

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
201367Orig1s000

OTHER REVIEW(S)

RPM FILING REVIEW
(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 201367	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Banzel Established/Proper Name: rufinamide Dosage Form: oral suspension Strengths: 40mg/mL		
Applicant: Eisai, Inc Agent for Applicant (if applicable):		
Date of Application: April 30, 2010 Date of Receipt: May 03, 2010 Date clock started after UN: N/A		
PDUFA Goal Date: 03/03/2011	Action Goal Date (if different):	
Filing Date: 07/02/2010	Date of Filing Meeting: 06/17/2010 12:00-13:00	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3		
Proposed indication(s)/Proposed change(s): adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome (LGS) in children 4 years and adults.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html <i>and refer to Appendix A for further information.</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input checked="" type="checkbox"/> NO <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical	

Other:	benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): (b) (4)				
Goal Dates/Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	x			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	x			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	x			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		x		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	x			Orphan Exception for user fee
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.</i>	Payment for this application: <input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).</i>				

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment																
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			x																	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).			x																	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? <i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>			x																	
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm If yes, please list below:			x																	
<table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>																				
Exclusivity	YES	NO	NA	Comment																
Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm				Clobazam Felbamate Lamotrigine Topirmate																
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i>		x																		
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>		x																		

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?		x		
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>			N/A	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance ¹ ? If not , explain (e.g., waiver granted).	x			
Index: Does the submission contain an accurate comprehensive index?	x			
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no , explain.	x			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? <i>If yes, date consult sent to the Controlled Substance Staff:</i>			x	
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes , BLA #			x	

Forms and Certifications				
<p><i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature?	x			
<i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	x			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a?	x			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature?	x			Clinical reviewer will review
<i>Forms must be signed by the APPLICANT, not an Agent.</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	x			
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? (<i>Certification is not required for supplements if submitted in the original application</i>)	x			
<i>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</i>				
<i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>				

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	x			

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>		x		It has Orphan designation
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>			x	
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>			x	
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</p> <p><i>If no, request in 74-day letter</i></p>			x	
<p><u>BPCA</u> (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</i></p>		x		

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.</i>			x	The submission was withdrawn by the sponsor
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU)-sub 2/4/11 <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	x			
Is the PI submitted in PLR format?	x			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>				Done on 5/30/2010
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	x			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? <i>(send WORD version if available)</i>	x			
REMS consulted to OSE/DRISK?	x			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	x			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				

Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	x			5/18/10 quality micro consult 6/24/10 DSI Bioequivalence Audit consult 12/03/10 DDMAC Labeling consult

Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>		x		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>		x		
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		x		

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

ATTACHMENT
MEMO OF FILING MEETING

DATE: 06/17/2010

NDA #: 201367

PROPRIETARY NAME: Banzel

ESTABLISHED/PROPER NAME: rufinamide

DOSAGE FORM/STRENGTH: oral suspension/ 40mg/mL

APPLICANT: Eisai, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in children 4 years and adults.

BACKGROUND:

BANZEL (rufinamide) is indicated for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in children 4 years and older and adults. The tablet dosage forms (200mg tablet, and 400mg tablet) was approved on November 14, 2008 under NDA# 021911.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Sulin Sun	Y
	CPMS/TL:	Norm Hershkowitz	Y
Cross-Discipline Team Leader (CDTL)	Norman Hershkowitz		Y
Clinical	Reviewer:	Steven Dinsmore	Y
	TL:	Norm Hershkowitz	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	
	TL:	N/A	

Clinical Pharmacology	Reviewer:	Veenta Tandon	Y
	TL:	Angela Men	Y
Biostatistics	Reviewer:	Not needed per TL 06/04/10	
	TL:	Not needed per TL 06/04/10	
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Edward J Fisher	Y
	TL:	Lois Freed	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	N/A	
	TL:	NA	
Product Quality (CMC)	Reviewer:	Akm Khairuzzaman	Y
	TL:	Martha Heimann	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Vinayak Pawar	N
	TL:	Jim McVey	N
CMC Labeling Review (<i>for BLAs/BLA supplements</i>)	Reviewer:	N/A	
	TL:	N/A	
Facility Review/Inspection	Reviewer:	N/A	
	TL:	N/A	
OSE/DMEPA (proprietary name)	Reviewer:	Cathy Miller	Y
	TL:	Zachary Oleszczuk	N
OSE/DRISK (REMS)	Reviewer:	Robin Duer	N
	TL:	Mary Dempsey	
Bioresearch Monitoring (DSI)	Reviewer:	Michael Skelly	Y
	TL:	Martin Yau	N

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input checked="" type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments: Need data set from the IND study</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments: Ideally would like to have BE study in Fasting State if possible. The submitted BE study in fat state is Okay.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter

<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments: no filing issue</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review (BLAs/BLA supplements only)</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Russell Katz	
21st Century Review Milestones (see attached) (optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original 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) 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, or
- (3) 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) 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, and.
- (3) 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) 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, or
- (3) 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 OND ADRA or OND IO.

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/s/

SU-LIN SUN
02/18/2011

Internal Consult

Pre-decisional Agency Information

To: Russell Katz, MD, Director, Division of Neurology Products (DNP)
Norman Hershkowitz, MD, Team Leader, DNP
Su-Lin Sun, PharmD, Regulatory Project Manager, DNP

From: Quynh-Van Tran, PharmD, BCPP
Regulatory Reviewer, Division of Drug Marketing, Advertising, and
Communications (DDMAC)

CC: Andy Haffer, Group Leader, DDMAC

Date: January 28, 2011

Re: Comments on draft labeling materials for Banzel Oral Suspension
NDA 201367

This consult is in response to DNP's December 3, 2010 request for DDMAC's review of labeling materials for Banzel Oral Suspension (Banzel).

DDMAC has reviewed the proposed prescribing information (FDA version dated 1/24/2011) and draft carton/container labeling for Banzel and we do not have any additional comments at this time.

We appreciate the opportunity to participate in labeling discussion meetings and provide comments on these labeling materials. If you have any questions, please contact Quynh-Van Tran at 301-796-0185 or quynh-van.tran@fda.hhs.gov.

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/s/

QUYNH-VAN TRAN
01/28/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: November 18, 2010

Application Type/Number: NDA 201367

To: Russell Katz, MD
Division of Neurology Products

Through: Zachary Oleszczuk, PharmD, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis (DMEPA)

From: Cathy A. Miller, MPH, BSN, Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name(s): Banzel (Rufinamide) Oral Suspension
40 mg/mL

Applicant/Sponsor: Eisai, Inc.

OSE RCM #: 2010-1356

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1 INTRODUCTION

This review responds the Applicant's submission of new drug application (NDA 201367) which included proposed labels and labeling for Banzel (Rufinamide) Oral Suspension 40 mg/mL for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LSG) in children four years and older, and adults. We provide recommendations in Section 4 that aim at reducing the risk of medication errors with regard to the proposed product label and labeling.

1.1 REGULATORY HISTORY

Banzel (Rufinamide) Tablets, 200 mg and 400 mg, were approved on November 14, 2008 under new drug application (NDA 021911) for the treatment of adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LSG) in children four years and older, and adults.

On April 30, 2010, the Applicant submitted a request for review a proposed oral suspension dosage form of Banzel. For administrative purposes, the proposed oral suspension dosage form was submitted under a new NDA (NDA 201367) however, all product information will be cross-referenced to the original new drug application (NDA 021911). In their submission letter, the Applicant stated that Banzel Oral Suspension was developed to provide a child friendly formulation to aid administration and the development of a suitable oral suspension formulation is expected to improve the treatment options for patients, particularly young children with Lennox-Gastaut Syndrome. The oral suspension also is expected to address the needs of older patients who are unable to or would prefer not to swallow a solid dosage form.

2 METHODS AND MATERIALS

For this review, DMEPA searched the FDA Adverse Event Reporting System (AERS) database and reviewed proposed container labels and carton labeling, along with samples of the proposed measuring devices for this product.

2.1 FDA ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE

The FDA Adverse Event Reporting System (AERS) database search conducted on September 14, 2010 used the following criteria. The search criteria used includes the MedRA High Level Group Terms (HLGT) "Medication Errors" and "Product Quality Issues" for Reactions, and for Products, the active ingredients "Rufinamide," and the trade name "Banzel," along with the verbatim substance terms "Banzel%" and "Rufinamide%." No date limitations were set.

Duplicate reports were combined into cases. The cases were manually reviewed to determine if a medication error occurred. Those cases that did not describe a medication error or did not describe an error applicable to this review were excluded from further analysis. The cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If a root cause was associated with the labels or labeling of the product, the case was considered pertinent to this review.

2.2 LABEL AND LABELING

Using failure mode and effects analysis (FMEA) and the principles of Human Factors, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the container labels and carton labeling (see Appendices A and B) submitted by the Applicant on April 30, 2010, the

most current version of the package insert labeling submitted on June 14, 2010, along with samples of the proposed measuring devices including [REDACTED] (b) (4) [REDACTED] a calibrated oral dosing syringe with press-in bottle adapter (PIBA) submitted by the Applicant to DMEPA on September 16, 2010.

3 RESULTS AND DISCUSSION

The following section describes DMEPA's findings from AERS and the review of labels and labeling.

3.1 ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE

DMEPA's search of the Adverse Event Reporting System database did not yield any reports of medication errors with Banzel

3.2 LABELS AND LABELING

The labeling risk assessment indicates that the presentation of information can be improved upon to help minimize the risk of errors and we have provided our recommendations in Section 4.

4 CONCLUSIONS AND RECOMMENDATIONS

Our evaluation noted areas where the presentation of information on the container labels, carton labeling, insert labeling and dispenser set measuring device labeling can be improved to minimize the potential for medication errors.

Section 4.1 Comments to the Division contains our recommendations on the insert labeling of Banzel. *Section 4.2 Comments to the Applicant* contains our recommendations for the container labels, carton labeling, and dispenser set measuring device labeling. We request the recommendations in Section 4.2 be communicated to the Applicant prior to approval of the supplement.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact Laurie Kelley, OSE Regulatory Project Manager, at 301-796-5068

4.1 COMMENTS TO THE DIVISION

A. Package Insert Labeling

- 1) DMEPA recommends that patient instructions for use be included with this product. The Applicant proposes [REDACTED] (b) (4) [REDACTED], a calibrated dosing syringe and a press-in bottle adapter (PIBA). However, the Applicant does not include patient instructions for use for the product (i.e. shaking the bottle vigorously and instructions for using the PIBA and oral dosing syringe). Since the measuring devices are packaged in the carton with the medication, instructions for use, specifically for the oral syringe, should be provided. The instructions provided in the package insert are geared towards the healthcare professionals and may not be suitable for consumers. When the instructions for use are submitted, please consult DMEPA and DRISK for review.
- 2) In conjunction with recommendation #1 above, DMEPA requests that the Applicant provide their rationale [REDACTED] (b) (4) [REDACTED] along with conducting a usability study of the measuring devices to ensure that the use of the wrong device does not occur to measure the product. While DMEPA understands that the volume of

Banzel Oral Suspension varies according the titrated dose and the patient's weight, we also recognize that postmarketing experience has also demonstrated that wrong dose medication errors have occurred when (b) (4)

(b) (4) DMEPA believes it is important to evaluate the patient's ability to accurately measure the correct volume (dose) of Banzel in conjunction with use of the appropriate device.

- 3) DMEPA recommends that instructions (b) (4) should be added to the Patient Counseling Section of the insert labeling and the Medication Guide. This information is currently included in paragraph two and three of Section 2 Dosage and Administration but all of the information is not included in the Patient Counseling Section or the Medication Guide. DMEPA believes these directions are important to the correct use of the product and should be included in the information provided to patients when the product is dispensed. (b) (4)

4.2 COMMENTS TO THE APPLICANT

A. Container Labels and Carton Labeling

- 1) Relocate the strength (40 mg/mL) to a location in close proximity to the proprietary and established name (adjacent to or directly underneath) on the container labels and carton labeling. The presentation of the strength (40 mg/mL) is currently located at the bottom right corner of the principal display panel below the total volume (460 mL) on the container label and carton labeling. The presentation for the strength for oral suspension products is typically presented in a prominent manner directly underneath the proprietary and established name to assure that the strength is clearly visible for proper dosing and administration.
- 2) There is no reference to the inclusion of measuring devices on the container label or carton labeling. Add a statement on the carton labeling that clearly indicates there are measuring devices included and they are for oral use. For example: "This product is packaged with a calibrated (milliliters) oral syringe (b) (4) for accurate dosing."
- 3) Add a statement to the principal display panel of the container label and the carton labeling stating that this product is "For Oral Administration Only." Postmarketing experience has demonstrated that wrong route of administration errors have occurred in the clinical setting when oral liquid products have been inadvertently been administered as injections. Because this product is an oral suspension (liquid), and the product is supplied with a syringe, DMEPA believes that there is a risk of wrong route of administration and the risk can be minimized by adding the "For Oral Administration Only" warning statement to the container label and carton labeling.
- 4) Assure that bar coding is included on the container labels and carton labeling. The images of the container label and carton labeling are not presented with a bar code. Pursuant to 21 CFR 201.25, "Manufacturers, repackers, relabelers, and private label distributors of a human prescription drug product or an over-the-counter (OTC) drug product that is regulated under the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act are subject to these bar code requirements unless they are exempt

from the registration and drug listing requirements in section 510 of the Federal Food, Drug, and Cosmetic Act.”

- 5) Add the instructions “Shake the bottle vigorously before administration” should be added to the container label and the carton labeling. These instructions are included in the package insert labeling Dosage and Administration section and therefore, should also be included on the container label and carton labeling to assure that the patient is given the appropriate instructions prior to administration.
- 6) Revise the font color presentation used the present the proprietary and established name on the carton labeling to increase the prominence. (b) (4)

[Redacted]

B. Dispenser Set (Oral Dosing Syringe (b) (4))

- 1) Remove the (b) (4) units of measure from the oral dosing syringe (b) (4)
[Redacted]
Banzel Oral Suspension is dosed in milliliters and therefore, milliliters (mL) should be the only unit of measure displayed on the syringe (b) (4)
Postmarketing experience has demonstrated that dosing errors have occurred when there is discordance between the units of measurement on the measuring device and product labeling.¹ DMEPA believes that in order to reduce the risk of wrong dose medication errors, only the intended unit of measurement (milliliters) should be displayed on the measuring syringe (b) (4)

- 2) [Redacted] (b) (4)

- 3) Add the product name (Banzel) to the oral dosing syringe (b) (4)
[Redacted] Since the Applicant is supplying this product with measuring devices specific to use with Banzel, we recommend that the product name is included on the measuring devices so that patients can readily identify the correct measuring device for this product and minimize confusion with other measuring devices they may have.

5 REFERENCES

1. *Adverse Events Reporting System (AERS)*

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufactures that have approved products in the U.S. The main utility of a spontaneous

(b) (4)

reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential post-marketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

APPEARS THIS WAY ON ORIGINAL.

Appendix A: Proposed Banzel Oral Suspension Container Label



Appendix B: Proposed Banzel Oral Suspension Carton Labeling



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/s/

ZACHARY A OLESZCZUK on behalf of CATHY A MILLER
11/18/2010

ZACHARY A OLESZCZUK
11/18/2010

CAROL A HOLQUIST on behalf of DENISE P TOYER
11/22/2010
For Denise Toyer

CAROL A HOLQUIST
11/22/2010

MEMORANDUM

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

DATE: November 19, 2010

TO: Russell G. Katz, M.D.
Director, Division of Neurology Products
Office of New Drugs (HFD-120)

FROM: Abhijit Raha, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: Martin K. Yau, Ph.D. *Martin K. Yau 11/19/10*
Acting Team Leader - Bioequivalence
GLP & Bioequivalence Branch
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDA 201-367, BANZEL™
(Rufinamide) Oral Suspension 40 mg/ml, sponsored
by Eisai, Inc.

At the request of the Division of Neurology Products (DNP), the Division of Scientific Investigations (DSI) audited the clinical portion of the following bioequivalence (BE) study.

Study Number: E2080-E044-003

Study Title: "A randomized, open-label, 4-period crossover trial to compare the bioavailability of single 400 mg doses of rufinamide (E2080) administered as the marketed tablet with 3 suspension formulations manufactured using different homogeneity speeds"

Clinical Site: Quintiles Ltd., Guys Drug Research Unit London, United Kingdom

Following the audit of the clinical records at Quintiles Ltd., Guys Drug Research Unit (October 4-8, 2010), there were no significant objectionable observations, and FDA Form 483, Inspectional Observations, was not issued. There were no discussion items with the firm.

Page 2 - NDA 201-367, BANZEL™ (Rufinamide) Oral Suspension,
40 mg/ml

Conclusion:

Based on the above audit findings, DSI recommends that the study data generated at Quintiles Ltd. (London, UNITED KINGDOM) for Study Number E2080-E044-003 be accepted for review.

After you have reviewed this transmittal memo, please append it to the original NDA submission.


Abhijit Raha, Ph.D.

Final Classification:

**Quintiles Ltd., Guys Drug Research Unit (GRDU), London,
UNITED KINGDOM - NAI (Clinical Site)**

(FEI Number: 3008488237)

cc: DARRTS

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DSI/Ball/Haidar/Yau/Raha/Rouba Ead/CF
OND/DNP/Russell Katz, Sulin Sun (HFD-120)
HFR-SW350/Linda Kuchenthal
Draft: AR 11/19/2010
Edit: MKY 11/19/2010 MKY 11/19/10
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/s/

ABHIJIT RAHA

11/19/2010

Dr. Martin K. Yau, Acting Bioequivalence Team Leader, signed the original paper copy of this document on November 19, 2010.

MEMORANDUM

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

DATE: September 15, 2010

TO: Russell G. Katz, M.D.
Director, Division of Neurology Products (DNP)

FROM: Martin K. Yau, Ph.D.
Abhijit Raha, Ph.D.
Pharmacologists
Division of Scientific Investigations (HFD-48)

THROUGH: Martin K. Yau, Ph.D. *Martin K. Yau 9/15/10*
Acting Team Leader - Bioequivalence
GLP and Bioequivalence Investigations Branch
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDA 201-367, BANZEL™
(Rufinamide) Oral Suspension, 40 mg/mL, Sponsored
by Eisai, Inc.

At the request of DNP, the Division of Scientific Investigations (DSI) audited the clinical and analytical portions of the following bioequivalence study:

Study Number: E2080-E044-003

Study Title: "A randomized, open-label, 4-period crossover trial to compare the bioavailability of single 400 mg doses of rufinamide (E2080) administered as the marketed tablet with three suspension formulations manufactured using different homogeneity speeds"

This memorandum covers the analytical audit of study E2080-E044-003 conducted at (b) (4) August 2-5, 2010.

Inspection of the clinical portion of study E2080-E044-003 at Quintiles Ltd., United Kingdom, is scheduled in October 2010. DSI will forward our evaluation of the clinical inspection to DNP when the clinical site inspection is completed.

Following inspection at the analytical site (August 2-5, 2010), a 3-item Form FDA-483 was issued (**Attachment 1**). DSI received the written response (dated August 25, 2010) from (b) (4) on August 27, 2010 (**Attachment 2**). Our evaluations of the Form FDA-483 observations (**in bold type**), and the firm's responses to the observations follow.

Analytical Site: (b) (4)

1. Incurred Sample Reproducibility (ISR) assessment for the LC/MS/MS assay was not conducted.

(b) (4) acknowledged the above observation during the inspection and said that this was an oversight. In their response, (b) (4) stated that a retrospective ISR assessment cannot be performed since subject samples from study E2080-E044-003 have been discarded as instructed by the sponsor. However, an ISR assessment of the same bioanalytical method conducted for another bioequivalence study shows that the rufinamide LC/MS/MS assay is reproducible in incurred subject samples. ISR data in **Attachment 3** show that 92% of incurred samples showed a difference of $\leq 20\%$ between the original and re-assay data.

2. Failure to fully validate the rufinamide LC/MS/MS assay.

a. Matrix effect on assay precision and accuracy was not evaluated.

(b) (4) conducted additional validation experiments after the inspection to assess the matrix effect on assay precision and accuracy. The results show that there is no matrix effect issue (**Attachment 4, page 11**).

b. The effect of contraceptives on assay precision and accuracy was not evaluated, although about 20% of study subjects were taking different contraceptives.

Following the inspection, (b) (4) conducted interference tests on five contraceptive compounds along

Page 3 - NDA 201-367, BANZEL™ (Rufinamide) Oral Suspension,
40 mg/ml

with acetaminophen and trimethoprim used by subjects in
study E2080-E044-003 and no interference was observed
(Attachment 4, page 13). Furthermore, (b) (4) stated
that they will be more proactive to follow-up with the
clinical site on the potential for concomitant medications
in use during studies in future.

Conclusion:

Following the inspection at (b) (4) and after
evaluating the response to the 483 observations submitted
by (b) (4) DSI recommends that the analytical
portion of study E2080-E044-003 be accepted for review.

After you have reviewed this transmittal memo, please
append it to the original NDA submission.

Martin K. Yau

Martin K. Yau, Ph.D.

Abhijit Raha

Abhijit Raha, Ph.D.

Final Classification:

(b) (4)

cc: DARRTS

CDER DSI PM TRACK
OND/DNP/Russell G. Katz, Sulin Sun (HFD-120)
HFD-48/Ball/Haidar/Yau/Rivera-Lopez/Raha/CF
HFR-CE1505/Joseph Despins
HFR-CE1515/Daniel Tammariello (BIMO)
HFR-CE100/Karyn Campbell (DIB)
Draft: AR 9/14/10
Edit: MKY 9/15/10
DSI: (b) (4); O:\BE\EIRCover\201367 (b) (4).ruf.doc
FACTS (b) (4)

ATTACHMENT 1: FORM FDA-483

FOR STUDY E2080-E044-003

(RUFINAMIDE)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT OFFICE ADDRESS AND PHONE NUMBER Food and Drug Administration U.S. Custom House, Room 900 2nd and Chestnut Streets Philadelphia, PA 19106 215-597-4390 Industry Information: www.fda.gov/oc/industry	DATE(S) OF INSPECTION 8/2, 3, 4, 5/2010
	FEI NUMBER (b) (4)

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED
TO: Song Li, Ph.D., President and Chief Executive Officer

FIRM NAME (b) (4)	STREET ADDRESS (b) (4)
CITY, STATE AND ZIP CODE (b) (4)	TYPE OF ESTABLISHMENT INSPECTED Biopharmaceutics Analytical Facility

THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS; AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.

DURING AN INSPECTION OF YOUR FIRM, **WAS** OBSERVED:

1. We observed the following in the bioanalytical portions of E2080-E044-003:

B. Rufinamide Study E2080-E044-003

4. Incurred Sample Reproducibility (ISR) assessment for the LCMS/MS assay was not conducted.
5. Failure to fully validate the rufinamide LC/MS/MS assay
 - a. Matrix effect on assay precision and accuracy was not evaluated.
 - b. The effect of contraceptives on assay precision and accuracy was not evaluated, although about 20% of study subjects were taking different contraceptives.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE <i>Joseph L. Despina</i> <i>Martin K. Yau</i> <i>Abhijit Raha</i>	EMPLOYEE(S) NAME AND TITLE (Print or Type) Joseph L. Despina, Ph.D., Investigator Martin K. Yau, Ph.D., Pharmacologist Abhijit Raha, Ph.D., Pharmacologist	DATE ISSUED 08/05/2010
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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201367	ORIG-1	EISAI INC	RUFINAMIDE ORAL SUSPENSION

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/s/

ABHIJIT RAHA

09/15/2010

Dr. Martin Yau, Acting Bioequivalence Team Leader, signed the original paper copy on 9/15/2010.

<p>DSI CONSULT</p> <p>Request for Biopharmaceutical Inspections</p>

DATE: June 18, 2010

TO: Associate Director for Bioequivalence
Division of Scientific Investigations, HFD-48

THROUGH: Russell Katz, MD
Director, Division of Neurology Products (DNP)

FROM: Sulin Sun, PharmD, Regulatory Project Manager, DNP

SUBJECT: Request for Biopharmaceutical Inspections
NDA 201367
Banzel (rufinamide) oral suspension 40mg/mL
Eisai, Inc.
100 Tice Blvd.
Woodcliff Lake, NJ 07677

Contact Name: Ira Do, PharmD, Senior Manager, Regulatory Affairs
Contact Info: (201) 949-4275 or Ira_Do@eisai.com

Study/Site Identification:

As discussed with you, the following studies/sites pivotal to approval (OR, raise question regarding the quality or integrity of the data submitted and) have been identified for inspection:

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
003 (Fed)	Quintiles Ltd. Guys Drug Research Unit (GDRU) 6 Newcomen Street London SE1 1YR United Kingdom Clinical investigator: Darren Wilbraham ,MBBS,DCPSA	(b) (4) 

International Inspections:

(Please note: International inspections require sign-off by the ORM Division Director or DPE Division Director.)

We have requested an international inspection because:

- x There is a lack of domestic data that solely supports approval;

Other (please explain):

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by **December 01, 2010**. We intend to issue an action letter on this application by **March 03, 2011**.

Should you require any additional information, please contact Sulin Sun, PharmD, Regulatory Project Manager at (301) 796-0036

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201367	ORIG-1	EISAI INC	RUFINAMIDE ORAL SUSPENSION

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/s/

SU-LIN SUN
06/18/2010

JACQUELINE H H WARE on behalf of RUSSELL G KATZ
06/24/2010