

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-911

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 21-911

SUPPL #

HFD # 120

Trade Name Banzel

Generic Name rufinamide

Applicant Name Eisai

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(1)

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

YES NO

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

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

d) Did the applicant request exclusivity?

YES NO

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

7 years

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

YES NO

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

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

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

YES NO

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES NO

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES NO

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

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

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

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

YES NO

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

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

YES NO

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

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

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

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

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

Investigation #2

YES
Explain:

!
!
! NO
! Explain:

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

YES NO

If yes, explain:

Name of person completing form: Susan Daugherty
Title: RPM
Date: 10-27-08

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

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Russell Katz
11/12/2008 08:31:52 PM

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹	
NDA # 21-911	
Proprietary Name: Banzel Established/Proper Name: rufinamide Dosage Form: Tablets	Applicant: Eisai Medical Research Agent for Applicant (if applicable):
RPM: Susan Daugherty	Division: DNP
<p>NDA: 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 NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>	<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(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"/> If no listed drug, check here and explain:</p> <p>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p> <p>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</p>
❖ User Fee Goal Date Action Goal Date (if different)	9/3/08 11/14/08
❖ Actions	
<ul style="list-style-type: none"> • Proposed action 	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 	<input type="checkbox"/> None AE 9/06
❖ Promotional Materials (<i>accelerated approvals only</i>) Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance www.fda.gov/cder/guidance/2197dft.pdf). If not submitted, explain _____	<input type="checkbox"/> Received

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

❖ Application ² Characteristics	
Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only): 1	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan drug designation	
<input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Direct-to-OTC	
NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520)	
BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42)	
Subpart I <input type="checkbox"/> Approval based on animal studies	
<input type="checkbox"/> Approval based on animal studies	
<input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC	
Comments: _____	
❖ Date reviewed by PeRC (<i>required for approvals only</i>) If PeRC review not necessary, explain: <u>N/A – orphan product</u>	
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action (by OEP)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

² All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

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

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

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

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

Yes No

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

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

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

Yes No

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

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

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

Yes No

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

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

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

Yes No

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

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

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
CONTENTS OF ACTION PACKAGE	
<p>❖ Copy of this Action Package Checklist³</p>	<p>included</p>
Officer/Employee List	
<p>❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)</p>	<p><input checked="" type="checkbox"/> Included</p>
<p>Documentation of consent by officers/employees</p>	<p><input checked="" type="checkbox"/> Included</p>
Action Letters	
<p>❖ Copies of all action letters (<i>including approval letter with final labeling</i>)</p>	<p>Action(s) and date(s) AE 9-15-06 and AP 11-14-08</p>
Labeling	
<p>❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)</p>	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	<p>N/A</p>
<ul style="list-style-type: none"> • Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 	<p>included</p>
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<p>included</p>
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
<p>❖ Medication Guide/Patient Package Insert/Instructions for Use (<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"/> None</p>

³ Fill in blanks with dates of reviews, letters, etc.
Version: 9/5/08

<ul style="list-style-type: none"> • Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> • Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 	N/A
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	N/A
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	N/A
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date at upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent division proposal for (only if generated after latest applicant submission) 	See approval letter
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling 	
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEDP <input type="checkbox"/> DRISK <input checked="" type="checkbox"/> DDMAC <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Review(s) (<i>indicate date(s)</i>) • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) 	9-5-06; 8-4-08; 9-2-08; 10-17-08
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents www.fda.gov/ora/compliance_ref/aip_page.html 	
<ul style="list-style-type: none"> • Applicant in on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>) 	N/A orphan product
<ul style="list-style-type: none"> ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>) 	<input checked="" type="checkbox"/> Verified, statement is acceptable
<ul style="list-style-type: none"> ❖ Postmarketing Requirement (PMR) Studies 	<input type="checkbox"/> None
<ul style="list-style-type: none"> • Outgoing communications (<i>if located elsewhere in package, state where located</i>) 	AE letter 9-15-06
<ul style="list-style-type: none"> • Incoming submissions/communications 	
<ul style="list-style-type: none"> ❖ Postmarketing Commitment (PMC) Studies 	<input type="checkbox"/> None
<ul style="list-style-type: none"> • Outgoing Agency request for postmarketing commitments (<i>if located elsewhere in package, state where located</i>) 	

⁴ Filing reviews for other disciplines should be filed behind the discipline tab.
Version: 9/5/08

• Incoming submission documenting commitment	
❖ Outgoing communications (<i>letters (except previous action letters), emails, faxes, telecons</i>)	included
❖ Internal memoranda, telecons, etc.	included
❖ Minutes of Meetings	
• PeRC (<i>indicate date; approvals only</i>)	<input checked="" type="checkbox"/> Not applicable
• Pre-Approval Safety Conference (<i>indicate date; approvals only</i>)	<input type="checkbox"/> Not applicable 9-8-08
• Regulatory Briefing (<i>indicate date</i>)	<input checked="" type="checkbox"/> No mtg
• Pre-NDA/BLA meeting (<i>indicate date</i>)	<input type="checkbox"/> No mtg
• EOP2 meeting (<i>indicate date</i>)	<input type="checkbox"/> No mtg
• Other (e.g., EOP2a, CMC pilot programs)	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None 11-13-08
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None 11-14-08
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	11-14-08; 9-8-06
• Clinical review(s) (<i>indicate date for each review</i>)	1-9-07; 4-9-08; 9-8-08; 11-14-08
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Safety update review(s) (<i>indicate location/date if incorporated into another review</i>)	See clinical review
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	See clinical review
❖ Clinical reviews from other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None 8-31-06
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ Risk Management	<input type="checkbox"/> None 8-31-06
• 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>)	
• REMS Memo (<i>indicate date</i>)	11-14-08
• REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>)	10-27-08
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested 7-7-06
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None

⁵ Filing reviews should be filed with the discipline reviews.
Version: 9/5/08

Clinical Microbiology Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None 8-26-06; 8-26-08
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 9-11-06; 8-4-08
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input type="checkbox"/> None 10-1-08
• Supervisory Review(s) (indicate date for each review)	<input type="checkbox"/> None 9-2-08
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None 9-22-06; 9-2-08
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input type="checkbox"/> No carc 8-9-06
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None 8-1-06 Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None requested
CMC/Quality <input type="checkbox"/> None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None 9-11-06
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• CMC/product quality review(s) (indicate date for each review)	<input type="checkbox"/> None 9-11-06; 9-22-08
• BLAs only: Facility information review(s) (indicate dates)	<input type="checkbox"/> None
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) (indicate date of each review)	<input checked="" type="checkbox"/> Not needed
• BLAs: Sterility assurance, product quality microbiology (indicate date of each review)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	
<input checked="" type="checkbox"/> Review & FONSI (indicate date of review)	9-12-06
<input type="checkbox"/> Review & Environmental Impact Statement (indicate date of each review)	

❖ NDAs: Methods Validation	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed
❖ Facilities Review/Inspection	
<ul style="list-style-type: none"> • NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date)</i> 	Date completed: 9-18-08 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<ul style="list-style-type: none"> • BLAs: <ul style="list-style-type: none"> ○ TBP-EER ○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) <i>(date completed must be within 60 days prior to AP)</i> 	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation Date completed: <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold

Appendix A to Action Package Checklist

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

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

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

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

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

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

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

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

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

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

/s/

Susan B. Daugherty
11/18/2008 01:58:55 PM

3 Page(s) Withheld

 X Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

Withheld Track Number: Administrative- 1

Daugherty, Susan B (CSO)

From: Daugherty, Susan B (CSO)
Sent: Wednesday, September 03, 2008 5:43 PM
To: 'Joseph_Zuccarini@eisai.com'
Cc: 'Martina_Struck@Eisai.com'
Subject: rufinamide container/carton labeling comment

Dear Joseph,

Please refer to your NDA 21-911 for rufinamide. The carton and container labeling review is complete and we have the following recommendations:



b(4)

In addition, we recommend that the "unit of use" bottles have a Child Resistant Closure (CRC) per the Poison Prevention Act. Please note that the name _____ was unacceptable. The Division has been discussing the proposed name, _____ I will let you know the outcome of the those discussions as soon as possible.

b(4)

Best Regards,
Susan

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

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

/s/

Susan B. Daugherty
9/3/2008 05:53:08 PM

2 Page(s) Withheld

X Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

Withheld Track Number: Administrative-2

Daugherty, Susan B (CSO)

From: Daugherty, Susan B (CSO)
Sent: Friday, June 27, 2008 3:25 PM
To: 'Joseph_Zuccarini@eisai.com'
Subject: information request for NDA 21-911 rufinamide

Good Afternoon Joseph,

I am forwarding the following request for information from my Medical Officer for NDA 21-911 rufinamide:

- A case from study CRUF331 0021P has features suggestive of a multiorgan hypersensitivity. Although the investigator indicated no association with the study medication the constellation of serious signs and symptoms were consistent with a multiorgan hypersensitivity syndrome. This is a more severe manifestation of hypersensitivity response. 0005_04408 study 21 is the case of concern. The patient symptom onset are temporally associated with beginning of open label treatment. There is a severe coetaneous reaction, pneumonia, severe hepatitis - fulfilling Hy's law, eosinophilia, which progress for 30 days until study medication is discontinued then improves within 11 days of medication cessation. This severe response warrants a search for any additional reactions that may allow additional risk assessment for the multiorgan hypersensitivity syndrome.
- In light of the above noted case we request that you examine the entire clinical database for cases of potential multiorgan hypersensitivity reactions. A suggested approach would be to look for internal organ involvement (i.e., hepatitis, nephritis, pneumonitis, carditis, colitis, encephalitis, pancreatitis, myositis, arthritis, or hematologic system involvement) combined with at least two of the following: fever, rash, lymphadenopathy.

We would appreciate a prompt response so that we may continue the review for your application.

Best Regards,
Susan

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

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

/s/

Susan B. Daugherty
6/27/2008 03:28:55 PM

Pre-mtg Mins

Meeting Date: December 18, 2006

Sponsor: Eisai

NDA 21-911

Introductory Comment: This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for December 18, 2006. This material is shared to promote a collaborative and successful discussion at the meeting. The minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact the RPM). If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face-to-face to telecom). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. Please note that if there are any major changes to your development plan/the purpose of the meeting/to the questions based on our responses herein, we may not be prepared to discuss or reach agreement on such changes at the meeting. If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact the Regulatory Project Manager to discuss the possibility of including these for discussion at the meeting.

QUESTIONS FOR THE AGENCY

1.1 CLINICAL/STATISTICAL QUESTIONS

1. Eisai believes that AE/ET1 and 21A are positive trials by test of their protocol specified primary endpoints. Does the Agency concur that these two trials meet the standard for two adequate and well-controlled trials to demonstrate a seizure-reducing effect of rufinamide as add-on treatment for adults with partial seizures?

2. The protocol specified analysis of AE/ET1 documents that there is a statistically significant relationship between rufinamide dose and reduction in seizure frequency.

b(4)

b(4)

3. With regard to study 21A, Eisai believes that the lack of statistical significance ($p=0.09$) on an ANCOVA analysis of a secondary endpoint (log transformed 28 day seizure frequency) is insufficient to negate the conclusion, based on the study's protocol specified primary endpoint analysis, that rufinamide is effective in adjunctive use in the management of partial onset seizures. Moreover, the lack of significance on this analysis is a reflection of the inadequacy of the log transformation of the seizure frequency (i.e., the transformed data were not normally distributed). In such circumstances, an ANCOVA rank analysis is more appropriate, and when performed, it demonstrated a statistically significant advantage for rufinamide. Considering that the primary endpoint was positive, and that the secondary endpoints, including 50% and 25% responder rates were also positive, does FDA concur that 21A is a positive trial based on its primary endpoint and supportive secondary endpoints?

Yes.

4. Eisai has submitted two other studies conducted in adult refractory patients with partial seizures (AE/PT2 as add-on therapy and 038 as short-term in-patient monotherapy). Does the FDA agree that studies AE/PT2 and 038 are positive trials and are supportive for the adult partial seizures indication?

No. The division would not agree that study AE/PT2 demonstrates a statistically significant effect. Analysis in this study was completely post-hoc in nature. The Sponsor analyzed a subset (44 of the 50 patients) of patients who retrospectively reported seizures 3 months prior to treatment. When this was performed a statistically significant effect was observed ($p=0.04$). But, when the true ITT analysis was performed, which included all patients, no statistical significance was observed ($p=0.071$). Because of this, the results of this study can, at best, be considered as non-contributory. Study 038 appears to be positive, but the results are not robust.

5. The FDA approvable letter makes several mentions of "effect size." While we acknowledge your concern that the change in median seizure frequency may seem modest, the proportion of patients experiencing a 50% reduction in seizures was also statistically significant and clinically relevant. The Agency has approved antiepileptic drugs based on trials showing a similar "effect size" to that of rufinamide. Does the Agency concur that rufinamide can be approved based on the effect size already demonstrated?

Yes. But we do not believe dose recommendations can be written with the data collected. We do not want to recommend a dose of 3200mg if 800mg will provide the same effect with a better adverse event profile (less vomiting for example). We do not believe there is enough evidence to support 400- _____ as described above.

b(4)

6. Because rufinamide has not been formally tested as an inhibitor for p-glycoprotein (p-gp), Eisai agrees to evaluate the in vitro p-gp inhibition potential of rufinamide and this study is in the planning stage. However, data suggest that the likelihood of this compound leading to inhibition of this transporter is very low. There have been two in-vitro studies performed investigating the transport of rufinamide across Caco-2 cell monolayers (DMPK(CH) R99-1620, and DMPK(CH) R99-2040). These studies indicated clearly that rufinamide is not a substrate for p-gp. Furthermore, the physicochemical properties of rufinamide suggest that it is unlikely to be a potent inhibitor of p-gp, given what is known about the structure-activity relationships for this transporter. Because of the structural evidence, lack of substrate activity, and lack of drug-drug interaction data suggesting p-gp inhibition, Eisai proposes that the results of this study could be provided after approval if the study is still ongoing at the time of the complete response. Does the Agency concur?

Yes.

7. Eisai plans to provide further justification for the name _____ in our complete response. Will the Agency agree to review our documentation?

b(4)

Yes. But we would advise you to make an alternative recommendation.

8. As of 01-NOV-2006 there are two patients ongoing in study 2301 and seven patients in baseline phase of the 301 study. Because of the small number of patients, Eisai proposes not to provide a new ISS update, but instead to provide narratives for any SAEs, withdrawals, or deaths, if they occur. Does the Agency agree?

Based on the above answers, we believe that you will need to perform an additional study. With that, a new ISS update would be needed.

1.2 NON-CLINICAL QUESTIONS

9. Although higher exposures of rufinamide could be achieved by oral gavage administration to rats, no PK/TK was measured in the three month oral gavage toxicity study. Marked reductions in body weight, body weight gain and food consumption were noted in males and females at 600 mg/kg. Slightly reduced body weight with reduced

weight gain was also noted in animals at 200 mg/kg, but these effects might become more pronounced and toxicologically significant after 2 years of dosing via gavage. Although decreased body weight and food consumption in the high-dose (200 mg/kg) males and females, and mid-dose (60 mg/kg) females were noted in the rat carcinogenicity study, the incidence of common tumor findings were similar and treatment related thyroid neoplastic findings were evident. Eisai plans to conduct a three-month oral gavage dose-ranging study to compare the levels of rufinamide to those in rats treated via diet admix in the completed study. The results will be submitted to the Agency for evaluation. If the results show more than three-fold differences in exposure in animals at mid- and high-dose of the existing rat carcinogenicity study, Eisai will conduct a repeat rat carcinogenicity study by oral gavage as a Phase IV commitment. Dose the Agency concur?

There is no requirement for a 3-fold difference in exposure. As stated in our letter, if similar or higher exposures could be achieved with gavage administration without the excessive body weight effects observed with dietary administration then the rat carcinogenicity study should be repeated. The timing of this requirement in relationship to approval will be dependent on several factors (eg, the duration and results of additional clinical study), but the study should be completed in a timely manner.

10. The in-vivo micronucleus assay (896146 dated 26-JUL-1990) was conducted in accordance with guidelines available at the time the study was conducted. Although only 1000 micronucleated polychromatic erythrocyte cells (PCE) from each animal were evaluated, the highest dose tested in this assay was 5000 mg/kg and the numbers of animals evaluated at this high dose level were 10 rats/sex at 24 hr, and 5 rats/sex each at 48 and 72 hr post dosing. The results were negative at all time points. In addition, data from the in-vitro assays (Ames test, chromosome aberration in CHO cells, point mutation test in CHO) as well as in-vivo tests (sister chromatic exchange and nucleus anomaly test in Chinese hamsters) clearly showed no evidence of genotoxicity. Based on statistical calculation, there would be no difference at 0.05 level if 2000 PCEs were evaluated in each animal or 1000 PCEs were evaluated when the male and female were combined as a group. Therefore, it is believed that the validity of this study is not compromised. In light of negative findings from all in-vitro and in-vivo genotoxicity studies, an additional micronucleus study will not change the conclusion of genotoxic finding; consequently, a repeat micronucleus study is not warranted. Does the Agency agree?

The need for evaluation of a minimum of 2000 micronucleated polychromatic erythrocytes per animal for a valid rodent micronucleus test is generally recognized. According to Adler et al. (Mutation Research 417, 19-20, 1998), a per animal sample size of 1000 PCEs is insufficient to detect at least one MN per animal when the control incidence is 1-2 MN/1000 PCE. In your study the negative control frequencies were

lower than 0.1%. Therefore, the study is not valid and should be repeated. This is particularly important given the inadequate rat carcinogenicity study.

11. The male fertility study (92-057 dated 07-DEC-1992) was conducted in accordance with guidelines available at the time the study was conducted. Although only 12 males per dose group were used and each male was paired with two females, male rats were treated for 64 days prior to mating and no impairment in fertility was found. The duration of treatment prior to mating is long enough to capture the effect on male fertility if it exists. In addition, there was no evidence of microscopic changes in the testes from rats treated for a duration of one, three, six, and 12 months, and two years. The histopathological examination of testes is the most sensitive to evaluate the effect on spermatogenesis. Although the mating ratio of 1:1 is the safest choice to obtain a good pregnancy rate when both male and female rats were treated, yet the results from the current study using a mating ratio of 2:1 did not compromise the results. Therefore, it is unlikely to obtain a different finding than no impairment in male fertility by conducting a repeat male fertility study with 20 male rats per dose group. Does the Agency agree?

Numbers per group were too low for both males and females in the rat fertility study. Females were divided into groups of 12/group and the pregnancy rate was low, resulting in only 8-10 litters/group in C-section females. Preimplantation loss was not evaluated in the delivery groups. According to the ICH S5A guidance, evaluation of between 16 to 20 litters is needed for adequate sensitivity in these studies. In addition, according to the guidance, a mating trial is considered important for evaluation of functional effects on male fertility that cannot be detected by histologic examination in repeated dose toxicity studies and effects on mating behavior in both sexes, and the preferred mating ratio is 1:1 for good pregnancy rates and avoiding incorrect analysis and interpretation of results. Therefore, the study needs to be repeated.

12. Results from the rabbit embryofetal development study (87-6148 dated 30-AUG-1989) showed significantly decreased food consumption during the treatment by 32-45% during Gestation Day (GD) 7-12 and 15% during GD 12-16, with body weight loss during GD 8-9/10, and reduced weight gain from GD 7-19 by 30-48% in dams at 200 and 700 mg/kg. Therefore, the MTD was achieved and the study was adequate. Does the Agency agree?

The rabbit embryofetal development study did not evaluate an adequately maternally toxic high dose as required by ICH S5A. There were no treatment-related clinical signs. Body weight gain was only transiently slightly reduced during the first week of dosing.

Weight effects were minimal for a rabbit study where you often seen significant weight gain reductions during early pregnancy in controls. In addition, resorptions and postimplantation loss were increased at HD, and fetal weights were dose-dependently reduced, so corrected BWs were only marginally different. However, if you can demonstrate that plasma levels could not be increased significantly at higher doses, then the need for a repeat study would be reconsidered.

13. a. In the definitive juvenile rat study (Study No. 998010), a decrease in body weight, reduced absolute brain weight, and increased relative brain weight were observed in the mid- and high-dose group sacrificed after 10 weeks of treatment. Therefore, the changes observed in absolute brain weight are secondary to the reduced body weight and not considered treatment related. Does the Agency agree?

b. The changes in regional brain (cerebellum, and medulla and pons) weights (post fixation) were not dose dependent or inconsistent. There was a high degree of individual variation within each treatment group including the control. It is difficult to draw a conclusion whether these changes were treatment related or of biological significance. No significant findings were observed in brain sections with H&E stain, which is considered the standard screening histopathological examination and is routine practice. However, Eisai plans to perform the expanded neuropathological evaluation on the brain sections with special stains (Klüver Barrera and Holmes). Does the Agency agree?

Like testes, ovaries, and adrenals, brain weights tend to be spared in toxicity studies, and therefore, use of organ-to-body weight ratios is not appropriate (see Bailey et al., Toxicologic Pathology 32:448-466, 2004). We agree that expanded neurohistopathology evaluations should be performed, as requested in the letter, but you should justify the procedures proposed.

14. Eisai will conduct a juvenile dog study to evaluate the effect of rufinamide on bone growth and brain development, if additional neuropathological evaluations of the existing rat juvenile animals are not possible because of the age or the availability of tissue samples. However, due to the lack of effect on the neurological functions and bone development in the rodent juvenile study as well as in the pre- and post-natal development study, Eisai would propose conducting the dog juvenile study as a post-marketing commitment. Does the Agency agree?

A dog study in which dosing is initiated at an earlier age (corresponding to the clinical age range) should be conducted, and endpoints of particular concern, such as bone growth and density and brain development should be included (in addition to the standard toxicity endpoints). The timing of this study remains to be determined (see #9).

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

/s/

Courtney Calder
12/15/2006 03:43:46 PM
CSO

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: June 12, 2006

TO: Courtney Clader, Pharm.D., Regulatory Project Manager
Norman Hershkowitz, M.D., Clinical Reviewer
Division of Neurology Products, HFD-120

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

FROM: Sherbet Samuels, R.N., M.P.H.

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-911

APPLICANT: Eisai Medical Research, Inc.

DRUG: Inovelon (Rufinamide)

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Adjunctive treatment of partial-onset seizures and seizures associated with Lennox-Gastaut syndrome.

CONSULTATION REQUEST DATE: January 18, 2006

DIVISION ACTION GOAL DATE: July 9, 2006

PDUFA DATE: September 17, 2006

I. BACKGROUND:

Inovelon (Rufinamide) is a new molecular entity that was studied for use as adjunctive treatment of partial seizures and seizures associated with Lennox-Gastaut Syndrome (a rare and severe form of epilepsy, classified by the International League Against Epilepsy as a cryptogenic or symptomatic generalized epilepsy). The goals of the inspections were to assess adherence to FDA regulatory requirements; specifically, investigator oversight, protocol compliance, accuracy of primary efficacy endpoint data, and protection of subjects' rights, safety, and welfare. Dr. Blanca Vazquez's site was selected for inspection because this was a relatively large center, and in this center, some patients from the placebo group have unusually high seizure frequencies in the double-blind period. Dr. Rajesh Sachdeo's site was selected for inspection because this site has the largest enrollment for protocol #3310101022. Dr. Alfredo Thomson

and Dr. Roberto De Arbelaz's sites were selected for inspection because some patients from the placebo group have unusually high seizure frequencies in the double blind period. Dr. Americo Sakamoto's site was selected for inspection because the review division is unfamiliar with the conduct of research in subjects with Lennox-Gastaut syndrome in Brazil and this site has the largest enrollment for that country. The following protocols were audited:

#AE/ET 1 entitled "Multi-center, double-blind, randomized, placebo-control, 5-arm parallel trial in in-or outpatients with partial seizures on up to three concomitant antiepileptic drugs to investigate efficacy and tolerability (dosages 200/400/800/1600 mg/d)."

#3310101022 entitled "Multicenter, randomized, double-blind, placebo-controlled, parallel trial comparing safety and efficacy of rufinamide as adjunctive therapy relative to placebo in patients with inadequately controlled Lennox-Gastaut syndrome."

#3310101021 entitled "A multicenter, double-blind, placebo-controlled, randomized, stratified, parallel-group trial of rufinamide as adjunctive therapy in children and adults with inadequately controlled partial seizures."

The sponsor-monitor inspection was requested because the investigational drug is a new molecular entity. Although, the NDA was submitted by Eisai Medical Research, Inc., the protocols were monitored by Novartis. Therefore, an inspection was conducted at Novartis. Monitoring of the aforementioned protocols were audited.

Summary Report of U.S. and Foreign Inspections

II. RESULTS (by protocol/site):

Name of CI/Sponsor and site #, if known	City, State	Country	Protocol	Insp. Date	EIR Received Date	Final Classification
Dr. Blanca Vazquez/1284	New York, NY	U.S.	3310101021	Mar. 2006	Apr. 14, 2006	NAI
Dr. Rajesh Sachdeo/1553	New Brunswick, NJ	U.S.	3310101022	Mar. 2006	Apr. 25, 2006	VAI
Dr. Americo Sakomoto	Ribeirao Preto	Brazil	3310101022	Apr. 2006	May 18, 2006	VAI
Dr. Alfredo Thomson	Buenos Aires	Argentina	AE/ET 1	Apr. 2006	May 25, 2006	NAI
Dr. Roberto De Arbelaz	Buenos Aires	Argentina	AE/ET 1	Apr. 2006	June 2, 2006	VAI
Novartis	East Hanover, NJ	U.S.	All of the above	Apr. 2006	May 26, 2006	VAI

Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability

OAI = Significant deviations from regulations. Data unreliable.

A. Protocol #3310101021

1. Dr. Blanca Vazquez (U.S. Center #1284)

New York University/Mount Sinai Comprehensive Medical Center
301 E. 17th St.
New York, NY 10016

a. What was inspected: Dr. Vazquez enrolled 29 subjects. The inspection encompassed an audit of 14 subjects' records. Primary endpoint efficacy data were verified for 14 subjects.

b. Limitations of inspection: None

c. General observations/commentary: No deviations from FDA regulations were observed.

d. Data from this site are acceptable.

B. Protocol #3310101022

1. Dr. Rajesh Sachdeo (U.S. Center # 1553)
4th Floor CARES Building
254 Easton Ave.
New Brunswick, NJ 08903

a. What was inspected: Dr. Sachdeo enrolled 14 subjects. The inspection encompassed an audit of 4 subjects' records. Primary endpoint efficacy data were verified for 4 subjects.

b. Limitations of inspection: None

c. General observations/commentary: The inspection found inadequate and inaccurate record keeping and inadequate drug accountability. Specifically:

Subject 2025: The data listings do not correspond to the source documents for tonic seizures reported from 10/21/98 to 11/3/98 and for atypical seizures reported from 11/4/98 to 12/1/98. The subject's diary reflects 2775 atypical absence seizures from 11/4/98 to 12/1/98, while the case report form and data listings reflect 2649 for the same time period.

Subject 2026: The subject's dairy documents 67 atypical absence seizures reported from 10/15-20/98. The case report form and data listings for this timeframe documents 87 atypical absence seizures.

Subject 2027: The case report form reflects 55 atypical absence seizures, 16 myoclonic seizures, and 13 tonic seizures from 10/15-20/98. The source summary and the data listings show 45 atypical absence seizures, 0 myoclonic seizures, and 9 tonic seizures for this timeframe.

Subject 2028: The data listings report 82 atypical absence seizures and 89 tonic seizures from 12/30/98 to 1/6/99. The subject's diary 12/30-12/31/98 has no data recorded on those days. The diary Data 1/1-1/6/99 shows 59 atypical absence seizures and 49 tonic seizures. Subject's dairy for 10/15/98-11/10/98 differs from data listings information in that 312 atypical absence seizures and 244 tonic seizures are reported in the subject's diary and 374 atypical absence seizures and 278 tonic seizures are reported in the data listings.

The Individual Patient Logs for at least four subjects (2025, 2026, 2027, and 2028) revealed that bottles of study drug were returned that were not documented as dispensed.

d. Due to the inability to validate data listings for subjects 2025, 2026, and 2028, the review division should consider whether efficacy data from these subjects should be excluded in data analysis.

2. Dr. Americo Sakamoto (Brazil center # 2)
Hospital das Clinicas de Ribeirao Preto (NOVO)
Campus Universitario, AV. Bandeirantes, 3900
Secao de Neurologia, 4. Andar, Cirep
14049-900 Ribeirao Preto-SP

a. What was inspected: Dr. Sakamoto enrolled 8 subjects. The inspection encompassed an audit of 8 subjects' records. Primary endpoint efficacy data were verified for all subjects.

b. Limitations of inspection: None

c. General observations/commentary: The inspection found that the baseline phase for subjects 2910 (11 days), 2911 (7 days), and 2919 (32 days) was not 28 days as required by the study protocol. The inspection also found discrepancies in drug accountability records for subjects 2919, 2912, 2911 and 2909 based on the titration schedule and the number of tablets used.

d. Data from this site are acceptable.

C. Protocol AE/ET 1

1. Dr. Alfredo Thomson (Argentina center # 1)
Hospital Britanico
Perdriel 74
RA-1280 Buenos Aires

a. What was inspected: Dr. Thomson enrolled 20 subjects. The inspection encompassed an audit of 8 subjects' records. Primary endpoint efficacy data were verified for 16 subjects.

b. Limitations of inspection: None

c. General observations/commentary: No deviations from FDA regulations were observed.

d. Data from this site are acceptable.

2. Dr. Roberto De Arbelaiz (Argentina center # 2)
Hospital de Clinicas 'Jose de San Martin'
Avenida Cordoba 2351
RA-1120 Buenos Aires

a. What was inspected: Dr. De Arbelaiz enrolled 18 subjects. The inspection encompassed an audit of all subjects' records. Primary endpoint efficacy data were verified for 18 subjects.

b. Limitations of inspection: None

c. General observations/commentary: The inspection found that diary for subject 7539, which recorded the number of seizures/auras, was not maintained. In addition, the inspection found that source records for EEGs performed at examination 3 (subject 7540 and 7526) and examination 12 (subject 7516, 7518, 7519, 7526, and 7528) were not maintained.

d. Data from this site are acceptable.

D. Sponsor Inspection

1. Novartis Pharmaceutical Corporation
One Health Plaza
East Hanover, New Jersey 07936

a. What was inspected: Twenty clinical centers were reviewed. Among the clinical investigators focused on were; Dr. Americo Sakamoto, Dr. Rajesh Sachdeo, and Dr. Blanca Vazquez.

b. Limitations of inspection: None

c. General observations/commentary: Regarding protocol 3310101021, the inspection found that center 1272 (Dr. David Ko) was not promptly brought into compliance once the sponsor discovered that the investigator was not complying with the signed agreement (Form FDA 1572). Specifically, monitoring reports for visits dated January 29, 2001, April 9, 2001, June 18, 2001, and November 5, 2001 documented

that the clinical investigator was not providing adequate supervision to the study coordinator. Once the sponsor discovered that an investigator was not complying with the signed agreement, the sponsor did not promptly secure compliance or discontinue shipments of the investigational new drug to the investigator and end the investigator's participation in the investigation.

d. Data monitored by Novartis are acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

As noted above, inspection of Drs. Vasquez and Thomson revealed that these investigators appear to have conducted the studies noted in accordance with FDA regulations. Inspection of Dr. Sakamoto revealed instances of protocol violations and inadequate drug accountability. Inspection of Dr. Arbelaz revealed instances of inadequate record keeping. Data from these four clinical investigators are acceptable in support of NDA 21-911.

Inspection of Dr. Sachdeo revealed that efficacy data listings for subjects 2025, 2026, and 2028 did not correspond to the subjects' source documents. The review division should consider whether the efficacy data from these subjects should be excluded in data analysis due to the inability to validate the data listings noted and should evaluate the adverse impact, if any, to overall data acceptability.

Inspection of Novartis revealed that center 1272 for protocol 3310101021 was not promptly brought into compliance once the sponsor discovered that the center was not performing the clinical investigations in accordance the signed agreement (Form FDA 1572). Other than this observation, the studies appear to have been monitored adequately, and the data submitted by the sponsor may be used in support of the respective indication.

{See appended electronic signature page}

Sherbet Samuels, R.N., M.P.H.

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

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

/s/

Sherbert Samuels
7/7/2006 12:17:37 PM
CSO

Constance Lewin
7/7/2006 01:21:09 PM
MEDICAL OFFICER