Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”
12. You must include the statement at the beginning of Section 17 “See FDA-approved patient labeling (Medication Guide).”

We request that you resubmit labeling that addresses these issues by March 26, 2012. The resubmitted labeling will be used for further labeling discussions.

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

**PROMOTIONAL MATERIAL**

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

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

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

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

### **REQUIRED PEDIATRIC ASSESSMENTS**

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

We acknowledge receipt of your request for a partial waiver of pediatric studies for patients 0-1 month of age for this application because studies are impossible/highly impracticable and the product would be ineffective or unsafe in more or more of the pediatric age groups(s) for which a waiver is being requested. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies for patients 1 month through 11 years of age for this application because adult studies are completed and ready for approval. We note you plan an open-label PK, Safety, and Tolerability study in pediatric patients 1 month to 11 years of age. We also note you plan a Randomized, Double-Blind, Placebo-Controlled Efficacy, Safety, and Tolerability study with open-label extension phase in pediatric patients 2 years to 11 years of age. However, please revise your plan to include efficacy and safety in pediatric patients 1 month to less than 2 years of age. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

We note you have submitted pediatric studies with this application for pediatric patients 12 years and older. Once the review of this application is complete, we will notify you whether you have fulfilled the pediatric study requirement for this age group for this application.

Please submit your response within 30 days of the date of this letter (See Draft Guidance for Industry, How to Comply with Pediatric Research Equity Act, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079756.pdf>).

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section

505A of the Act. If you wish to qualify for pediatric exclusivity please consult Division of Neurology Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

If you have any questions, contact Stephanie N. Parncutt, Regulatory Health Project Manager, at (301) 796-4098.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.  
Director  
Division of Neurology Products  
Office of Drug Evaluation 1  
Center for Drug Evaluation and Research

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/s/  
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RUSSELL G KATZ  
03/02/2012



NDA 202834

**REQUEST FOR METHODS  
VALIDATION MATERIALS**

Eisai, Inc.  
Attention: Heather A. Bradley, MPH  
Senior Manager, Regulatory Affairs  
100 Tice Boulevard  
Woodcliff Lake, NJ 07667

Dear Ms. Bradley:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Fycompa (perampanel tablets) 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg tablets.

We will be performing methods validation studies on Fycompa (perampanel tablets) 2 mg and 12 mg tablets, as described in NDA 202834.

In order to perform the necessary testing, we request the following sample materials and equipments:

**Method Current Version**

Assay and related substances (Tablet)

**Samples and Reference Standards**

|        |                                    |                   |
|--------|------------------------------------|-------------------|
| 200 mg | Perampanel reference standard      |                   |
| 50 mg  |                                    | (b) (4) reference |
|        | standard for system suitability    |                   |
| 50     | 2 mg Fycompa (perampanel tablets)  |                   |
| 50     | 12 mg Fycompa (perampanel tablets) |                   |

**Equipment (These will be returned)**

|   |         |
|---|---------|
| 1 | (b) (4) |
|---|---------|

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration  
Division of Pharmaceutical Analysis  
Attn: Michael L. Trehy  
1114 Market Street, Room 1002  
St. Louis, MO 63101

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Michael L. Trehy  
MVP coordinator  
Division of Pharmaceutical Analysis, HFD-920  
Office of Testing and Research  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

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/s/  
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MICHAEL L TREHY  
02/17/2012



NDA 202834

**ACKNOWLEDGE CORPORATE  
NAME/ADDRESS CHANGE**

Eisai, Inc.  
Attention: Heather A. Bradley, MPH  
Senior Manager, Regulatory Affairs  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677

Dear Ms. Bradley:

We acknowledge receipt on February 9, 2012, of your February 9, 2012 correspondence notifying the Food and Drug Administration (FDA) that the corporate name and/or address has been changed from

Eisai, Inc.  
300 Tice Boulevard  
Woodcliff Lake, NJ 07677

To

Eisai, Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677

for the following new drug application (NDA):

NDA 202834 for FYCOMPA (perampanel) Tablets 2mg, 4mg, 6mg, 8mg, 10mg, 12mg.

We have revised our records to reflect this change.

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) 796-4098.

Sincerely,

*{See appended electronic signature page}*

Stephanie N. Parncutt  
Regulatory Health Project Manager  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

-----  
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/s/  
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STEPHANIE N PARNCUTT  
02/14/2012

**From:** [Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)  
**To:** [Parncutt\\_Stephanie](mailto:Parncutt_Stephanie)  
**Subject:** Re: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets  
**Date:** Tuesday, January 31, 2012 4:33:07 PM

---

Dear Stephanie,  
I'd like to update you on the status of our response to the Information Requests from both the Clinical Safety Team and the CSS Statistician, both received on Friday, 27 Jan 2012.

We plan to respond to both requests via a gateway submission of an Information Amendment to the NDA as sequence 0014 on Monday, 6 Feb 2012, which will be day 10 from the date of the requests.

Sequence 0014 will contain a response to every item in the Clinical Safety and CSS Information Requests, with the exception of the datasets related to Clinical Safety question 11, which requests a new "emergent flag" and "safety flag" to be added to each individual study dataset. Due to the size of the datasets and the time required to publish them, these will be separated into a subsequent Information Amendment to be submitted as sequence 0015. I will e-mail you zipped files with the datasets (without define.pdfs) on day 10, Monday 6 Feb, and the official submission (with define.pdfs) will follow later that week. This is the same approach we took with the CSS information request and datasets for sequence 0012.

If you have any questions or need further information, please let me know.

Thanks,  
Heather

Heather A. Bradley, MPH  
Associate Director, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677  
Tel: 201-949-4691  
Cell: (b) (6)  
Fax: 201-949-4595  
[heather\\_bradley@eisai.com](mailto:heather_bradley@eisai.com)

**From:** "Parncutt, Stephanie" <Stephanie.Parncutt@fda.hhs.gov>  
**To:** "Heather\_Bradley@Eisai.com" <Heather\_Bradley@Eisai.com>  
**Date:** 01/27/2012 03:48 PM  
**Subject:** FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

---

Attached is a request from the Clinical Safety team related to their ongoing review of the FYCOMPA application (N 202-834). Please submit your response to this request in electronic archival format as an amendment to the above NDA. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

\* [Please see the attachment below from the Clinical Safety team reviewer:](#)

Please respond to this request within 7-10 days; if you are unable to meet this timeframe, please contact me to discuss.

Thank you,

~~~~~  
Stephanie N. Parncutt  
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](mailto:stephanie.parncutt@fda.hhs.gov)

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[attachment "(1-27-12)SAFETY Requests for Perampanel.doc" deleted by Heather Bradley/RIG/EisaiInc]

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**Parncutt, Stephanie**

---

**From:** Heather\_Bradley@Eisai.com  
**Sent:** Friday, January 13, 2012 4:34 PM  
**To:** Parncutt, Stephanie  
**Subject:** Re: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets  
**Attachments:** E2007-024-tables-npar-friedman-combined-2012-01-12.pdf; E2007-024-tables-npar-friedman-by-gender-2012-01-12.pdf; adpdtm.zip; A\_16\_1\_9\_3.zip; A\_16\_1\_9\_2.zip

Dear Stephanie,

In response to the CSS Statistical Reviewer's request below, attached please find the following:

**Tables from E2007-A001-024 CSR (s0000) requiring being re-run with Friedman's Test instead of the Kruskal-Wallis Test**

**Tables from E2007-A001-024 by-gender analyses (s0011) requiring being re-run with Friedman's Test instead of the Kruskal-Wallis Test**

**Analysis datasets**

**Statistical appendices submitted as part of the E2007-A001-024 addendum (s0011) by-gender analyses with Friedman's Test instead of the Kruskal-Wallis Test**

We will submit an official Information Amendment to NDA 202834 next week, including a define.pdf for the analysis datasets.

Please let me know if you or the CSS statistical reviewer have any questions.

Regards,  
Heather

Heather A. Bradley, MPH  
Associate Director, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677  
Tel: 201-949-4691  
Cell: (b) (6)  
Fax: 201-949-4595  
heather\_bradley@eisai.com

**From:** "Parncutt, Stephanie" <Stephanie.Parncutt@fda.hhs.gov>  
**To:** "'Heather\_Bradley@Eisai.com'" <Heather\_Bradley@Eisai.com>  
**Date:** 01/05/2012 01:32 PM  
**Subject:** FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

Heather,

Below is a request from the CSS Statistical team related to their ongoing review of the FYCOMPA application (N 202-834). Please submit your response to this request in electronic archival format as an amendment to the above NDA. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

\* [Please see the comment below from the CSS Statistical reviewer:](#)

**Attached is the data request for my statistical analysis. In addition, when the model assumptions were not satisfied, the sponsor used non-parametric statistical analysis. Overall Treatment Effect was assessed using Kruskal-Wallis test. Kruskal-Wallis test is for the comparison among three or more independent samples. In a crossover study, a sequence is a complete block. The Sponsor should use Friedman's test for overall effect. Please request the sponsor make the correction on their analysis, and send the revised analysis results to the FDA.**

#### Analysis Data Set Request

Variable Name	Label	Type	Comments
USUBJID	Unique Subject Identifier	char	
SEQ	Sequence Number	num	
QSSEQ	Sequence	char	For example: ACBDE, or ABDCE
PERIOD	Period Number	num	
VSIT	Visit Name	char	
VSITNUM	Visit Number	num	
TRT	Treatment	num	
TRTNAME	Name of Treatment	char	
QSTEST	Question Name	char	For example: Drug Liking
QSCAT	Category of Question	char	VAS or ARCI
PRERESP	Pre-dose Response	num	
QSSTRESN	Numerical Results	num	
EMAX	Maximum Response	num	
QSTPTNUM	Planned Time Point Number	num	For example: 0.5, 1.0
QSELTM	Elapsed Time from Reference Point	char	For example: 5min or 15min
QSBLFL	Baseline Flag (pre-dose flag)	char	
COMPID	Completer Identifier	char	
SEX	Gender	char	
DPFL	Dummy Placebo Identifier	char	Yes or No

Please respond to this request within 7-10 days; if you are unable to meet this timeframe, please contact me to discuss.

Thank you,

Stephanie N. Parncutt

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/s/  
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STEPHANIE N PARNCUTT  
03/01/2012

**Parncutt, Stephanie**

---

**From:** Heather\_Bradley@Eisai.com  
**Sent:** Friday, January 13, 2012 4:34 PM  
**To:** Parncutt, Stephanie  
**Subject:** Re: FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets  
**Attachments:** E2007-024-tables-npar-friedman-combined-2012-01-12.pdf; E2007-024-tables-npar-friedman-by-gender-2012-01-12.pdf; adpdtm.zip; A\_16\_1\_9\_3.zip; A\_16\_1\_9\_2.zip

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We will submit an official Information Amendment to NDA 202834 next week, including a define.pdf for the analysis datasets.

Please let me know if you or the CSS statistical reviewer have any questions.

Regards,  
Heather

Heather A. Bradley, MPH  
Associate Director, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677  
Tel: 201-949-4691  
Cell: (b) (6)  
Fax: 201-949-4595  
heather\_bradley@eisai.com

**From:** "Parncutt, Stephanie" <Stephanie.Parncutt@fda.hhs.gov>  
**To:** "'Heather\_Bradley@Eisai.com'" <Heather\_Bradley@Eisai.com>  
**Date:** 01/05/2012 01:32 PM  
**Subject:** FDA Request for Information - NDA 202834/FYCOMPA(perampanel) Tablets

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**Attached is the data request for my statistical analysis. In addition, when the model assumptions were not satisfied, the sponsor used non-parametric statistical analysis. Overall Treatment Effect was assessed using Kruskal-Wallis test. Kruskal-Wallis test is for the comparison among three or more independent samples. In a crossover study, a sequence is a complete block. The Sponsor should use Friedman's test for overall effect. Please request the sponsor make the correction on their analysis, and send the revised analysis results to the FDA.**

#### Analysis Data Set Request

Variable Name	Label	Type	Comments
USUBJID	Unique Subject Identifier	char	
SEQ	Sequence Number	num	
QSSEQ	Sequence	char	For example: ACBDE, or ABDCE
PERIOD	Period Number	num	
VSIT	Visit Name	char	
VSITNUM	Visit Number	num	
TRT	Treatment	num	
TRTNAME	Name of Treatment	char	
QSTEST	Question Name	char	For example: Drug Liking
QSCAT	Category of Question	char	VAS or ARCI
PRERESP	Pre-dose Response	num	
QSSTRESN	Numerical Results	num	
EMAX	Maximum Response	num	
QSTPTNUM	Planned Time Point Number	num	For example: 0.5, 1.0
QSELTM	Elapsed Time from Reference Point	char	For example: 5min or 15min
QSBLFL	Baseline Flag (pre-dose flag)	char	
COMPID	Completer Identifier	char	
SEX	Gender	char	
DPFL	Dummy Placebo Identifier	char	Yes or No

Please respond to this request within 7-10 days; if you are unable to meet this timeframe, please contact me to discuss.

Thank you,

Stephanie N. Parncutt

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interpreted to include a digital or electronic signature that can be used to authenticate an agreement, contract or other legal document, nor to reflect an intention to be bound to any legally-binding agreement or contract.]

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/s/

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STEPHANIE N PARNCUTT  
01/26/2012



NDA 202834

**ACKNOWLEDGE RESUBMISSION  
AFTER REFUSE-TO-FILE**

Eisai, Inc.  
Attention: Heather A Bradley, MPH  
Senior Manager, Regulatory Affairs  
100 Tice Boulevard  
Woodcliff Lake, NJ 07667

Dear Ms. Bradley:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act in response to our July 21, 2011, refusal to file letter for the following:

Name of Drug Product: FYCOMPA (perampanel) Tablets 2mg, 4mg, 6mg, 8mg, 10mg, 12mg

Review Priority Classification: Standard (S)

Date of Application: December 22, 2011

Date of Receipt: December 22, 2011

Our Reference Number: NDA 202834

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 20, 2012, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 22, 2012.

Under 21 CFR 314.102(c) of the new drug regulations you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

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

for a waiver and deferral of pediatric studies for this application. Once the application has been filed we will notify you whether we have waived and/or deferred the pediatric study requirement for this application.

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) 796-4098.

Sincerely,

*{See appended electronic signature page}*

Stephanie N. Parncutt  
Regulatory Health Project Manager  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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STEPHANIE N PARNCUTT  
01/03/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR DRISK LABELING REVIEW CONSULTATION</b>	
TO: <b>CDER-DMPP-PatientLabelingTeam</b>		FROM: (Name/Title, Office/Division/Phone number of requestor) <b>Russell Katz, MD, Division of Neurology Products</b>	
REQUEST DATE <b>January 3, 2012</b>	IND NO.	NDA/BLA NO. <b>202-834</b>	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW) <b>New original NME NDA/Resubmission to RTF</b>
NAME OF DRUG <b>FYCOMPA (perapanel) Tablets</b>	PRIORITY CONSIDERATION <b>Standard</b>	CLASSIFICATION OF DRUG <b>1</b>	DESIRED COMPLETION DATE <b>July 2012</b>
NAME OF FIRM: <b>Eisai, Inc.</b>		PDUFA goal date: <b>October 22, 2012</b>	
<b>TYPE OF LABEL TO REVIEW</b>			
<b>TYPE OF LABELING:</b> (Check all that apply) <input type="checkbox"/> PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input type="checkbox"/> CARTON/CONTAINER LABELING <input type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)		<b>TYPE OF APPLICATION/SUBMISSION</b> <input checked="" type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	
<b>REASON FOR LABELING CONSULT</b> <input type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION			
<b>EDR link to submission:</b> The entire submission may be accessed at: <a href="\\CDSESUB1\EVSPROD\NDA202834\202834.ENX">\\CDSESUB1\EVSPROD\NDA202834\202834.ENX</a>			
COMMENTS/SPECIAL INSTRUCTIONS: NDA 202834 was received on May 25, 2011 and provides for treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older. This is a NME. The Resubmission, in response to our 7/21/11 RTF communication, was sent in on 12/22/11. Application includes a PI, MedGuide, and Container Labels.  Mid-Cycle Meeting: May 22, 2012  Labeling Meetings: Starting August 7, 2012; September 4 and 26; October 2, 4, 9, 11, 16, 18  Wrap-Up Meeting: August 23, 2012			
SIGNATURE OF REQUESTER <b>Stephanie Parcutt, Regulatory Project Manager, DNP</b> <b>Food and Drug Administration</b> <b>Phone: 301-796-4098</b> <b>Email: stephanie.parcutt@fda.hhs.gov</b>			
SIGNATURE OF RECEIVER		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> eMAIL <input type="checkbox"/> HAND	

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/s/  
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STEPHANIE N PARNCUTT  
01/03/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR DDMAC LABELING REVIEW CONSULTATION</b> <b>**Please send immediately following the Filing/Planning meeting**</b>	
TO: <b>CDER-DDMAC-RPM</b>		FROM: (Name/Title, Office/Division/Phone number of requestor) <b>Russell Katz, MD, Division of Neurology Products</b>	
REQUEST DATE <b>December 28, 2011</b>	IND NO.	NDA/BLA NO. <b>202-834</b>	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW) <b>New original NME NDA/Resubmission to RTF</b>
NAME OF DRUG <b>FYCOMPA (perapanel) Tablets</b>	PRIORITY CONSIDERATION <b>Standard</b>	CLASSIFICATION OF DRUG <b>1</b>	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) <b>Wrap Up mtg: August 23, 2012</b>
NAME OF FIRM: <b>Eisai, Inc.</b>		PDUFA goal date: <b>October 22, 2012</b>	
<b>TYPE OF LABEL TO REVIEW</b>			
<b>TYPE OF LABELING:</b> (Check all that apply) <input type="checkbox"/> PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input type="checkbox"/> CARTON/CONTAINER LABELING <input type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)		<b>TYPE OF APPLICATION/SUBMISSION</b> <input checked="" type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	
<b>REASON FOR LABELING CONSULT</b> <input type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION			
<b>EDR link to submission:</b> The entire submission may be accessed at: <a href="\\CDSESUB1\EVSPROD\NDA202834\202834.ENX">\\CDSESUB1\EVSPROD\NDA202834\202834.ENX</a>			
<b>Please Note:</b> There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.			
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b> NDA 202834 was received on May 25, 2011 and provides for treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older. This is a NME. The Resubmission, in response to our 7/21/11 RTF communication, was sent in on 12/22/11. Application includes a PI, MedGuide, Container Labels to be reviewed by DDMAC.			
Mid-Cycle Meeting: May 22, 2012  Labeling Meetings: Starting August 7, 2012; September 4 and 26; October 2, 4, 9, 11, 16, 18  Wrap-Up Meeting: August 23, 2012			
<b>SIGNATURE OF REQUESTER</b> Stephanie Parcutt, Regulatory Project Manager, DNP Food and Drug Administration Phone: 301-796-4098 Email: stephanie.parcutt@fda.hhs.gov			
SIGNATURE OF RECEIVER		<b>METHOD OF DELIVERY (Check one)</b> <input checked="" type="checkbox"/> eMAIL <input type="checkbox"/> HAND	

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/s/  
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STEPHANIE N PARNCUTT  
12/28/2011

# REQUEST FOR CONSULTATION

TO (Office/Division): **PMHS**  
Attn: Rosemary Addy

FROM (Name, Office/Division, and Phone Number of Requestor):  
**Russell Katz, MD, Division of Neurology Products**

DATE December 28, 2011	IND NO.	NDA NO. 202-834	TYPE OF DOCUMENT New original NME NDAs/Resubmission	DATE OF DOCUMENT December 22, 2011
NAME OF DRUG FYCOMPA (perapanel) Tablets		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE August 22, 2012 PDUFA goal date: October 22, 2012

NAME OF FIRM: **Eisai, Inc.**

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |  |  |
|--|--|
| <input type="checkbox"/> NEW STANDARD NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW                  |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> PHARMACOLOGY                      |
| <input type="checkbox"/> CONTROLLED STUDIES      | <input type="checkbox"/> BIOPHARMACEUTICS                  |
| <input type="checkbox"/> PROTOCOL REVIEW         | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW):  |  |

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** On May 25, 2011, we received the following NDA submission for NDA 202-834 FYCOMPA (perampanel) tablets:  
Electronic link is: \\CDSESUB1\EVSPROD\NDA202834\202834.ENX. I also sent you an email with the updated links on 12/28/11.  
The Pediatric information can be found in m1.9 of the 5/25/11 submission. You will also find that the sponsor has submitted a Deferral and Partial Waiver notification. The filing meeting for NDA 202834 is scheduled for 1/26/12 at 1:30pm (WO 22 Rm. 4201) if you or someone from your group would like to attend.

SIGNATURE OF REQUESTOR <b>Stephanie Parncutt, Regulatory Project Manager, DNP</b> Food and Drug Administration Phone: 301-796-4098 Email: <a href="mailto:stephanie.parncutt@fda.hhs.gov">stephanie.parncutt@fda.hhs.gov</a>	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DARRTS <input checked="" type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
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PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER
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/s/

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STEPHANIE N PARNCUTT  
12/28/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Division/Office): Division of Biostatistic VI Attention: Karl Lin		FROM: <b>Russell Katz, MD, Division of Neurology Products (DNP), HFD-120</b>		
DATE December 28, 2011	IND NO.	NDA NO. 202-834	TYPE OF DOCUMENT New original NME NDAs/Resubmission after RTF	DATE OF DOCUMENT December 22, 2012
NAME OF DRUG <b>FYCOMPA (perapanel) Tablets</b>		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG 1	DESIRED COMPLETION DATE July 22, 2012 PDUFA goal date: October 22, 2012
NAME OF FIRM: Eisai, Inc.				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):				
<b>II. BIOMETRICS</b>				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input checked="" type="checkbox"/> <b>PHARMACOLOGY - CAC statistical data</b> <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
<b>III. BIOPHARMACEUTICS</b>				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG EXPERIENCE</b>				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
<p><b>REQUEST:</b> NDA 202834 was received on May 25, 2011 and provides for treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older. This is a NME. A RTF communication was issued to the sponsor on 7/21/11 and they have sent in their resubmission on 12/22/11. The application has a new PDUFA goal date of 10-22-2012. The entire submission may be accessed at : \\CDSESUB1\EVSPROD\NDA202834\202834.ENX. <b><u>Please review and comment on the acceptability of the carcinogenicity statistical information submitted in NDA 202834.</u></b> The filing meeting for NDA 202834 is scheduled for 1/26/12 at 1:30pm (WO 22 Rm. 4201) if you or someone from your group would like to attend. Electronic datasets have been provided for both of the carcinogenicity toxicity studies in m4.2.3.4</p>				
SIGNATURE OF REQUESTER Stephanie Parcutt, Regulatory Project Manager, DNP Food and Drug Administration Reference ID: 3064818 Phone: 301-796-4098		METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> Email		

Email: stephanie.parncutt@fda.hhs.gov	
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/  
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STEPHANIE N PARNCUTT  
12/28/2011

## REQUEST FOR CONSULTATION

TO (Office/Division): **HFD-009/Controlled Substances Staff**  
Attention: Corinne Moody/ Michael Klein

FROM (Name, Office/Division, and Phone Number of Requestor): **Russell Katz, MD, Division of Neurology Products**

DATE  
December 28, 2011

IND NO.

NDA NO.  
202-834

TYPE OF DOCUMENT  
New original NME  
NDAs/Resubmission

DATE OF DOCUMENT  
December 22, 2011

NAME OF DRUG  
**FYCOMPA (perapanel)  
Tablets**

PRIORITY CONSIDERATION  
Standard

CLASSIFICATION OF DRUG  
1

DESIRED COMPLETION DATE  
August 22, 2012

NAME OF FIRM: **Eisai, Inc.**

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** NDA 202834 was received on May 25, 2011 and provides for treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older. This is a NME. The sponsor was issued a RTF communication on 7/21/11. They have sent in their resubmission on 12/22/11 and the application has a new PDUFA goal date of 10-22-2012. The entire submission may be accessed at : \\CDSESUB1\EVSPROD\NDA202834\202834.ENX. Please review and comment on the acceptability of the abuse liability studies submitted in NDA 202834. The filing meeting for NDA 202834 is scheduled for 1/26/12 at 1:30pm (WO 22 Rm. 4201) if you or someone from your group would like to attend.

SIGNATURE OF REQUESTOR  
**Stephanie Parncutt, Regulatory Project Manager, DNP**  
Food and Drug Administration  
Phone: 301-796-4098

METHOD OF DELIVERY (Check one)  
 DFS       EMAIL       MAIL       HAND

Email: <a href="mailto:stephanie.parncutt@fda.hhs.gov">stephanie.parncutt@fda.hhs.gov</a>	
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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STEPHANIE N PARNCUTT  
12/28/2011



NDA 202834

**MEETING MINUTES**

Eisai, Inc.  
Attention: Heather A Bradley, MPH  
Senior Manager, Regulatory Affairs  
100 Tice Boulevard  
Woodcliff Lake, NJ 07667

Dear Ms. Bradley:

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

We also refer to the meeting between representatives of your firm and the FDA on September 26, 2011

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

If you have any questions, contact Stephanie N. Parncutt, Regulatory Health Project Manager, at (301) 796-4098.

Sincerely,

*{See appended electronic signature page}*

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

ENCLOSURE:  
Meeting Minutes

## MEMORANDUM OF MEETING MINUTES

**Meeting Type:** Type C/Undefined  
**Meeting Category:** Informal Meeting

**Meeting Date and Time:** September 26, 2011; 1:00 – 2:00 PM EST  
**Meeting Location:** CDER WO Room 1311

**Application Number:** NDA 202834  
**Product Name:** FYCOMPA (perampanel) Tablets  
**Indication:** **Treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older.**  
**Sponsor/Applicant Name:** Eisai, Inc.

**Meeting Chair:** Russell Katz, M.D.  
**Meeting Recorder:** Stephanie N. Parncutt

### FDA ATTENDEES

Russell Katz, M.D.  
Norman Hershkowitz, M.D.  
Martin Rusinowitz, M.D.  
Angela Men, M.D., Ph.D.  
Mary Doi, M.D.  
Sally Yasuda, PharmD  
Alicja Lerner, M.D.  
Virginia Elgin  
Teresa McMillan  
Zachary Oleszczuk  
Martha Heimann  
Angelica Dorantes  
Laura Jaeger

### SPONSOR ATTENDEES

Lynn Kramer, M.D.  
Andrew Satlin, M.D.  
Antonio Laurenza, M.D.  
Haichen Yang, M.D.  
Jim Ferry, Ph.D.  
Zhengning Lin, Ph.D.  
Mark Taisey  
Martina Struck, Ph.D.  
Jin Zhu, Ph.D.  
Heather Bradley, M.P.H.  
Robert Clark  
Tushar Kokate, Ph.D.

Olga Alfieri, MBA, RAC

## **BACKGROUND**

Reference is made to the Refuse to File correspondence dated July 21, 2011, regarding the FYCOMPA (perampanel) Tablets 2mg, 4mg, 6mg, 8mg, 10mg, 12mg for NDA 202834, submitted on May 25, 2011. Eisai, Inc. requested a face-to-face meeting to discuss the Division's decision, as offered in the Refuse to File communication.

## **2. MEETING MINUTES**

**QUESTION 1:** Could the Division provide guidance on how a sponsor can obtain feedback earlier in a program heading towards an NDA filing in order to avoid filing delays or RTF letters?

### **FDA Preliminary Response**

*For reasons of limited staffing, it is the Division's policy not to grant a preNDA meeting or answer preNDA type questions until we believe there is an indication of potential efficacy, based upon the results of two adequately designed studies. Under special circumstance we may respond to a few simple well circumscribed questions. We do, however, believe that a meeting is the best way to provide the needed preNDA guidance to the Sponsor.*

### **Meeting Discussion**

No further discussion.

**QUESTION 2:** Beginning on page 3 of the RTF letter and continuing to the bottom of page 4, under the statement "We also request that you submit the following information," there is a list of 12 items under categories of CMC, Biopharmaceutics, Pharmacology/Toxicology, and Controlled Substance Staff. Eisai does not have a clear understanding whether this section of the letter represents critical RTF issues, or non-filing issues. Are any of these items critical RTF issues that must be addressed in the resubmitted NDA in order for it to be accepted for full review?

### **FDA Preliminary Response**

*Pharmacology/Toxicology: the items listed in this section of the RTF letter are not RTF issues. However, they should be addressed in the Complete Response in order to facilitate our review of the NDA.*

### **Meeting Discussion**

No further discussion.

**QUESTION 3:** Please refer to the Clinical Safety/Datasets Issue 1 a-c on page 2 of the **RTF** letter. Eisai will convert all non-epilepsy and Phase 1 safety datasets to SDTM format conforming to CDISC standards for inclusion in the NDA resubmission. Raw datasets provided in the original NDA and subsequent information amendments will be maintained in the resubmission. Based on the rationale and placement proposed below, does the Division agree that the dataset content and placement in the NDA resubmission are acceptable?

#### **FDA Preliminary Response**

*Yes, the dataset content and placement in the NDA resubmission are acceptable provided that SDTM datasets are provided for all of the epilepsy, non-epilepsy, and Phase I studies. Raw datasets should also be provided for these studies where data was not originally collected in SDTM format.*

*Datasets related to efficacy or other datasets not part of the ISS analyses for non-epilepsy and Phase I studies should also be converted to SDTM format if these datasets are necessary for the comprehensive review of safety.*

#### **Meeting Discussion**

The Sponsor asked the Division to clarify the last statement in the Preliminary Response above, "Datasets related to efficacy or other datasets not part of the ISS analyses for non-epilepsy and Phase 1 studies should also be converted to SDTM format if these datasets are necessary for the comprehensive review of safety." For clarification, the datasets related to efficacy for non-epilepsy studies do not need to be converted to SDTM format for the initial resubmission. If, however, during the safety review the datasets related to efficacy for non-epilepsy studies contain components that are necessary for the comprehensive review of safety, then the SDTM formatted datasets may be required in the future.

#### **Additional FDA Comments**

The Agency offers a process for submitting sample standardized datasets for validation. The following is the link on how to submit a sample CDISC/SDTM submission to the FDA:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

**QUESTION 4:** Please refer to the Clinical Safety/Datasets Issue 1b on page 2 of the **RTF** letter. Does the Division agree that the requested integrated dataset for the non-epilepsy studies should be provided at the ADaM level, rather than the SDTM level stated in this request?

#### **FDA Preliminary Response**

*Yes, the integrated dataset for the non-epilepsy studies should be provided at the ADaM level conforming to CDISC standards. Any and all studies or trials performed in support of this product by the current or a previous applicant should be submitted in a format using acceptable data and file standards in order to make full NDA review possible. Please see:*

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

#### **Meeting Discussion**

No further discussion.

**QUESTION 5:** Please refer to Format/Organization Issue 2 a-d on page 2 of the **RTF** letter. For the ISS, Eisai will ensure that all individual narratives and Case Report Forms (CRFs) are fully hyperlinked. For non-epilepsy and Phase 1 CSRs, Eisai will verify the content and organization of the safety sections for all studies in which there were subject deaths, SAEs or discontinuations due to adverse events to confirm that there are appropriate hyperlinks to supporting narratives and subject CRFs, producing CSR amendments or addendums as needed. Does the Division agree that our plan to review and revise the safety sections of CSRs where there were subject deaths, SAEs or discontinuations due to adverse events is acceptable?

#### **FDA Preliminary Response**

*Yes, this plan is acceptable provided that issue 3a in the RTF letter is also addressed (that narrative summaries and CRFs from all studies are included for all deaths, SAEs, and discontinuations due to AEs).*

#### **Meeting Discussion**

No further discussion.

**QUESTION 6:** Please refer to Issue 3c on page 2 of the **RTF** letter and to **RTF Appendix Table 1**. Eisai has defined the safety analysis population groups in the ISS as subjects who took at least one dose of study drug (including perampanel and placebo) and had at least one safety assessment after taking the first dose of study drug. Table 1 in the appendix to the RTF letter defines each pool based on subjects who received  $\geq 1$  dose of perampanel, without any qualifier of required safety assessments. Eisai proposes to maintain the original NDA definition of the safety analysis group (i.e., subjects with one dose plus one post-dose safety assessment). Is this acceptable to the Division?

#### **FDA Preliminary Response**

*Yes, this plan is acceptable to maintain the original NDA definition of the safety analysis group as subjects with one dose plus one post-dose safety assessment.*

### Meeting Discussion

No further discussion.

**QUESTION 7:** Please refer to **RTF Appendix Table 1**. For the pool of epilepsy Phase 2 studies with a definition of “Subjects with epilepsy who received  $\geq 1$  dose of perampanel from Phase 2, DB studies,” **Table 1** includes study J081-231 in this pool. Study J081-231 was an open-label study, therefore does not meet the criteria of this pool definition. Eisai proposes to remove study J081-231 from this pool (it will be included in the 10-study “Epilepsy study pool” as defined in row 1 of Table 1). Is this acceptable to the Division?

### FDA Preliminary Response

*Yes, the study J081-231 should be removed from the Epilepsy Phase 2 Study pool. Information included in Table 1 of the RTF letter (in the appendix) was taken from the list of studies provided in the Section 1.2.1 (page 21) of the ISS. Please correct the discrepancies between the list of studies on page 21, Table 1 (of the ISS, starting on page 23), and Table 1 (in this Type A Meeting Briefing Document, page 10). For example, on page 21 of the ISS, the study G000-207 is included in the list of the epilepsy OLE studies, while the study A001-207 is listed under the epilepsy OLE studies in Table 1 (of the ISS, page 24). Additional discrepancies are noted for the following studies: E044-214 (A001-214), E044-202 (E049-202), E044-303 (G000-303), E044-318 (G000-318), E044-220 (A001-220).*

### Meeting Discussion

No further discussion.

**QUESTION 8:** Please refer to Pharmacology/Toxicology Issue 3 on page 4 of the RTF letter. Included in the list of studies for which the Division is requesting signed and dated Pathology Reports are four non-GLP dose range-finding studies (reports: TKB00006, TKB00007, TKB00008, and TKB01016). Eisai will include signed pathology reports for all GLP studies in the NDA resubmission. It is Eisai’s understanding that signed pathology reports are only required for GLP studies and that GLP regulations do not apply to non-GLP studies. Therefore, it has not been Eisai’s standard practice to prepare signed pathology reports for non-GLP studies. Does the Division agree that:

- signed and dated Pathology Reports are not required for non-GLP studies?
- if required, that retrospective reports/signatures are acceptable for these non-GLP studies?

### FDA Preliminary Response

*As noted in our preliminary response to Question 2, the absence of signed and dated Pathology Reports for studies TKB00006, TKB00007, TKB00008, and TKB01016 are*

*not RTF issues; however, if available, they should be submitted. If Pathology Reports are not available for these studies, it will not be necessary to provide retrospective signed reports.*

### **Meeting Discussion**

Eisai clarified that they did not need to submit signed pathology reports for non-GLP studies. FDA concurred that Eisai did not have to retrospectively sign non-GLP pathology reports and that they will not be provided in the resubmission.

**QUESTION 9:** Please refer to CSS Issue 3 on page 4 of the **RTF** letter which requests that Eisai provide data on receptor binding for GABAA receptor subunits  $\alpha 1$ ,  $\alpha 2$ ,  $\alpha 3$ ,  $\alpha 4$ ,  $\alpha 5$ , and  $\alpha 6$  for all of the four concentrations of perampanel that were used in the submitted receptor binding studies. Eisai believes that the available human and animal abuse liability data in conjunction with the already conducted receptor binding studies are sufficient to make labeling and scheduling decisions on abuse liability. Does the Division agree that the requested binding data are not essential to include in the NDA resubmission or to support a potential approval?

### **FDA Preliminary Response**

*CSS accepts this response however they would like to encourage the Sponsor to perform the receptor binding study; this would provide more data and would assist in making the schedule assignment for the drug.*

### **Meeting Discussion**

Eisai advised that they have conducted electrophysiology studies, and the report will be included in the resubmission.

### **CSS Response**

CSS accepts this response; however this will be a review issue that we will address during the review.

**QUESTION 10:** Please refer to non-filing issue 3 on page 5 of the **RTF** letter. Eisai will provide listings for TEAEs, SAEs, and AEs leading to discontinuation by study with subjects'/investigators' verbatim terms for all epilepsy and non-epilepsy studies. These listings will be run after all studies have been recoded to MedDRA 13.1 (per non-filing issue 2 on page 5 of the RTF letter). Eisai proposes to provide these listings as an appendix to the ISS with links back to the original CSRs. The individual CSRs will not be amended to include the new listings with verbatim terms, and individual CSRs will not link out to the new listings in the ISS. Is this proposal acceptable to the Division?

### **FDA Preliminary Response**

*The individual CSRs do not need to be amended to include the new listings but should be linked out to the new listings in the ISS.*

### **Meeting Discussion**

The Sponsor asked whether verbatim terms need to be included for the Phase I studies. The Division stated that these verbatim terms for the Phase I studies were not needed at this time.

**QUESTION 11:** Please refer to non-filing issue 6 on page 5 of the **RTF** letter. Consistent with the original NDA submission, Eisai will provide narratives and CRFs for any case of death, SAE, or discontinuation due to adverse event in all studies, as required in 21 CFR 314.50(f)(2). Narratives and CRFs for discontinuations due to subject choice and “other” reasons, as requested by the Division, are not routinely collected and prepared for submission. Upon preliminary review of non-epilepsy Phase 2 and 3 studies, the incidence of discontinuation due to subject choice or “other” is generally low and similar across treatment groups, including placebo. Given that this discontinuation incidence is up to 7.0% for placebo and 4.4% for perampanel in the double-blind studies, does the Division still consider that narratives and CRFs for discontinuations due to subject choice and “other” reasons are necessary?

### **FDA Preliminary Response**

*Yes, the narratives and CRFs for discontinuations due to subject choice and “other” reasons should be provided so that a comprehensive safety review can be performed. Please refer to 21CFR §314.50(f)(3).*

### **Meeting Discussion**

The Sponsor agreed to include a listing of the “other” reasons for discontinuations and to include CRFs for those discontinuations where the reasons were not immediately explained by the listing (e.g., incarceration).

**QUESTION 12:** Please refer to non-filing issue 13 on page 5 of the **RTF** letter. Tables of Demographics by Geographic region were provided in the ISS of the original NDA submission for the epilepsy Phase 3 double-blind and epilepsy all treated pools (Table 20.2-1.5 page 370 and Table 20.2-2.5 page 442, respectively). Please confirm that issue 13 is requesting a similar analysis for non-epilepsy Phase 2 and 3 studies only. Phase 1 studies are single-center studies and do not have demographic sub-groups by Geographic region.

### **FDA Preliminary Response**

*Issue 13 in the RTF letter is requesting that Table 23, Demography and Baseline Characteristics (of the ISS), list the category of Geographic region (in addition to the categories of age, sex, race, weight, height, and BMI). This table should be provided for every pooled safety analysis group.*

**Meeting Discussion**

No further discussion.

**QUESTION 13:** Please refer to non-filing issue 14 on page 5 of the **RTF** letter. Below is the table of exposure to perampanel by dose for non-epilepsy studies requested by the Division. Does the Division agree:

a) with the table format as **outlined below**?

b) that this table can be provided after initial resubmission as an amendment to a pending application or as part of the 120-day update?

**FDA Preliminary Response**

*a) Yes, the table format is acceptable. However, this table of extent of exposure should also be provided for maximum daily dose and mean daily dose (in addition to modal dose). Additionally, these tables should be provided for both epilepsy and non-epilepsy studies. Please note that non-filing issue 14 also contains a request to include a table of overall perampanel exposure with total number of unique exposures listed for each pooled group based upon modal dose.*

*b) Please provide the requested tables and analyses in the ISS at the initial resubmission of the NDA. Technically this is not a filing issue. However, as there are so many such issues, we would strongly advise that you provide it in the initial submission. Because these issues are so numerous, if these are not provided in the initial submission the review process may be slowed down leading to the need for a second cycle of review.*

**Meeting Discussion**

No further discussion.

**QUESTION 14:** Please refer to non-filing issue 15 on page 5 of the **RTF** letter. Does the Division agree to receive these tables of laboratory analyses after the initial resubmission as an amendment to a pending application or as part of the 120-day update? A proposed table shell for presentation of TEAEs relating to lab abnormalities is provided below for consideration. (Please refer to Briefing Document for table)

**FDA Preliminary Response**

*Please provide the requested tables and analyses in the ISS at the initial resubmission of the NDA. Technically this is not a filing issue. However, as there are so many such*

*issues, we would strongly advise that you provide it in the initial submission. Because these issues are so numerous, if these are not provided in the initial submission the review process may be slowed down leading to the need for a second cycle of review.*

*Please include tables of laboratory analyses using Tables 3, 4, and 5 in the Appendix of the RTF letter. These tables in the Appendix categorize the TEAEs by specific laboratory parameters (e.g.  $WBC \leq 3.0 \times 10^9/L$ ) and do not categorize TEAEs by MedDRA SOC (as in the proposed table shell provided here after Question 14).*

### **Meeting Discussion**

No further discussion.

### **Additional Comments**

Non-filing issue 15 does include a request for tables of laboratory analyses using Tables 3, 4, and 5 in the Appendix of the RTF letter. It also includes a request for a subsection which summarizes abnormal values reported as TEAEs.

- a) For example, in the hematology laboratory section, please include a table that summarizes the hematology abnormalities reported as TEAEs. Specifically, this table would include the number of subjects in each dose group who reported an AE in the MedDRA SOC, Blood and lymphatic system disorders (including all relevant preferred terms such as neutropenia, anemia, etc) and the MedDRA SOC, Investigations (including all relevant preferred terms such as WBC count decreased, hemoglobin decreased, occult blood, etc).
- b) For the other sections, relevant preferred terms may be found in the following MedDRA SOCs: investigations, metabolism and nutrition disorders, renal and urinary disorders, endocrine disorders, and hepatobiliary disorders.
- c) Please be comprehensive in providing all relevant preferred terms.

**QUESTION 15:** Please refer to non-filing issue 17 on page 6 of the RTF letter. The parameters relating to metabolic syndrome were not assessed, or not consistently assessed, across all studies. HDL was not assessed in any study, and fasting blood glucose and triglycerides were assessed only in Study 210. Only BMI, weight and BP can be provided for all studies. Does the Division agree:

- a) that the requested tables of metabolic syndrome analyses can be provided only for those studies, parameters, and subjects for which it was originally collected?
- b) that these tables can be provided after the initial resubmission as an amendment to a pending application or as part of the 120-day update.

### **FDA Preliminary Response**

*a) Yes, the requested tables of metabolic syndrome analyses can be provided only for those studies for which the parameters were originally collected. (However, for clarification, Tables 6, 7, and 8 should be provided for all of the studies).*

*b) Please provide the requested tables and analyses in the ISS at the initial resubmission of the NDA. Technically this is not a filing issue. However, as there are so many such issues, we would strongly advise that you provide it in the initial submission. Because these issues are so numerous, if these are not provided in the initial submission the review process may be slowed down leading to the need for a second cycle of review.*

#### Meeting Discussion

No further discussion.

**QUESTION 16:** Please refer to non-filing issue 18 on page 6 of the RTF letter. Does the Division agree that the definition of ECG abnormalities suggestive of MI and ischemia can be represented by ST elevation, T-wave flattening or inversion, and Q wave abnormalities? Does the Division agree that the requested tables of ECG analyses can be provided by pool and submitted after the initial resubmission as an amendment to a pending application or as part of the 120-day update?

#### FDA Preliminary Response

*The definition of ECG abnormalities suggestive of MI and ischemia should include the following ECG changes: ST elevation, ST depression, T-wave flattening or inversion, peaked T waves, and Q wave abnormalities.*

*Please provide the requested ECG tables and analyses in the ISS at the initial resubmission of the NDA. Technically this is not a filing issue. However, as there are so many such issues, we would strongly advise that you provide it in the initial submission. Because these issues are so numerous, if these are not provided in the initial submission the review process may be slowed down leading to the need for a second cycle of review.*

#### Meeting Discussion

No further discussion.

**QUESTION 17:** Eisai used a data cut-off of 1 Dec 2010 for the original 25 May 2011 filing of NDA 202834. Pending the outcome of this Type A meeting, Eisai plans to resubmit NDA 202834 by December 2011. Does the Division agree that the existing data cut-off of 1 Dec 2010 can still be used for all existing and new tables to be included in the NDA resubmission? Listings of deaths and SAEs up to 1 Jul 2011 will also be provided.

#### FDA Preliminary Response

*Yes, the existing data cut-off of 1 Dec 2010 can still be used for all existing and new tables to be included in the NDA resubmission provided that a listing of deaths and SAEs (for all epilepsy and non-epilepsy studies) up to 1 Jul 2011 is included in the ISS.*

### Meeting Discussion

No further discussion.

**QUESTION 18:** Per [esub@fda.hhs.gov](mailto:esub@fda.hhs.gov) recommendations, Eisai plans to resubmit the NDA 202834 application as a “resubmission” and will list the original submission sequence 0000 as the related sequence number. In response to the RTF letter and to address deficiencies in the original application, all documents submitted will use lifecycle operators (append, delete, replace and new) as applicable. We plan to submit the resubmission application via gateway. Pending submission size, Eisai is considering the use of a secure external USB drive in addition to the existing accepted media types. Is this resubmission plan acceptable to the Division?

### FDA Preliminary Response

*This plan is acceptable.*

### Meeting Discussion

No further discussion.

### Clinical Pharmacology comments:

*1. In study report for the relative BA study E2007-E044-028, you mentioned that the details on the analytical methodology, the method of validation, and the analytical within-study quality control procedures are included in Appendix 16.1.13. However, the appendix is not included. You should submit the sample analysis report for this study.*

*2. You need to submit the Bioanalytical Data Report [REDACTED] (b) (4) [REDACTED] for study E2007-E044-037. You also need to submit the bioanalytical reports for study E2007-E044-030, E2007-E044-023 and E2007-A001-024.*

*3. In your previous pre-NDA meeting request, you mentioned that the datasets from two Phase 1 studies (010 and 026) in Japanese healthy volunteers would not be translated or submitted. You should translate and submit the PK concentrations raw datasets in .xpt format, as well as the bioanalytical reports, in resubmission. In addition, you should submit the raw dataset of PK concentrations and bioanalytical report for the Phase 2 study (E2007-J081-231) that was conducted in Japanese patients.*

*4. There was no raw dataset of PK concentrations for these Clinical Pharmacology studies (001, 002 and 003). Please provide the datasets in .xpt format.*

**5. For bioequivalence studies (008 and 037), please provide dataset in .xpt format for PK parameters.**

### **Meeting Discussion**

The sponsor acknowledged the comments and confirmed that the requested reports and data will be included in the resubmission.

### **Additional FDA issues**

- 1. *The Division would also like to discuss the pending PPSR submitted by the Sponsor.***
- 2. *The Sponsor inquired on 9/20/11: "In relation to Item 10 of the non-RTF issues, we plan to use modal dose only where the primary analysis is for exposure. Otherwise, randomized dose or actual dose will be used, as shown in the table examples in the RTF letter. The table shells we provided in the letter for Question 12 and 14 incorrectly included modal dose in the title, but will be done using actual dose." We believe that this is adequate. However, if the assigned dose is significantly discrepant from the median or modal dose, the differences will need to be clearly discussed in the ISS in the section where such data are presented.***

### **Meeting Discussion**

In the original NDA submission, the randomized dose was used in the safety analyses. The Sponsor stated that these same analyses will be performed using actual dose. The Sponsor mentioned that these analyses using actual dose are not typically performed for the ISS or for use in drug labeling. The Division clarified that actual dose has been requested and used in previous applications. The Division agreed with the Sponsor's plan for safety analyses to be performed using both randomized and actual dose.

The discussion also included the doses for the non-epilepsy studies. The Sponsor stated that lower doses were studied in the non-epilepsy studies than the epilepsy studies. The Sponsor requested that the safety analyses for the non-epilepsy studies be performed for only doses  $\geq 4$  mg (thereby omitting 2 mg dose data), which are the doses that the Sponsor is using as effective therapy in partial-onset seizures. The Division agreed with this plan to include only doses  $\geq 4$  mg for the safety analyses for the non-epilepsy studies.

### **Post Meeting Comments**

However, if dose-response relationships are seen in these safety analyses for the non-epilepsy studies, data regarding the 2 mg dose should be included.

During the meeting, the Sponsor gave support to using actual dose for the safety analyses because of the lack of down-titration that was performed in the studies. However, upon further review of the Clinical Study Protocols of the three main double-blind placebo controlled epilepsy trials, (G000-304, G000-305, G000-306), the following information regarding down-titration is included in Section 9.1.2.1 Titration Period:

“According to the investigators’ clinical judgment, subjects experiencing intolerable AEs could remain on the same dose or have their dose reduced to the previously tolerated dose. In general, more than one down-titration was discouraged; however, if the subject continued to have significant intolerable AE(s) and the investigator deemed it necessary, the dose was reduced further. Subjects whose dose was down-titrated could have their dose increased again, as soon as the tolerability improved.”

Therefore, during periods of down-titration, the actual dose may not accurately reflect the dose with which the AE occurred. This information regarding the number of patients where down-titration occurred should be included for each dose in the ISS.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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RUSSELL G KATZ  
11/06/2011

**From:** [Heather Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)  
**To:** [Keefe, Stephanie;](#)  
**Subject:** RE: Type A Meeting date for NDA 202834  
**Date:** Tuesday, August 30, 2011 4:15:53 PM

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Received, thank you.

Heather A. Bradley, MPH  
Senior Manager, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677  
Tel: 201-949-4691  
Cell: (b) (6)  
Fax: 201-949-4595  
[heather\\_bradley@eisai.com](mailto:heather_bradley@eisai.com)

From: "Keefe, Stephanie" <[Stephanie.Keefe@fda.hhs.gov](mailto:Stephanie.Keefe@fda.hhs.gov)>  
To: "'[Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)'" <[Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)>  
Date: 08/30/2011 11:22 AM  
Subject: RE: Type A Meeting date for NDA 202834

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[Heather,](#)

[Attached is your meeting confirmation letter. Please confirm receipt.](#)

[Stephanie](#)

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**From:** [Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com) [[mailto:Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)]  
**Sent:** Thursday, August 25, 2011 2:04 PM  
**To:** Keefe, Stephanie  
**Subject:** RE: Type A Meeting date for NDA 202834

Hi Stephanie,

Hope all is OK at work and home with earthquake damage. We felt it here too, but much less. Now everyone is focused on the hurricane.

Sorry to bother you again about the meeting date, but has the 26th been confirmed?

Heather A. Bradley, MPH  
Senior Manager, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677  
Tel: 201-949-4691  
Cell: (b) (6)  
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heather\_bradley@eisai.com

From: "Keefe, Stephanie" <Stephanie.Keefe@fda.hhs.gov>  
To: "'Heather\_Bradley@Eisai.com'" <Heather\_Bradley@Eisai.com>  
Date: 08/24/2011 02:04 AM  
Subject: RE: Type A Meeting date for NDA 202834

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We were released today because of the earthquake that hit. I will have more information for you on Wednesday.

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**From:** Heather\_Bradley@Eisai.com [[mailto:Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)]  
**Sent:** Tuesday, August 23, 2011 4:04 PM  
**To:** Keefe, Stephanie  
**Subject:** RE: Type A Meeting date for NDA 202834

Hi Stephanie,  
Have you been able to confirm Sept. 26 with Dr. Katz?

Thanks,  
Heather

Heather A. Bradley, MPH

Senior Manager, Global Regulatory Affairs

Eisai Inc.  
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Tel: 201-949-4691  
Cell: (b) (6)  
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heather\_bradley@eisai.com

From: "Keefe, Stephanie" <Stephanie.Keefe@fda.hhs.gov>  
To: "'Heather\_Bradley@Eisai.com'" <Heather\_Bradley@Eisai.com>  
Date: 08/22/2011 02:24 AM  
Subject: RE: Type A Meeting date for NDA 202834

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Monday or Tuesday I plan to send you an official meeting confirmation letter. I'm waiting on our Director to confirm this meeting date on his calendar.

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**From:** Heather\_Bradley@Eisai.com [[mailto:Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)]  
**Sent:** Friday, August 19, 2011 11:53 AM  
**To:** Keefe, Stephanie  
**Subject:** RE: Type A Meeting date for NDA 202834

Hi Stephanie,  
Monday, September 26th works for us. Thanks for letting me know. Mid-October would be too late to confirm our proposals and resubmit quickly.

Can I expect a formal confirmation of the meeting date on Monday (22 Aug)?

Thanks,  
Heather

Heather A. Bradley, MPH  
Senior Manager, Global Regulatory Affairs

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heather\_bradley@eisai.com

From: "Keefe, Stephanie" <Stephanie.Keefe@fda.hhs.gov>  
To: "'Heather\_Bradley@Eisai.com'" <Heather\_Bradley@Eisai.com>  
Date: 08/19/2011 11:23 AM  
Subject: RE: Type A Meeting date for NDA 202834

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Heather,

We were able to block Monday, September 26 from 1-2pm EST. I am waiting for our Director to return from leave this Monday so he can confirm his availability. The next available date was mid-October. Will this date work for you and your team?

Stephanie

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**From:** Heather\_Bradley@Eisai.com [[mailto:Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)]  
**Sent:** Friday, August 19, 2011 9:20 AM  
**To:** Keefe, Stephanie  
**Subject:** Type A Meeting date for NDA 202834

Hi Stephanie,  
How is it going for finding a meeting date for our Type A meeting to discuss the NDA 202834 RTF?

Thanks,  
Heather

Heather A. Bradley, MPH  
Senior Manager, Global Regulatory Affairs

Eisai Inc.

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[attachment "(8-25-11)Mtg granted notification.doc" deleted by Heather Bradley/RIG/EisaiInc]

Dear Ms. Bradley,

Please refer to your Informal Meeting Request dated August 5, 2011 and received August 5, 2011. Your meeting request refers to the NDA number 202834. Please refer to this number in all communications regarding this submission.

The meeting is scheduled for:

Date: September 26, 2011  
Time: 1:00 – 2:00 PM EST  
Location: FDA White Oak Campus; 10903 New Hampshire Ave.,  
Silver Spring, MD; Building 22, Rm. 1311

**Current Planned CDER Participants:**

**Division Director** – Russell Katz  
**Office Director(s)** – Robert Temple, Ellis Unger  
**Clinical Team Leader** – Norman Hershkowitz  
**Clinical Reviewer** – Martin Rusinowitz  
**Safety Clinical Reviewer** – Sally Yasuda, Mary Doi  
**Safety RPM** – Kelly Summers  
**Non-Clinical Team Leader** – Lois Freed  
**Non-Clinical Reviewer** – Christopher Toscano  
**CMC Team Leader** – Martha Heimann (Ramesh Sood/Angelica Dorantes)  
**CMC Reviewer** – Lyudmila Soldatova  
**ONDQA Biopharm Reviewer** – Albert (Tien Mien) Chen  
**Biostatistics Team Leader** – Kun Jin  
**Biostatistics Reviewer** – Ququyan (Cherry) Liu  
**Clinical Pharmacology TL** – Angela Men  
**Clinical Pharmacology Reviewer** – Xinning Yang  
**Clinical Pharmacology Safety Reviewers** – Jane Bai, Darrell Abernethy  
**Pharmacometrics TL** – Yaning Wang  
**Pharmacometrics Reviewer** – Lee, Joo-Yeon  
**Pharmacogenomics TL** – Mike Pacanowski  
**Pharmacogenomics Reviewer** – Hobart Rogers  
**Compliance (OC/DMPQ)** – Derek Smith  
**Compliance Reviewer** – Yanyan (Jenny) Qin  
**DSI Reviewers** -- Antoine El-Hage  
**OSE Project Manager** – Laurie Kelley  
**OSE/DMEPA** – Zach Oleszczuk, Cathy Miller, Teresa MacMillan  
**OSE/DRISK** – Melissa Hulett, Robin Duer, Mary Demspey, LaShawn Griffiths  
**DDMAC** – Quynh-Van Tran and Meeta Patel  
**Carcinogenicity Stat Reviewer** – Karl Lin, Matthew Jackson  
**PEDS PM** – Denise Pica-Branco  
**PEDS Medical Officer** – Virginia, Elgin, Courtney Suggs, Millie Wright (Lisa Mathis, Rosemary Addy, Hari Sachs)  
**CSS TL** – Silvia Calderon, Sandra Saltz  
**CSS Reviewer** – Alicja Lerner  
**Regulatory Project Manager** -- Stephanie Keefe-Parncutt

**Visiting FDA:**

Please email Stephanie Keefe-Parncutt a list of your attendees 48 hours in advance of the meeting. If you plan on having foreign attendees, in your party, please submit foreign visitor forms to Stephanie Keefe-Parncutt, via email, two weeks prior to the scheduled meeting with the Agency. In addition, please ensure all foreign attendees have passports available, to present to security.

Be sure to include me as the FDA contact to call when you arrive, as all visitors must be escorted by an FDA employee at all times. Upon arrival at FDA, give the guards either of the following numbers to request an escort to the meeting room: Stephanie's number, 301-796-4098; the division secretary, 301-796-2250. The FDA contact will be called to escort sponsor attendees throughout the building.

The north parking lot has been subdivided with barriers, and the area farthest from the building is designated for visitor parking. All visitors for building 21 and 22 should park in this area. The visitor portion of the lot is open from 6:00 AM - 6:00 PM Monday through Friday.

Buses or limos bearing visitors may be allowed to drop and pick up passengers in front of building 22, if prior notice is given. The drivers can move to the visitor lot and wait for their party, or they may go off-site.



WO Visitor  
arking.pdf (181 KB).

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance.

If you have questions, please email or call me at the following:

(Email: [Stephanie.Keefe@fda.hhs.gov](mailto:Stephanie.Keefe@fda.hhs.gov); phone (301) 796-4098)

Also, please let me know if you have received this information.

Sincerely,

Stephanie N. Keefe-Parncutt, RPM

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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STEPHANIE N KEEFE  
09/01/2011



NDA 202834

**REFUSAL TO FILE**

Eisai, Inc.  
Attention: Heather A Bradley, MPH  
Senior Manager, Regulatory Affairs  
100 Tice Boulevard  
Woodcliff Lake, NJ 07667

Dear Ms. Bradley:

Please refer to your May 25, 2011, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for FYCOMPA (perampanel) Tablets 2mg, 4mg, 6mg, 8mg, 10mg, 12mg.

We also refer to your submissions dated June 16, 2011; June 22, 2011; June 27, 2011; June 30, 2011; July 7, 2011 and July 12, 2011.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

Pharmacology/Toxicology

- 1) You have not provided the individual animal line listings for fetal observations in the pivotal embryo-fetal development studies (#200420, #250520, and #250526). Without these data, it is not possible to adequately determine individual fetal or litter effects. The missing data must be incorporated into each of these study reports.
- 2) Signed and dated Pathology Reports were not provided for a number of nonclinical studies, including the 13-week toxicity (#B-4954) and the 2-year carcinogenicity (#B-4955) studies in mouse. Without a signed and dated Pathology Report, the data are considered to be incomplete (cf. 21 CFR 58.185; 52 Fed. Reg. 33770 [September 4, 1987]). For the NDA, signed Pathology Reports must be provided for the 13-week and 2-year studies in mouse.
- 3) Pages 21 through 209 of the 26-week oral toxicity study in rat (Study #S05107) are missing from the study report. The complete study report must be submitted for review.

Clinical Safety

1. Datasets:

- a. Datasets for the studies performed for the non-epilepsy indications were not submitted in the initial NDA application package. For the non-epilepsy studies, fifteen datasets were submitted after May 25, 2011, many of which were submitted after June 17, 2011. Twelve of these datasets are raw datasets and are not in SDTM format conforming to CDISC standards that would allow reasonable review of the data.
  - b. Please provide an integrated dataset for these non-epilepsy studies in SDTM format conforming to CDISC standards (similar to the integrated dataset provided for the epilepsy studies in eCTD section 5.3.5.3).
  - c. Please also provide datasets for all 27 Phase 1 studies (although this is not a filing issue).
2. Format/Organization:
- a. Please be comprehensive in providing hyperlinks in documents; some hyperlinks are missing. For example:
  - b. Hyperlinks from ISS to individual CRFs and narratives are missing for deaths (page 148).
  - c. Hyperlinks in other Clinical Study Reports were not provided (e.g. Clinical Study Report E2007-E044-301 page 104, hyperlinks to various Sections are missing).
  - d. Please correct this throughout the ISS and pertinent study reports.
3. Safety:
- a. Narratives for some Serious Adverse Events and Dropouts due to AEs are missing (e.g., in study E2007-G000-304, the narratives are missing for subjects 17014011, 51164007, 51284011). Please make sure that narrative summaries from all studies for all deaths, serious adverse events, and dropouts due to adverse events are included.
  - b. Analysis and presentation of the integrated safety data in the ISS for the studies performed for the non-epilepsy indications (and Phase 1 studies) are inadequate. The ISS should not merely summarize findings in the 15 non-epilepsy and 27 Phase 1 studies. The ISS should comprehensively integrate safety findings and provide an analysis for all TEAEs, deaths, serious adverse events, discontinuations for TEAEs, TEAEs of special interest, subgroups analyses, vital sign analyses, laboratory analyses, ECG analyses. For these studies, the ISS lacked analyses for TEAEs of special interest, subgroups, vital signs, laboratory tests, ECGs, and a pooled analysis for all TEAEs.
  - c. Please conduct and present ALL safety data analyses (for all treatment-emergent adverse events including deaths, serious adverse events, discontinuations for TEAEs, TEAEs of special interest, subgroups analyses, vital sign analyses, laboratory analyses, ECG analyses) for the 15 studies for the non-epilepsy indications and the 27 Phase 1 studies pooled according to Table 1 (in the Appendix of this letter).
  - d. Please conduct and present all analyses of demographic characteristics (including baseline disease characteristics, concomitant diseases, and concomitant medications [both AEDs and non-AEDs]), disposition, and extent of exposure for the 15 studies for the non-epilepsy indications pooled according to Table 1 (in the Appendix of this letter). Please also conduct and present all analyses of demographic characteristics, disposition, and extent of exposure for the 27 Phase

- 1 studies pooled together. Please provide summaries of these analyses at the end of each section (e.g. Summary of subject disposition).
- e. Please include the information from the non-epilepsy studies and the Phase 1 studies in the ISS Section 1.2.3 Analysis Populations. Please provide a table similar to Table 4 of the ISS (Number of Subjects From Each Study Included in the Pool of...) for these other studies.

We also request that you submit the following information:

*Chemistry, Manufacturing and Controls*

1. Your application includes container labels for 30- and 90-count bottles and a 2 mg/4 mg professional sample “starter pack.” Please clarify whether the higher strengths (6 mg, 8 mg, 10 mg and 12 mg) will be distributed in blister packaging. If so please provide appropriate container labels.

*Biopharmaceutics*

You proposed 6 strengths of tablets for commercial use (Formulations C and D; the to-be-marketed formulation). However, certain dissolution information could not be located in the submission. Please submit the following:

1. As the 8 and 10 mg strengths were not clinically tested nor included in the bioequivalence studies submitted a biowaiver request is required for these strengths.
2. Mean dissolution profiles and dissolution data (mean and individual; n=12 tablets/batch) for all the 6 strengths, from either clinical biobatch or primary stability batches are required.
3. Please provide a complete summary table for the manufacturing information on all the proposed 6 tablet strengths employed in the above dissolution testing (date, site, and size of the batch manufactured) that is similar to Table 3.2.P.2.2-3 (Module 3.2.P.2.2, p. 22 of 40).

If you already provided the above information, please identify the Module, Section, Volume, and Page numbers in the NDA where these may be located.

*Pharmacology/Toxicology*

1. There appears to be formatting issues that make it difficult to review certain documents. For example:
  - a. One PK/ADME Study (#B04002) has several lines that contain what appears to be missing words that were replaced with two bullet points (e.g. page 9).
  - b. Table 2.6.6.3 on page 13 of the Toxicology Tabulated Summary (2.6.7.) appears to be misaligned and/or incomplete.

2. When reviewing these electronic documents, the following error message is displayed: “The Japanese Language Support Package is required to display this page properly. Under the current configuration, this resource is not available.” This issue should be addressed in these and any other similarly affected documents.
3. Signed and dated Pathology Reports should be provided for the following study reports: #TKB00007, #TKB00006, #S04007, #TKB00008, #TKB01016, #SBL-47-47 (see –Nonclinical Filing Issue #2).

#### Controlled Substance Staff

1. For both human abuse potential studies and for all measures and AEs, you should submit the gender breakdown and an analysis of gender differences, as mentioned in Abuse Potential Evaluation Report, page 67 of 155, and requested by CSS in the letter from Dec 17, 2009
2. You should provide numbers and hyperlinks for the cited pre-clinical studies in the Abuse Potential Evaluation Report, section 5.3.5.3. Additionally, you should provide a table that identifies all preclinical and clinical studies that are related to the assessment of abuse potential and include hyperlinks to these studies.
3. You should provide data on receptor binding for GABA<sub>A</sub> receptor subunits  $\alpha 1$ ,  $\alpha 2$ ,  $\alpha 3$ ,  $\alpha 4$ ,  $\alpha 5$  and  $\alpha 6$  for all of the 4 concentrations of perampanel that you used in the submitted receptor binding studies.
4. You should provide the following studies mentioned in the Abuse Potential Evaluation Report, Mod 5.3.5.3 that could not be found in the NDA:
  - a. “Tamperability and Potential Routes of Administration,” referenced on page 25 of the Abuse potential evaluation report, Mod 5.3.5.3.
  - b. “Similarity to Commonly used Anti-epileptic Drugs (7 drugs) and Drugs of Abuse (only 3 drugs),” Tanimoto similarity scores, referenced on page 23.
5. You should provide tabulation of patients who discontinued the study, or dropped for reasons related to potential abuse and diversion with narratives regarding the reasons and follow-ups.

Although not filing issues, please submit the following:

#### Clinical Safety

Please provide the following:

1. The reasoning for not performing the QT interval studies at doses higher than 12 mg/day to cover the anticipated increases in perampanel plasma concentrations in the patient population due to CYP3A4 inhibition and hepatic impairment (please refer to the End of Phase 2 meeting minutes, QT-IRT Comments for Question 11 on page 6).

2. A summary table of the original AE coding dictionaries for ALL studies (epilepsy, non-epilepsy, and Phase 1). Please recode all investigator terms to MedDRA, Version 13.1 to standardize the terminology for the summary of the 15 studies non-epilepsy studies.
3. The subjects'/investigators' verbatim terms described in the CRFs for every AE (in addition to the preferred terms). Please include these verbatim terms as a column in the line listing of treatment emergent adverse events, adverse events identified as leading to discontinuation, and serious adverse events for ALL studies (epilepsy and non-epilepsy studies).
4. A Case Report Form summary page (with hyperlinks to CRFs) for every study.
5. A summary page of all of the narratives (with hyperlinks to individual narratives) for every study.
6. Narratives and CRFs for discontinuations due to subject choice and "other" reasons.
7. A table of all "normal" reference values and your proposed thresholds for each potentially clinically significant/markedly abnormal high and low values.
8. Change the age categories for the subgroup analysis to <17 years, ≥17 to <65 years, and ≥65 years to reflect the definition of pediatric population in 21 CFR 201.57 (c)(9)(iv).
9. Results of orthostatic changes for vital signs for every study that included these measurements in the study protocol. Please make this a TEAE of special interest. Please include the criteria for clinically significant orthostatic values that were used (if any).
10. Tables using modal dose (or daily dose of maximum duration) for analyses presented in the body of the ISS for the following pools: Epilepsy study pool and Other Indications pool (see Table 1 for list of analysis pools). Please use randomized treatment dose group for analyses presented in the body of the ISS for all other study pools. Other tables using mean daily dose, last daily dose, and maximum daily dose should be included in the Appendix.
11. Tables of Common TEAEs by preferred term for TEAEs in ≥ 2% of the Subjects by dose group for every pooled safety analysis group. Please also include a summary table for TEAEs reported by ≥ 2% of perampanel-treated subjects by study pool (specifically with two columns representing the Epilepsy Study Pool and Other Indications Study Pool).
12. Tables of TEAEs leading to discontinuation of study drug in ≥ 1% of the subjects by dose group for every pooled safety analysis group.
13. Tables of Demographics stratified by an additional category of Geographic region.
14. Table of Exposure to perampanel by dose (see Table 2 in the Appendix of this letter). Please include a table of overall perampanel exposure with total number of unique exposures listed for each pooled group based upon modal dose.
15. Tables of laboratory analyses using Tables 3, 4, 5 in the Appendix of this letter. In each section (e.g. hepatobiliary, renal, etc) of the Clinical Laboratory Tests, please also include a subsection which summarizes abnormal values reported as TEAEs.
  - a. For example, in the hematology laboratory section, please include a table that summarizes the hematology abnormalities reported as TEAEs. Specifically, this table would include the number of subjects in each dose group who reported an AE in the MedDRA SOC, Blood and lymphatic system disorders (including all relevant preferred terms such as neutropenia, anemia, etc) and the MedDRA SOC, Investigations (including all relevant preferred terms such as WBC count decreased, hemoglobin decreased, occult blood, etc).

- b. For the other sections, relevant preferred terms may be found in the following MedDRA SOCs: investigations, metabolism and nutrition disorders, renal and urinary disorders, endocrine disorders, and hepatobiliary disorders.
  - c. Please be comprehensive in providing all relevant preferred terms.
16. A line listing, narrative, and case report form of all subjects who fit the criteria of Hy's Law case definition.
17. Tables of vital sign and body weight analyses using Tables 6, 7, 8 in the Appendix of this letter. Please provide an analysis of the metabolic effects of perampanel. Specifically, please provide a table with the number of subjects in each study who had weight gain (categorized as >5%, >7%, and >10%) stratified by the number of subjects who also developed the other metabolic syndrome parameters during the study (triglycerides  $\geq$  150 mg/dl, BP  $\geq$  130/85 mmHg, HDL < 40 mg/dl, fasting BG  $\geq$  100 mg/dl, and BMI > 30 kg/m<sup>2</sup>). Please also stratify these tables by dose.
18. Tables of ECG analyses using Table 9 and 10 in the Appendix of this letter for all studies in which ECGs were performed. Please also provide a table with the incidence of treatment-emergent cardiac and ECG AEs by dose group (using preferred terms in the MedDRA SOCs, cardiac disorders, investigations, and general disorders and administration site conditions).

We will refund 75% of the total user fee submitted with the application.

Within 30 days of the date of this letter, you may request in writing a meeting about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee.

If you have any questions, contact Stephanie N. Keefe, Regulatory Project Manager, at (301) 796-4098.

Sincerely,

*{See appended electronic signature page}*

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

Enclosure: Appendix

## Appendix

Table 1 - Overview of Integrated Analysis Pools

Pool	Pool definition	Trials included
<b>Subjects with partial-onset seizures</b>		
Epilepsy study pool (10 studies)	Subjects with epilepsy who received $\geq 1$ dose of perampanel from DB studies and subjects who received $\geq 1$ of perampanel in OLE studies	G000-304, -305, -306, -307, -207 E049-203 A001-206 G000-208 J081-231, -233
Epilepsy Phase 3 Study pool	Subjects with epilepsy who received $\geq 1$ dose of perampanel from Phase 3, DB studies	G000-304, -305, -306
Epilepsy Phase 2 Study pool	Subjects with epilepsy who received $\geq 1$ dose of perampanel from Phase 2, DB studies	E049-203 A001-206 G000-208 J081-231
<b>Subjects with non-epilepsy indications</b>		
Other indications study pool (15 studies)	Subjects (with PD, MS, neuropathy, migraine) who received $\geq 1$ dose of perampanel from DB studies and subjects who received $\geq 1$ of perampanel in OLE studies	E044-301, -202, -204, -214 A001-302 G000-309 E044-205, -318, -220, -303 A001-218 G000-227, -228 E049-201 A001-210
Other indications double-blind (DB) pool	Subjects who received $\geq 1$ dose of perampanel from DB trials	E044-301, -202, -204, -214 A001-302, -218 G000-309, -227 E049-201 A001-210
Parkinson's disease (PD) double-blind pool	Subjects with PD who received $\geq 1$ dose of perampanel from DB trials	E044-301, -202, -204, -214 A001-302 G000-309
Neuropathy double-blind pool	Subjects with diabetic neuropathy or postherpetic neuropathy who received $\geq 1$ dose of perampanel from DB trials	A001-218 G000-227
<b>Healthy subjects</b>		
Phase I study pool (27 studies)	Subjects who received $\geq 1$ dose of perampanel	E044-017, -003, -016, -037 A001-008, -040, -039 E044-001, -002 J081-010, -026 E044-015, -004, -007 E044-005, -006, -025, -029, -030 A001-014 E055-019 E044-009, -020, -028 A001-013, -023, -024

Table 2 – Exposure to perampanel by dose

\*\*(please make separate tables for modal, maximum daily dose, and mean daily dose)

Duration (weeks)	Placebo	Dose 1	Dose 2	Dose 3	Dose 4	Any dose (%)
0-1 week						
>1 to 2						
>2 to 4						
>4 to 6						
>6 to 8						
>8 to 10						
>10 to 12						
>12 to 14						
>14 to 16						
>16 to 18						
>18 to 20						
>20 to 26						
>26 to 51						
>51 to 102						
>102 to 153						
>153 to 204						
>204 to 255						
...						
Duration of exposure (wks)						
n						
mean (SD)						
median						
min, max						
Number of subject-weeks						

Table 3 – Mean Change from Baseline for Laboratory Parameters

Parameter	Placebo			Dose 1			(Similar columns for other doses)
	n	mean	SD	n	mean	SD	
(list here all laboratory parameters including hepatobiliary, renal, hematologic, electrolytes, and other chemistry parameters)							

Table 4 – Incidence of Potentially Clinically Significant Changes in Laboratory Parameters (for subjects who were normal at baseline)

Parameter	Placebo			Dose 1			(Similar columns for other doses)
	n	# abnormal	%	n	# abnormal	%	
list here all laboratory parameters (including hepatobiliary, renal, hematologic, electrolytes, and other chemistry parameters) and potentially clinically significant changes (e.g. WBC count $\leq 3.0 \times 10^9/L$ )							

Table 5 – Shift from baseline to maximum value during treatment by multiple of ULN for LFTs and Creatinine

Parameter	Maximum Post-Baseline				Missing
	<1x ULN	1 to <2x ULN	2 to <3x ULN	≥3x ULN	
ALT					
Placebo					
Dose 1					
Dose 2					
Dose 3					
Dose 4					
AST					
Placebo					
Dose 1					
Dose 2					
Dose 3					
Dose 4					
Total bilirubin					
Placebo					
Dose 1					
Dose 2					
Dose 3					
Dose 4					
GGT					
Placebo					
Dose 1					
Dose 2					
Dose 3					
Dose 4					
Alkaline phosphatase					
Placebo					
Dose 1					
Dose 2					
Dose 3					
Dose 4					
Creatinine					
Placebo					
Dose 1					
Dose 2					
Dose 3					
Dose 4					

Table 6 – Incidence of Abnormal Vital Signs During Treatment

<b>Abnormal Vital Sign (VS) Parameters Relative to Baseline/Pre-treatment VS</b>	Placebo	Dose 1	Dose 2	Dose 3	Dose 4	Any dose
<b>Supine</b>						
SBP increment $\geq 20$ mm Hg						
SBP increment $\geq 40$ mm Hg						
SBP decrement $\geq 20$ mm Hg						
SBP decrement $\geq 40$ mm Hg						
DBP increment $\geq 10$ mm Hg						
DBP increment $\geq 20$ mm Hg						
DBP decrement $\geq 10$ mm Hg						
DBP decrement $\geq 20$ mm Hg						
Pulse increment $\geq 15$ bpm						
Pulse increment $\geq 30$ bpm						
Pulse decrement $\geq 15$ bpm						
Pulse decrement $\geq 30$ bpm						
<b>Standing</b>						
SBP increment $\geq 20$ mm Hg						
SBP increment $\geq 40$ mm Hg						
SBP decrement $\geq 20$ mm Hg						
SBP decrement $\geq 40$ mm Hg						
DBP increment $\geq 10$ mm Hg						
DBP increment $\geq 20$ mm Hg						
DBP decrement $\geq 10$ mm Hg						
DBP decrement $\geq 20$ mm Hg						
Pulse increment $\geq 15$ bpm						
Pulse increment $\geq 30$ bpm						
Pulse decrement $\geq 15$ bpm						
Pulse decrement $\geq 30$ bpm						
<b>Change from Supine to Standing</b>						
SBP increment $\geq 20$ mm Hg						
SBP increment $\geq 40$ mm Hg						
SBP decrement $\geq 20$ mm Hg						
SBP decrement $\geq 40$ mm Hg						
DBP increment $\geq 10$ mm Hg						
DBP increment $\geq 20$ mm Hg						
DBP decrement $\geq 10$ mm Hg						
DBP decrement $\geq 20$ mm Hg						
Pulse increment $\geq 15$ bpm						
Pulse increment $\geq 30$ bpm						
Pulse decrement $\geq 15$ bpm						
Pulse decrement $\geq 30$ bpm						

SBP = systolic blood pressure

DBP = diastolic blood pressure

Patients are counted once during treatment regardless of number of times achieving the threshold change.

Table 7 – Summary of changes from baseline in supine vital sign measurements and body weight

Parameter	Placebo			Dose 1			(Similar columns for other doses)
	n	mean	SD	n	mean	SD	
SBP (mmHg)							
baseline							
change end of treatment							
DBP (mmHg)							
baseline							
Δ end of treatment							
Pulse rate (bpm)							
baseline							
Δ end of treatment							
Weight (kg)							
baseline							
Δ end of treatment							
Δ end of 6 months							
Δ end of 12 mos							
Δ end of 24 mos							
Δ end of 36 mos							
Δ end of 48 mos							
Δ end of 60 mos							

Table 8 – Summary of orthostatic changes in vital signs

Parameter	Placebo			Dose 1		
	n	mean	SD	n	mean	SD
SBP (mmHg)						
placebo						
dose 1						
dose 2						
dose 3						
dose 4						
DBP (mmHg)						
placebo						
dose 1						
dose 2						
dose 3						
dose 4						
Pulse rate (bpm)						
placebo						
dose 1						
dose 2						
dose 3						
dose 4						

Table 9 – Summary of changes from Baseline in ECG parameters

Parameter	Placebo			Dose 1			(Similar columns for other doses)
	n	mean	SD	n	mean	SD	
Heart rate (bpm)							
baseline							
Δ end of treatment							
PR interval (ms)							
baseline							
Δ end of treatment							
QRS duration (ms)							
baseline							
Δ end of treatment							
QTcF (ms)							
baseline							
Δ end of treatment							
QTcB (ms)							
baseline							
Δ end of treatment							

Table 10 – Summary of subjects with selected treatment-emergent ECG abnormalities

<b>ECG findings</b>	Placebo	Dose 1	Dose 2	Dose 3	Dose 4	Any dose
Rate						
Sinus bradycardia (HR<60 bpm)						
Sinus tachycardia (HR>100 bpm)						
Atrial-related conduction						
First-degree AVB (PR>200 ms)						
Ventricular-related conduction						
Intraventricular block (QRS>120 ms)						
Repolarization-related						
Prolonged QT						
Ischemia and infarction-related						

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/s/  
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RUSSELL G KATZ  
07/21/2011

**Parncutt, Stephanie**

---

**From:** Heather\_Bradley@Eisai.com  
**Sent:** Tuesday, July 19, 2011 11:24 AM  
**To:** Keefe, Stephanie  
**Subject:** RE: Information Request - NDA 202834 / Report  
**Attachments:** emfinfo.txt

Hi Stephanie,

I wanted to update you on the requested ECG analysis dataset. We have prepared the requested dataset, and it will be delivered via the Gateway later today.

I also wanted to let you know that I received the NDA Acknowledgment Letter (signed 12 Jul), and wanted to confirm that the proposed labeling in SPL format, as requested in the letter, was included in the original application.

You had also mentioned in a previous e-mail that the Day 45 meeting was taking place last week. Is there any update you could provide? As you can imagine, we are eager to learn if our application will be filed and move forward to a full review, and Day 60 (24 Jul) is coming up this weekend. Anything you could share would be appreciated.

Thanks and regards,  
Heather

Heather A. Bradley, MPH  
Senior Manager, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677  
Tel: 201-949-4691  
Cell: (b) (6)  
Fax: 201-949-4595  
heather\_bradley@eisai.com

---

**From:** "Keefe, Stephanie" <Stephanie.Keefe@fda.hhs.gov>  
**To:** "Heather\_Bradley@Eisai.com" <Heather\_Bradley@Eisai.com>  
**Date:** 07/11/2011 01:11 PM  
**Subject:** RE: Information Request - NDA 202834 / Report

---

Heather,

I will confirm receipt of the Electronic receipt once we receive that. In the meantime I will forward your email attachment for review. In addition, an additional request has been made by the clinical team:

In addition to the ClinPharm table, please ask the sponsor to submit ECG analysis dataset (which is the average of triplicate ECGs at each time point). The analysis data set should include QTcl, QTcl correction factor, QT, QTCB, QTCF, PR, HR, RR, QRS, single delta (change from baseline for all those parameters) and visit/day/time point information.

Please let me know if you have further questions. This information also needs to be submitted formally to the NDA. Thank you,

Stephanie

---

**From:** Heather\_Bradley@Eisai.com [[mailto:Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)]

**Sent:** Monday, July 11, 2011 12:59 PM

**To:** Keefe, Stephanie

**Subject:** Re: Information Request - NDA 202834 / Report

Dear Stephanie,

Please find attached the requested Highlights of Clinical Pharmacology document completed with perampanel information.

This document will also be submitted formally to NDA 202834 as an Amendment to Pending Information: Efficacy Information Amendment (Module 1.11.3). I will send you confirmation when it has been successfully delivered via the Electronic Gateway.

Regards,  
Heather

Heather A. Bradley, MPH  
Senior Manager, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677  
Tel: 201-949-4691  
Cell: (b) (6)  
Fax: 201-949-4595  
[heather\\_bradley@eisai.com](mailto:heather_bradley@eisai.com)

**From:** "Keefe, Stephanie" <Stephanie.Keefe@fda.hhs.gov>  
**To:** "Heather\_Bradley@Eisai.com" <Heather\_Bradley@Eisai.com>  
**Date:** 07/08/2011 11:08 AM  
**Subject:** Information Request - NDA 202834 / Report

---

Heather,

One of our Clinical teams has asked that you complete the attached report and send it back, both officially to the NDA 202834 and via email, as soon as possible. Thank you,

Stephanie

[attachment "HighlightsofClinicalPharmacology.doc" deleted by Heather Bradley/RIG/EisaiInc]

[This e-mail message may contain privileged, confidential and/or proprietary information of Eisai. If you believe that it has been sent to you in error, please contact the sender immediately and delete the message including any attachments, without copying, using, or distributing any of the information contained therein. This e-mail message should not be interpreted to include a digital or electronic signature that can be used to authenticate an agreement, contract or other legal document, nor to reflect an intention to be bound to any legally-binding agreement or contract.]

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/s/  
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STEPHANIE N PARNCUTT  
01/26/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR DDMAC LABELING REVIEW CONSULTATION</b> <b>**Please send immediately following the Filing/Planning meeting**</b>	
TO: <b>CDER-DDMAC-RPM</b>		FROM: (Name/Title, Office/Division/Phone number of requestor) <b>Russell Katz, MD, Division of Neurology Products</b>	
REQUEST DATE <b>July 14, 2011</b>	IND NO.	NDA/BLA NO. <b>202-834</b>	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW) <b>New original NME NDA</b>
NAME OF DRUG <b>FYCOMPA (perapanel) Tablets</b>	PRIORITY CONSIDERATION <b>Standard</b>	CLASSIFICATION OF DRUG <b>1</b>	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) <b>Wrap Up mtg: January 26, 2012</b>
NAME OF FIRM: <b>Eisai, Inc.</b>		PDUFA goal date: <b>March 25, 2012</b>	
<b>TYPE OF LABEL TO REVIEW</b>			
<b>TYPE OF LABELING:</b> (Check all that apply) <input type="checkbox"/> PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input type="checkbox"/> CARTON/CONTAINER LABELING <input type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)		<b>TYPE OF APPLICATION/SUBMISSION</b> <input checked="" type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	
<b>REASON FOR LABELING CONSULT</b> <input type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION			
<b>EDR link to submission:</b> The entire submission may be accessed at: <a href="\\CDSESUB1\EVSPROD\NDA202834\202834.ENX">\\CDSESUB1\EVSPROD\NDA202834\202834.ENX</a>			
Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.			
COMMENTS/SPECIAL INSTRUCTIONS: NDA 202834 was received on May 25, 2011 and provides for treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older. This is a NME. Application includes a PI, MedGuide, Container Labels to be reviewed by DDMAC.  Mid-Cycle Meeting: October 18, 2011  Labeling Meetings: Starting January 12, 2012; February 9 & 23, 2012; Additional meeting to be scheduled  Wrap-Up Meeting: January 26, 2012			
SIGNATURE OF REQUESTER <b>Stephanie Keefe, Regulatory Project Manager, DNP</b> Food and Drug Administration Phone: 301-796-4098 Email: <a href="mailto:stephanie.keefe@fda.hhs.gov">stephanie.keefe@fda.hhs.gov</a>			
SIGNATURE OF RECEIVER		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> eMAIL <input type="checkbox"/> HAND	

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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STEPHANIE N KEEFE  
07/14/2011



NDA 202834

**NDA ACKNOWLEDGMENT**

Eisai, Inc.  
Attention: Heather A Bradley, MPH  
Senior Manager, Regulatory Affairs  
100 Tice Boulevard  
Woodcliff Lake, NJ 07667

Dear Ms. Bradley:

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: FYCOMPA (perampanel) Tablets 2mg, 4mg, 6mg, 8mg, 10mg, 12mg

Date of Application: May 25, 2011

Date of Receipt: May 25, 2011

Our Reference Number: NDA 202834

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 July 24, 2011, in accordance with 21 CFR 314.101(a).

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

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

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

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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, call me at (301) 796-4098.

Sincerely,

*{See appended electronic signature page}*

Stephanie N. Keefe-Parncutt  
Regulatory Health Project Manager  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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STEPHANIE N KEEFE  
07/12/2011

**Parncutt, Stephanie**

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**From:** Heather\_Bradley@Eisai.com  
**Sent:** Monday, July 11, 2011 12:59 PM  
**To:** Keefe, Stephanie  
**Subject:** Re: Information Request - NDA 202834 / Report  
**Attachments:** HighlightsofClinicalPharmacology\_11Jul\_final.doc

Dear Stephanie,

Please find attached the requested Highlights of Clinical Pharmacology document completed with perampanel information.

This document will also be submitted formally to NDA 202834 as an Amendment to Pending Information: Efficacy Information Amendment (Module 1.11.3). I will send you confirmation when it has been successfully delivered via the Electronic Gateway.

Regards,  
Heather

Heather A. Bradley, MPH  
Senior Manager, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677  
Tel: 201-949-4691  
Cell: (b) (6)  
Fax: 201-949-4595  
heather\_bradley@eisai.com

---

**From:** "Keefe, Stephanie" <Stephanie.Keefe@fda.hhs.gov>  
**To:** "Heather\_Bradley@Eisai.com" <Heather\_Bradley@Eisai.com>  
**Date:** 07/08/2011 11:08 AM  
**Subject:** Information Request - NDA 202834 / Report

---

Heather,

One of our Clinical teams has asked that you complete the attached report and send it back, both officially to the NDA 202834 and via email, as soon as possible. Thank you,

Stephanie

[attachment "HighlightsofClinicalPharmacology.doc" deleted by Heather Bradley/RIG/EisaiInc]

[This e-mail message may contain privileged, confidential and/or proprietary information of Eisai. If you believe that it has

been sent to you in error, please contact the sender immediately and delete the message including any attachments, without copying, using, or distributing any of the information contained therein. This e-mail message should not be interpreted to include a digital or electronic signature that can be used to authenticate an agreement, contract or other legal document, nor to reflect an intention to be bound to any legally-binding agreement or contract.]

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/s/  
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STEPHANIE N PARNCUTT  
01/26/2012

**Parncutt, Stephanie**

---

**From:** Heather\_Bradley@Eisai.com  
**Sent:** Thursday, July 07, 2011 4:18 PM  
**To:** Keefe, Stephanie  
**Subject:** RE: NDA 202834 --Clinical Information Request  
**Attachments:** emfinfo.txt

Dear Stephanie,

I'd like to inform you that the requested datasets in your communication dated June 10, 2011 have now all been successfully submitted via the Electronic Gateway to NDA 202834, as described below:

- Sequence 0002 on 22 Jun:

Two double-blind studies (E2007-A001-218; E2007-G000-227) and one OLE study (E2007-G000-228) in subjects with painful diabetic neuropathy (PDN) or posterheptic neuralgia (PHN)

- Sequence 0003 on 27 Jun:

One double-blind study (E2007-E044-204) and one OLE study (E2007-E044-205) in subjects with Parkinson's disease and one double-blind study (E2007-E049-201) in subjects with multiple sclerosis

- Sequence 0004 on 30 Jun 2011:

Three double-blind studies (E2007-E049-202, E2007-A001-214, E2007-G000-309) and two OLE studies (E2007-A001-220, E2007-G000-318) in subjects with Parkinson's disease

- Sequence 0005 on 7 Jul 2011:

Two double-blind studies (E2007-E044-301, E2007-A001-302) and one OLE study (E2007-G000-303) in subjects with Parkinson's disease and one double-blind study (E2007-A001-210) in subjects with migraine headache

The above list represents 15 of the 17 requested studies. The remaining 2 were not submitted, as communicated via e-mail on June 14, 2011, because one study (E2007-E044-213) was not conducted, and another (E2007-A001-226) enrolled only one subject, whose complete CRF was submitted in the NDA.

The list of studies conducted in humans was also provided via e-mail on June 14, 2011 and as part of sequence 0002 on June 22. This completes the list of requested information in your communication on June 10.

According to our calculations from the submission date of May 25, 2011, the Day 45 meeting should be coming up within the next few days. We would appreciate if you could let us know the outcome of this meeting so that we could address any other potential issues. Also, please confirm that we can expect formal communication on the acceptability of NDA 202834 by Day 74, which should fall on or around August 7, 2011.

Please confirm receipt of this correspondence.

Thanks and regards,  
Heather

Heather A. Bradley, MPH  
Senior Manager, Global Regulatory Affairs

Eisai Inc.  
 155 Tice Boulevard  
 Woodcliff Lake, NJ 07677  
 Tel: 201-949-4691  
 Cell: (b) (6)  
 Fax: 201-949-4595  
 heather\_bradley@eisai.com

From: "Keefe, Stephanie" <Stephanie.Keefe@fda.hhs.gov>  
 To: "Heather\_Bradley@Eisai.com" <Heather\_Bradley@Eisai.com>  
 Date: 06/29/2011 11:04 AM  
 Subject: RE: NDA 202834 --Clinical Information Request

---

Heather,

- With regard to email dated June 22, we want to confirm that we have received the referenced datasets.
- With regard to your questions posed in your June 14 email ("Submitting the 15 requested datasets according to the schedule outlined above will ensure that all requested datasets are delivered prior to the Day 45 review meeting *Please confirm this is acceptable*"), we want to refer you to our email sent on June 14, 2011 stating:

**We have reviewed your response in your email dated June 10, 2011 regarding missing datasets. In order to perform a comprehensive review of the NDA we would require that the application be reviewable at the time of submission. The missing datasets make this impossible. We therefore ask that, like the prior epilepsy datasets, the missing datasets (SDTM) conform to the CDISC Standard with coding of adverse events in MedDRA, along with verbatim terms and that these be submitted by this coming Friday (June 17, 2011). We should note that the submission of datasets beyond this coming Friday would result in a loss of more than 1 month of review time.**

[As well as our initial email on June 10, 2011:](#)

In your NDA 202834 application package, the datasets for the studies for the non-epilepsy indications were not submitted.

Please submit all of the datasets (for the 17 studies listed below) with coding of adverse events in MedDRA, along with verbatim terms. Whenever possible, please submit the datasets in data tabulation datasets (SDTM) conforming to the CDISC Standard. Please also provide a complete listing of all trials performed in humans. Please provide all of this information within one week.

Please submit the datasets for the double-blind study, E2007-E044-213, in subjects with Parkinson's Disease along with the 16 studies that are listed on page 21 of the Integrated Summary of Safety:

**Perampanel was also evaluated in other indications. The following studies are included in**

**this submission to support the safety findings of the epilepsy studies:**

- Seven double-blind studies (E2007-E044-301, E2007-A001-302, E2007-G000-309,

E2007-E044-226, E2007-E044-202, E2007-E044-204, E2007-E044-214) and four OLE

studies (E2007-E044-205, E2007-E044-318, E2007-E044-220, E2007-E044-303) in

**subjects with Parkinson's disease (PD)**

- **Two double-blind studies (E2007-A001-218, E2007-G000-227) and one OLE study (E2007-G000-228) in subjects with painful diabetic neuropathy (PDN) or postherpetic neuropathy (PHN)**

- **One double-blind study (E2007-E049-201) in subjects with multiple sclerosis (MS)**

- **One double-blind study (E2007-A001-210) in subjects with migraine headache**

Thank you for your time,

Stephanie Keefe-Parncutt

---

**From:** Heather\_Bradley@Eisai.com [[mailto:Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)]

**Sent:** Wednesday, June 22, 2011 1:36 PM

**To:** Keefe, Stephanie

**Subject:** RE: NDA 202834 --Clinical Information Request

Dear Stephanie,

In accordance with our proposal as communicated via e-mail on 14 Jun 2011(below), I'd like to confirm that datasets for the following studies were submitted to NDA 202834 as sequence 0002 via the Electronic Gateway, and were confirmed as received by CDER as of 12:49pm today, June 22:

- SDTM datasets conforming to CDISC standards for two double-blind studies (E2007-A001-218, E2007-G000-227) and one OLE study (E2007-G000-228) in subjects with painful diabetic neuropathy (PDN) or postherpetic neuralgia (PHN)

The list of perampanel studies in humans provided in the June 14 e-mail was also included in sequence 0002.

Preparation of the remaining datasets, to be submitted in bundles, is ongoing, with the next submission by Monday, June 27.

Please confirm receipt of this e-mail and contact me with any questions.

Thanks and regards,  
Heather

Heather A. Bradley, MPH  
Senior Manager, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677  
Tel: 201-949-4691  
Cell: (b) (6)  
Fax: 201-949-4595  
[heather\\_bradley@eisai.com](mailto:heather_bradley@eisai.com)

**From:** Heather Bradley/RIG/EisaiInc  
**To:** "Keefe, Stephanie" <[Stephanie.Keefe@fda.hhs.gov](mailto:Stephanie.Keefe@fda.hhs.gov)>  
**Date:** 06/14/2011 03:10 PM  
**RE:** NDA 202834 --Clinical Information Request

Subject:

Dear Stephanie,

Regarding the Clinical Information Request you provided last week (June 10, 2011), I have the following response updates.

As I was preparing to send this to you, I also received an e-mail from you with a response from the Safety team to our clarifying questions (submitted via e-mail Friday, June 10, 4:23pm), but I then received a recall message from you. Please confirm if that response is still valid?

**Request:** Please provide a complete listing of all trials performed in humans.

**Response:** A list of all trials performed in humans has been extracted from the listing of all submitted reports provided in 5.2 of sequence 0000 and is attached. This listing will be formally submitted to the NDA in an information amendment when the first set of study datasets is provided, per the proposed schedule outlined below.

[attachment "1.11.3 Appendix 1 List of Human Studies.pdf" deleted by Heather Bradley/RIG/EisaiInc]

**Request:** Please submit the datasets for the double-blind study E2007-E044-213 in subjects with Parkinson's disease.

**Response:** Study E2007-E044-213 was not conducted. A study protocol had been written, but no subjects were enrolled, therefore no subject data for this study exists and no datasets will be submitted.

**Request:** Please submit all of the datasets (for study E2007-E044-213 and the 16 studies that are listed on page 21 of the ISS) with coding of adverse events in MedDRA, along with verbatim terms. Whenever possible, please submit the datasets in data tabulation datasets (SDTM) conforming to the CDISC standard.

**Response:** Eisai will prepare datasets with coding of adverse events in MedDRA, along with verbatim terms, for 15 of the 17 requested studies:

One study (E2007-E0444-213) was not conducted, as noted above.

Study E2007--A001-226 in subjects with Parkinson's disease enrolled only 1 subject. This subject received 2 mg perampanel and completed the study with no SAEs and 3 AEs. The complete CRF for this subject was submitted in sequence 0000. Eisai proposes not to prepare or submit datasets for this one subject. **Please confirm this is acceptable.**

For the remaining 15 studies in the original list of 17 requested study datasets, Eisai will prepare and submit the requested datasets, but is unable to accommodate this request in the 1 week timeframe given in the request. We propose to submit the datasets accordingly:

- For the two double-blind studies (E2007-A001-218, E2007-G000-227) and one OLE study (E2007-G000-228) in subjects with painful diabetic neuropathy (PDN) or postherpetic neuralgia (PHN) the SDTM datasets conforming to CDISC standards will be submitted no later than *Wednesday, June 22, 2011*.
- For the double-blind and OLE studies in subjects with Parkinson's disease, multiple sclerosis or migraine headache (listed below), raw datasets will be prepared and submitted no later than *Friday, July 8, 2011*. These can be submitted either in bundles or on a rolling basis, if the review team has a preference.

<u>PD double-blind</u>	<u>PD OLE</u>	<u>MS double-blind</u>	<u>Migraine double-blind</u>
E2007-E044-301	E2007-E044-205	E2007-E049-201	E2007-A001-210
E2007-E044-302	E2007-E044-318		
E2007-G000-309	E2007-E044-220		
E2007-E044-202	E2007-E044-303		
E2007-E044-204			
E2007-E044-214			

- Submitting the 15 requested datasets according to the schedule outlined above will ensure that all requested datasets are delivered prior to the Day 45 review meeting. **Please confirm this is acceptable.**

Please contact me with any questions.

Heather A. Bradley, MPH  
Senior Manager, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677  
Tel: 201-949-4691  
Cell: (b) (6)  
Fax: 201-949-4595  
heather\_bradley@eisai.com

From: "Keefe, Stephanie" <Stephanie.Keefe@fda.hhs.gov>  
To: "Heather\_Bradley@Eisai.com" <Heather\_Bradley@Eisai.com>  
Date: 06/10/2011 03:29 PM  
Subject: RE: NDA 202834 --Clinical Information Request

---

Heather,

I apologize, but our clinical team has modified their Information Request. Please confirm receipt of this updated version:

In your NDA 202834 application package, the datasets for the studies for the non-epilepsy indications were not submitted.

Please submit all of the datasets (for the 17 studies listed below) with coding of adverse events in MedDRA, along with verbatim terms. Whenever possible, please submit the datasets in data tabulation datasets (SDTM) conforming to the CDISC Standard. Please also provide a complete listing of all trials performed in humans. Please provide all of this information within one week.

Please submit the datasets for the double-blind study, E2007-E044-213, in subjects with Parkinson's Disease along with the 16 studies that are listed on page 21 of the Integrated Summary of Safety:

Perampanel was also evaluated in other indications. The following studies are included in

this submission to support the safety findings of the epilepsy studies:

- Seven double-blind studies (E2007-E044-301, E2007-A001-302, E2007-G000-309, E2007-E044-226, E2007-E044-202, E2007-E044-204, E2007-E044-214) and four OLE studies (E2007-E044-205, E2007-E044-318, E2007-E044-220, E2007-E044-303) in subjects with Parkinson's disease (PD)
- Two double-blind studies (E2007-A001-218, E2007-G000-227) and one OLE study (E2007-G000-228) in subjects with painful diabetic neuropathy (PDN) or postherpetic

neuropathy (PHN)

- One double-blind study ([E2007-E049-201](#)) in subjects with multiple sclerosis (MS)
- One double-blind study ([E2007-A001-210](#)) in subjects with migraine headache

Thanks,

Stephanie

---

**From:** Heather\_Bradley@Eisai.com [[mailto:Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)]  
**Sent:** Friday, June 10, 2011 3:27 PM  
**To:** Keefe, Stephanie  
**Subject:** Re: NDA 202834 --Clinical Information Request

Hi Stephanie,  
Receipt confirmed. We are looking at the request and may have clarifying questions shortly.

Thanks,  
Heather

Heather A. Bradley, MPH  
Senior Manager, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677  
Tel: 201-949-4691  
Cell: (b) (6)  
Fax: 201-949-4595  
[heather\\_bradley@eisai.com](mailto:heather_bradley@eisai.com)

From: "Keefe, Stephanie" <Stephanie.Keefe@fda.hhs.gov>  
To: "Heather\_Bradley@Eisai.com" <Heather\_Bradley@Eisai.com>  
Date: 06/10/2011 02:55 PM  
Subject: NDA 202834 --Clinical Information Request

---

Heather,

Please see the Information Request below, from our Clinical team and please confirm receipt:

**In your NDA 202834 application package, the datasets for the studies for the non-epilepsy indications were not submitted.**

**Please submit all of the datasets (for the 17 studies listed below) in data tabulation datasets (SDTM) conforming to the CDISC Standard with coding of adverse events in MedDRA, along with verbatim terms. Please also provide a complete listing of all trials performed in humans. Please provide all of this information within one week.**

Please submit the datasets for the double-blind study, E2007-E044-213, in subjects with Parkinson's Disease along with the 16 studies that are listed on page 21 of the Integrated Summary of Safety:

Perampanel was also evaluated in other indications. The following studies are included in

this submission to support the safety findings of the epilepsy studies:

- Seven double-blind studies (E2007-E044-301, E2007-A001-302, E2007-G000-309, E2007-E044-226, E2007-E044-202, E2007-E044-204, E2007-E044-214) and four OLE studies (E2007-E044-205, E2007-E044-318, E2007-E044-220, E2007-E044-303) in subjects with Parkinson's disease (PD)
- Two double-blind studies (E2007-A001-218, E2007-G000-227) and one OLE study (E2007-G000-228) in subjects with painful diabetic neuropathy (PDN) or postherpetic neuropathy (PHN)
- One double-blind study (E2007-E049-201) in subjects with multiple sclerosis (MS)
- One double-blind study (E2007-A001-210) in subjects with migraine headache

Thank you,

Stephanie

---

**From:** Heather\_Bradley@Eisai.com [[mailto:Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)]  
**Sent:** Wednesday, May 25, 2011 4:28 PM  
**To:** Keefe, Stephanie  
**Subject:** NDA 202834

Dear Stephanie,

I wanted to make you aware that NDA 202834 was delivered today to the CDER document room, as per the attached receipt-stamped cover letter.

I'm looking forward to working with you as this NDA progresses through filing and review.

Enjoy your holiday weekend!

Regards,  
Heather

Heather A. Bradley, MPH  
Senior Manager, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677  
Tel: 201-949-4691

Cell: (b) (6)  
Fax: 201-949-4595  
heather\_bradley@eisai.com

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/s/  
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STEPHANIE N PARNCUTT  
01/26/2012

## REQUEST FOR CONSULTATION

TO (Office/Division): **OND /Div Cardiology and Renal Products IRT-QT**  
Attn: **Devi Kozeli (WO22/Room 4183)**

FROM (Name, Office/Division, and Phone Number of Requestor): **Russell Katz, MD, Division of Neurology Products**

DATE  
**July 7, 2011**

IND NO.

NDA NO.  
**202834**

TYPE OF DOCUMENT  
**QT Study Report**

DATE OF DOCUMENT  
**5/25/2011**

NAME OF DRUG  
**FYCOMPA (perapanel) Tablets**

PRIORITY CONSIDERATION  
**Standard**

CLASSIFICATION OF DRUG  
**Partial onset-seizures**

DESIRED COMPLETION DATE  
**December 25, 2011**

NAME OF FIRM: **Eisai, Inc.**

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input checked="" type="checkbox"/> PROGRESS REPORT      | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

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| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

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|--|--------------------------------------|
| <input checked="" type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
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**COMMENTS / SPECIAL INSTRUCTIONS:** NDA 202834 was received on May 25, 2011 and provides for treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older. This is a NME. The application has a PDUFA goal date of 3-25-12. Please review and comment on the thorough QT study contained in this submission. The entire submission may be accessed at :\\CDSESUB1\EVSPROD\NDA202834\202834.ENX. The filing meeting for NDA 202834 is scheduled for 7/14 at 9:00am (WO 22 Rm. 4201) if you or someone from your group would like to attend.

SIGNATURE OF REQUESTOR  
**Stephanie Keefe, Regulatory Project Manager, DNP**  
Food and Drug Administration  
Phone: 301-796-4098

METHOD OF DELIVERY (Check one)  
 DFS       EMAIL       MAIL       HAND

Email: <a href="mailto:stephanie.keefe@fda.hhs.gov">stephanie.keefe@fda.hhs.gov</a>	
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/  
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STEPHANIE N KEEFE  
07/07/2011

## REQUEST FOR CONSULTATION

TO (Office/Division): **PMHS**  
Attn: Rosemary Addy

FROM (Name, Office/Division, and Phone Number of Requestor):  
**Russell Katz, MD, Division of Neurology Products**

DATE <b>June 6, 2011</b>	IND NO.	NDA NO. <b>202-834</b>	TYPE OF DOCUMENT <b>New original NME NDAs</b>	DATE OF DOCUMENT <b>May 25, 2011</b>
NAME OF DRUG <b>FYCOMPA (perapanel) Tablets</b>		PRIORITY CONSIDERATION <b>Standard</b>	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE <b>January 25, 2012</b> PDUFA goal date: <b>March 25, 2011</b>

NAME OF FIRM: **Eisai, Inc.**

### REASON FOR REQUEST

#### I. GENERAL

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| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

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| <input type="checkbox"/> NEW STANDARD NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW                  |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> PHARMACOLOGY                      |
| <input type="checkbox"/> CONTROLLED STUDIES      | <input type="checkbox"/> BIOPHARMACEUTICS                  |
| <input type="checkbox"/> PROTOCOL REVIEW         | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW):  |  |

#### III. BIOPHARMACEUTICS

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| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

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|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

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| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** On May 25, 2011, we received the following NDA submission for NDA 202-834 FYCOMPA (perampanel) tablets:

Electronic link is: \\CDSESUB1\EVSPROD\NDA202834\202834.ENX

I wanted to touch base with you, as this application is eligible for the pilot program, as an NME. The Pediatric information can be found in m1.9. You will also find that the sponsor has submitted a Deferral and Partial Waiver notification. The filing meeting for NDA 202834 is scheduled for 7/14 at 9:00am (WO 22 Rm. 4201) if you or someone from your group would like to attend.

SIGNATURE OF REQUESTOR <b>Stephanie Keefe, Regulatory Project Manager, DNP</b> Food and Drug Administration Phone: 301-796-4098 Email: <a href="mailto:stephanie.keefe@fda.hhs.gov">stephanie.keefe@fda.hhs.gov</a>	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DARRTS <input checked="" type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
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/s/  
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STEPHANIE N KEEFE  
06/06/2011

## REQUEST FOR CONSULTATION

TO (Office/Division): HFD-009/Controlled Substances Staff  
Attention: Corinne Moody/ Michael Klein

FROM (Name, Office/Division, and Phone Number of Requestor): Russell Katz, MD, Division of Neurology Products

DATE  
June 6, 2011

IND NO.

NDA NO.  
202-834

TYPE OF DOCUMENT  
New original NME NDAs

DATE OF DOCUMENT  
May 25, 2011

NAME OF DRUG  
**FYCOMPA (perapanel)  
Tablets**

PRIORITY CONSIDERATION  
Standard

CLASSIFICATION OF DRUG  
1

DESIRED COMPLETION DATE  
January 25, 2012  
PDUFA goal date:  
March 25, 2011

NAME OF FIRM: Eisai, Inc.

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

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|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

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| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

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|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

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| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** NDA 202834 was received on May 25, 2011 and provides for treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older. This is a NME. The application has a PDUFA goal date of 3-25-2012. The entire submission may be accessed at : \\CDSESUB1\EVSPROD\NDA202834\202834.ENX. Please review and comment on the acceptability of the abuse liability studies submitted in NDA 202834. The filing meeting for NDA 202834 is scheduled for 7/14 at 9:00am (WO 22 Rm. 4201) if you or someone from your group would like to attend. Please see attached information from the sponsor, below.

SIGNATURE OF REQUESTOR  
Stephanie Keefe, Regulatory Project Manager, DNP  
Food and Drug Administration

METHOD OF DELIVERY (Check one)  
 DFS       EMAIL       MAIL       HAND

Phone: 301-796-4098 Email: stephanie.keefe@fda.hhs.gov	
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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STEPHANIE N KEEFE  
06/06/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Division of Biostatistic VI Attention: Karl Lin		FROM: <b>Russell Katz, MD, Division of Neurology Products (DNP), HFD-120</b>		
DATE June 6, 2011	IND NO.	NDA NO. 202-834	TYPE OF DOCUMENT New original NME NDAs	DATE OF DOCUMENT May 25, 2011
NAME OF DRUG <b>FYCOMPA (perapanel) Tablets</b>		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG 1	DESIRED COMPLETION DATE December 25, 2011 PDUFA goal date: March 25, 2011
NAME OF FIRM: Eisai, Inc.				
REASON FOR REQUEST I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input checked="" type="checkbox"/> PHARMACOLOGY - CAC statistical data <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
<p><b>REQUEST:</b> NDA 202834 was received on May 25, 2011 and provides for treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older. This is a NME. The application has a PDUFA goal date of 3-25-2012. The entire submission may be accessed at : \\CDSESUB1\EVSPROD\NDA202834\202834.ENX. <b>Please review and comment on the acceptability of the carcinogenicity statistical information submitted in NDA 202834.</b> The filing meeting for NDA 200896 is scheduled for 7/14 at 9:00am9 (WO 22 Rm. 4201) if you or someone from your group would like to attend. Electronic datasets have been provided for both of the carcinogenicity toxicity studies in m4.2.3.4</p>				
SIGNATURE OF REQUESTER Stephanie Keefe, Regulatory Project Manager, DNP Food and Drug Administration Phone: 301-796-4098 Email: stephanie.keefe@fda.hhs.gov		METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> Email		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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/s/  
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STEPHANIE N KEEFE  
06/06/2011

## MEMORANDUM OF MEETING MINUTES

**Meeting Date:** December 5, 2007  
**Application:** IND 68,368 ; Perampanel  
**Indication:** Epilepsy  
**Type of Meeting:** EOP2  
**Meeting Chair:** Russell Katz, M.D.  
**Meeting Recorder:** Melina Griffis, R.Ph.

### **FDA Attendees:**

Russell Katz, M.D., Division Director	Norman Hershkowitz, M.D., Clinical TL
Philip Sheridan, M.D., Clinical Reviewer	Lois Freed, Ph.D., Nonclinical
Ed Fisher, Ph.D., Nonclinical	Ramana Uppoor, Ph.D., Biopharm
Sharon Yan, Ph.D., Statistics	Christine Garnett, Pharm D, QT
Melina Griffis, R.Ph., Project Manager	

### **Eisai Attendees:**

Lynn Kramer - Executive Vice President  
Mark Taisey - Vice President, Regulatory Affairs  
Martina Struck - Senior Director, Drug Regulatory Affairs  
Josie Yang - Director, Nonclinical Regulatory Affairs  
Bob Clark - Associate Director, CMC Regulatory Affairs  
Heather Bradley - Manager, Drug Regulatory Affairs  
Nichole Zasa - Associate, Drug Regulatory Affairs  
Taka Maeda - Director, Global Regulatory Affairs  
Julia Yang - Senior Director, CNS II  
Jim Ferry - Associate Vice President, Clinical Pharmacology  
Dinesh Kumar - Associate Director, Biostatistics  
Zhengning Lin - Director, Biostatistics  
Simon Ashworth - Head of Product Safety

### **Discussion Points: Below are the sponsor's questions with the appropriate FDA responses.**

The following were the key items discussed and agreements reached at the meeting as well as the preliminary communication sent to the sponsor; a number of the sponsor's original questions were fully addressed through the preliminary communication alone and were not discussed further at the meeting. All items addressed are summarized below each of the sponsor's original questions.

1. Eisai believes that the non-clinical data, as detailed in the briefing package, supports the proposed clinical Phase 3 development of perampanel in patients with partial seizures. Does the Division agree?

**1) The completed chronic nonrodent toxicity study is inadequate because exposures achieved at the highest dose tested are significantly lower than**

those expected in humans at the maximum proposed doses for the planned Phase 3 clinical studies. A 9-month monkey study testing higher doses is currently ongoing; the adequacy of this study will be a matter of review. However, it should be noted that for a drug with a novel mechanism of action for which we have limited human or animal long-term safety data, the duration of the chronic nonrodent toxicity study is generally expected to be 12 months.

2) The in vivo metabolism of your drug has not been adequately elucidated across species. Based on the in vitro metabolism data, it appears that there may be human metabolites that are not produced in rodents. The need for additional studies will depend on the quantities of these metabolites present systemically in humans. Therefore, the in vivo metabolism of your drug in the animals used in the pivotal toxicology studies and in humans needs to be characterized qualitatively and quantitatively.

3) The adequacy of the rat fertility study should be addressed, as previously indicated (cf meeting minutes August 28, 2007).

These issues will need to be explicitly addressed prior to Phase 3 clinical trials.

Meeting Discussion: For items 2 & 3 the sponsor stated they have more data available which will be submitted. The sponsor explained the tolerability difficulties with the ongoing monkey study and stated that dose escalation occurred over a 3 month period and that dosing would be for a 9 month duration which appeared to be acceptable to the Division. A responses to items 1, 2, & 3 above should be submitted prior to or at the time of the phase III protocols.

2. Does the Division agree that the program of completed and planned/ongoing non-clinical studies is adequate to support NDA filing of perampanel for the proposed indication?

**It appears so at this time but the decision is made after NDA filing.**

#### **Nonclinical Comments:**

**In addition to the issues outlined above, we have the following comments:**

1) The potential for phototoxicity should be fully evaluated according to Agency guidelines, particularly in light of the positive photo-chromosomal aberration test and higher clinical doses being proposed.

2) Recent animal studies examining the abuse potential of your drug will be evaluated by Agency Controlled Substance Staff, who may request additional nonclinical information.

3) It should be noted that for pediatric development of your drug, juvenile toxicity studies in a nonrodent as well as rodent species will be required.

Meeting Discussion: It was conveyed to the sponsor that the in vivo photo irritation data available (currently blinded in an ongoing clinical study) may not be adequate

since it doesn't incorporate high enough doses and adequate durations of exposure. The sponsor was asked to consider how best to assess this issue and provide this to the Division along with any relevant data. The division also noted that in the interim investigators should use directed questions in clinical studies to examine for this potential adverse event.

Juvenile animal studies were discussed. The sponsor noted that they are not ready to submit such studies. The sponsor noted that they will defer pediatric studies till they obtain such information. The division noted, that while Sponsors will generally defer pediatric development till latter on, the division would prefer it to be initiated as soon as possible.

3. Does the Division agree that the overall study design of the three proposed Phase 3 studies, the duration, the inclusion and exclusion criteria, and the choice and definition of the primary efficacy endpoint, i.e. percent change in seizure frequency per 28 days in the Double-blind Phase (Titration Period + Maintenance Period), are acceptable to support the intended Claimed Use: "Perampanel is indicated as an adjunctive therapy in patients 12 years of age and older with partial onset seizures including secondarily generalized seizures"?

**In general, yes. See discussion of ITT population definition in question 4. Did the power calculations take into account the rate of dropouts from the studies?**

**Clinical Pharm: We recommend that you quantify the relationship between perampanel exposure (AUC for example) and the primary endpoint in the three Phase-III studies. This will help in better dose selection in future pediatric studies.**

[Meeting Discussion: See below](#)

4. Since steady-state of perampanel is not typically achieved until at least 14 days of multiple dosing, less than 2 weeks of epilepsy data will not provide a valid estimate of the average seizure frequency. Therefore, Eisai plans to exclude subjects who have less than 2 weeks of seizure diary data in the Double-Blind Phase from the ITT population analysis. Does the Division agree to this definition of the ITT population?

**Defining the ITT population as proposed is unconventional when compared to similar studies and may potentially lead to problems in the final analyses.**

**In most studies, patients receiving any dosing during the Double-Blind Phase are included in the ITT population analysis. If only a few patients have less than 2 weeks of dosing, the effect on analysis would be minimal and would make the proposed adjustment to the definition of the ITT population unnecessary. On the other hand, if there were a substantial number of dropouts during these first two weeks, the proposed adjustment to the definition of the ITT population might lead to an uninterpretable study.**

Furthermore, it is unclear which 2 weeks are referred to in the question. We are assuming that, in protocols 304 and 305, “first two weeks of multiple dosing” refer to weeks 2 and 3 of the titration phase for both the 8 mg and 12 mg active arms (assuming that the “first two weeks of multiple dosing” refers to the titration period rather than the maintenance period.) Presumably, the intent of the Sponsor is to exclude subjects from the ITT population who are lost from the study before completing the third week of Titration but to include those who are lost from the study in the third week of the six weeks of titration.

It is noted that the 8 mg arm is at full dosage at the start of week 4 (although not at steady state) but the 12 mg arm will not be at full dosage until the start of week 6. Therefore, the ITT population in the 8 mg arm will have no patients that dropped out prior to reaching full dosage but the 12 mg arm might have such patients. A steady state would not have been reached in either arm after “first two weeks of multiple dosing”.

Given these concerns, the Division does not agree to the proposed adjustment to the definition of the ITT population without further discussion at the meeting

Meeting Discussion: The Division conveyed that if there were a large number of dropouts in the trial this proposal could be problematic and that when analyzed we would be looking at both analyses. The sponsor was also invited to present an argument as to why their analyses proposal should be acceptable.

5. Eisai will study the 2mg and 4mg dose in one of the three proposed trials (E2007-G000-306), which is designed with enough sample size to establish a minimally effective dose. Does the Division agree that the 306 trial as designed, if positive, in conjunction with existing POC study (206), could provide sufficient evidence to establish a minimally effective dose that can be labeled as such?

**Yes, this could provide such evidence.**

Meeting Discussion: None

6. The 8mg dose will be studied in all three proposed trials. Does the Division agree that this dose can be registered as an effective dose if found to be statistically significant in at least two of the three trials?

**Yes. This still remains a review issue with other factors, such as tolerance at this dose and effectiveness at lower doses, considered in the final review.**

Meeting Discussion: None

7. Eisai plans to perform routine safety monitoring of the Phase 3 program. Does the Division agree that the proposed safety monitoring strategy is adequate?

**Yes, although the full protocols are not yet available for review. See question 12.**

Meeting Discussion: None

8. Does the Division agree that the estimates of study drug exposure from the four Phase II epilepsy studies (three double-blind studies [203, 206 and 208] and an open-label extension study 207) and the four Phase III studies (three double-blind studies [304, 305 and 306] and an open-label extension study 307) alone or in combination with exposure data from other indications will be sufficient to meet ICH (E1A) and Division guidelines for the extent of study drug exposure to assess clinical safety for the proposed indication?

**Yes, given answer to question 11 below about possible need for more ECGs during the Phase 3 studies.**

Meeting Discussion: None

9. Eisai believes that integration of all data obtained, including that in the phase III program outlined in this document, will provide an adequate and comprehensive understanding of the pharmacokinetics of perampanel. Does the Division agree with this strategy?

**Generally yes, with a few additional recommendations:**

- **In vitro metabolism study has been done using recombinant assay. Further in vitro metabolism should be investigated using human liver microsomes, as recombinant assays alone are not always conclusive. The Sponsor should refer to the draft preliminary concept paper “Drug Interaction Studies – Study design, data Analysis, and Implications for Dosing and Labeling” for guidance on conducting such studies (available at [http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4079B1\\_04\\_Topic2-TabA.pdf](http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4079B1_04_Topic2-TabA.pdf))**
- **Based on the mass balance study only 70% of the drug is accounted for and as such is not adequate to characterize the fate of the drug.**
- **Include Phase 3 data to characterize the dose proportionality of perampanel in the therapeutic dose range of 4-12 mg.**
- **For comments on the Population PK and PK-PD analysis plan detailed population PK and PK-PD protocol for Phase 3 studies (#304, 305 and 306) should be submitted. The Population PK analysis amongst other covariates should evaluate the effect of age. The sponsor should also quantify the effects of renal impairment on the pharmacokinetics of E2007 by Population analysis in the absence of a definitive PK study.**

Meeting Discussion: The sponsor stated that items under bullets 1 & 4 are planned in future studies. For bullet # 2 the sponsor will be providing update data.

10. Based on the results of both in vitro and clinical studies, Eisai does not expect any clinically relevant interactions with concomitant anti-epileptic drugs or other common concomitant medications used in this population which are metabolized principally by cytochrome P450 enzymes. Further assessment of effects on glucuronidation (inhibition and induction) and specifically the effect of valproate on the metabolic profile of perampanel is planned. Does the Division agree with this strategy?

**Yes**

Meeting Discussion: None

11. Eisai is conducting a study (E2007-E044-013) to evaluate the effects of perampanel on QT interval. In the event that the outcome of study E2007-A001-013 clearly demonstrates no effect on QT interval, Eisai believes that a repeated study at higher doses is not necessary. If a positive signal was obtained in study 013, then further discussion would be required to ensure that an adequate and acceptable risk assessment could be provided. Does the Division agree with this strategy?

#### **QT-IRT Comments**

**1. We recommend that the sponsor amends the current protocol to include studying doses higher than 12 mg/day, if higher doses are supported by safety data. This may still be possible since enrollment for the TQT study started in September 2007.**

**2. If the sponsor cannot amend the current protocol, then we suggest a repeat TQT study with higher doses. The dose selected for this repeat TQT study should cover the anticipated increases in perampanel plasma concentrations in the patient population due to CYP3A4 inhibition and hepatic impairment.**

**3. If perampanel prolongs the QT interval, we recommend more frequent acquisition of subject ECGs during clinical trials to enhance subject safety and to collect an adequate safety database.**

Meeting Discussion: It was conveyed to the sponsor that there is a concern with adequate coverage of the therapeutic doses of the current study. The division suggested that a possible alternative may be to incorporate formal QT study techniques (as outlined in the ICH guidance) into phase 3 trials. This however, is not a preferred solution and therefore an argument would need to be presented as to why the current QT study can't be amended to incorporate higher doses.

12. Since non-clinical data reveal low risk, no additional clinical studies to evaluate phototoxicity potential are planned. Does the Division agree with this approach?

**The extent of screening for phototoxicity potential in patients receiving higher doses (8 -12 mg) during clinical studies is not clear. The need for such screening in the Phase 3 studies (e.g. guided interview questions during assessment visits) can be discussed at the meeting.**

Meeting Discussion: A suggestion to incorporate directed interviews was made.

13. Eisai believes that a dose of 20mg in the current design of study 024 to evaluate the abuse liability potential also covers the doses used in the epilepsy development program. Does the Division agree with this strategy?

**CSS Response**

**\* CSS has not previously been consulted on the design of the human abuse potential studies. If the Sponsor submits the complete protocols for these studies, CSS will review them for adequacy.**

**\* In general, the drug doses used in human abuse potential studies should be 2-3 times the highest proposed therapeutic dose for any indication, if this can be done safely.**

Meeting Discussion: None

14. Eisai proposes that a food effect study with an 8mg tablet will not provide any additional data that will add value to the assessment of the product and therefore does not propose to include such a study in the development plan. Does the Division agree with this strategy?

**Acceptable, however rationale for not evaluating food effect with the highest strength should be provided in the NDA.**

Meeting Discussion: None

15. Will the Division consider [REDACTED] (b) (4)  
[REDACTED] in the Clinical Pharmacology/Pharmacokinetics section of the product label?

[REDACTED] (b) (4)

**As perampanel is likely to be used in children with intractable seizures if it is marketed for adults, a pediatric waiver is not appropriate.**

**A deferral of pediatric efficacy studies could be considered at the meeting**

**Additional Statistical Comments:**

- It is not clear which analysis method, Wilcoxon rank sum test or rank ANCOVA, will be used to analyze the primary efficacy endpoint. If the sponsor intends to use rank ANCOVA, the sponsor needs to pre-specify what covariate(s) will be included in the ANCOVA model.
- The sample size calculation should take into account the potential dropout.

Meeting Discussion: None

Linked Applications

Sponsor Name

Drug Name

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IND 68368

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EISAI MEDICAL  
RESEARCH INC

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E2007-MARS

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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RUSSELL G KATZ

01/09/2008