

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
201367Orig1s000

CHEMISTRY REVIEW(S)

NDA 201-367

**BanzelTM (rufinamide) Oral Suspension
40mg/ml**

Eisai Medical Research Inc.

**Akm Khairuzzaman, Ph.D.
ONDQA/DNDQA1/Branch 1**

Reviewed for the Division of Neurology Products, HFD-120

Chemistry Review Data Sheet

1. NDA 201-367
2. REVIEW #: 2
3. REVIEW DATE: 23-Feb-2011
Revised:
4. REVIEWER: Akm Khairuzzaman, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
CMC Information amendment	10-Jan-2010

7. NAME & ADDRESS OF APPLICANT:

Name	Eisai Medical Research
Address	300 Tice Boulevard Woodcliff Lake, NJ 07677, USA.
Representative	Kevin McDnald, Assistant Director, Reg. Affairs
Telephone	(201) 627-2292
FAX Number	(201) 949-4915

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name	Banzel™
Non-Proprietary Name (USAN)	Rufinamide
Code Names	N/A
Chemistry Type	5
Submission Priority	S

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)
10. PHARMACOL. CATEGORY: Anti-epileptic
11. DOSAGE FORM: Suspension
12. STRENGTH/POTENCY: 40mg/ml
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: X Rx OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

 SPOTS product – Form Completed

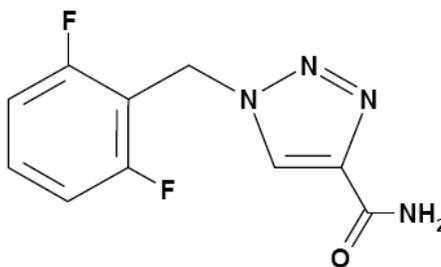
 X Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Names: 1-[(2,6-difluorophenyl)methyl]-1*H*-1,2,3-triazole-4 carboxamide

US Adopted Name (USAN): Rufinamide

Laboratory Codes: N/A



Chemical Formula: $C_{10}H_8F_2N_4O$

Molecular Weight: 238.2

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED
(b) (4)	III		(b) (4)	4	Adequate	-
	III		4	Adequate	-	
	III		3	Adequate	07-Sept-2010 (Anamitro Banerjee)	
	III		3	Adequate	17-Nov-2003 (Donald N. Klein)	
	III		1	Adequate	29-Nov-2010 (Akm Khairuzzaman)	
	III		1	Adequate	29-Nov-2010 (Akm Khairuzzaman)	

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21-911	Banzel Tablets

18. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	12/21/2010	E. Johnson
LNC	N/A	----	----
Methods Validation	Not Necessary	----	----
OSE-DMEPA		----	----
EA	Categorical Exclusion: Acceptable	See Review Date Above	A. Khairuzzaman
Microbiology	Acceptable	11/09/2010	Vinayak B Pawar
Biopharmaceutics	Dissolution methods: Acceptable	12/15/2010	Akm Khairuzzaman

The Chemistry Review for NDA 201-367

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The original CMC review (review # 1, dated 12/16/2010) for this NDA concluded as “not approvable” due to deficiency of some CMC information. Based on the information provided by the sponsor on January 10, 2010, this new drug application (22-462) **can be recommended for approval from the perspective of chemistry, manufacturing, and controls.**

The Office of Compliance has given an acceptable recommendation for the manufacturing and testing facilities (see Establishment Evaluation Summary).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no Phase 4 commitments.

II. Summary of Information Amendment

A. Description of the Drug Product(s) and Drug Substance(s)

Rufinamide is not a ‘new molecular entity. It is currently available in the market (as immediate release tablets with a proprietary name of Banzel™, 200 mg and 400 mg, ref NDA # 21-911) for the treatments of partial seizures and for seizures associated with Lennox-Gastaut Syndrome. Due to complications associated with tablet swallow in pediatric and senior population, Eisai Medical Research has developed a suspension formulation (Banzel™) for the same drug and filed this NDA under the regulatory provision of 505(b)(1). Banzel™ is an aqueous suspension for oral administration in children 4 years and older and adults oral administration for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome. The recommended target doses are 3200 mg/day for adults and 45 mg/kg/day (to a maximum 3200 mg/day) for children, administered in two equally divided doses.

The CMC information submitted in this application was fairly acceptable and summarized in the CMC review # 1 (dated 12/16/2010). However, the reviewer found that there were some deficiency in the application and asked the sponsor to provide adequate response. This review primarily addresses the sponsor’s response in addition to the changes made in to the dosing device (b) (4) 20 ml.

Chemistry Assessment Section

Drug Substance

The drug substance, rufinamide (chemical name: 1-(2,6-difluorobenzyl)-1*H*-1,2,3-triazole-4-carboxamide) is a triazole derivative structurally unrelated to other currently marketed antiepileptic drugs. It exist as a white, crystalline, odorless, slightly bitter tasting, neutral powder. Rufinamide is not a new molecular entity and classified as BCS III by the sponsor. The molecule was well characterized and detail information was submitted in the approved NDA # 21-911 in support of Rufinamide Tablets. Therefore, very limited information on the drug substance has been submitted under this application since it is the same manufacturer with same specification. Rufinamide has no ionizable functionality and is poorly soluble (approximately 27-31 mg/L at 25°C and 40-70 mg/L at 37°C) in water, gastric fluid and intestinal fluid. The critical quality attributes of the drug substance identified in the original NDA for rufinamide were bulk density, polymorphic transition, particle size and shape. These physico chemical attributes of the API could also play a critical role in the ultimate performance of this finished dosage form (suspension) as discussed in details under respective section in the review # 1. There were four (4) polymorphic reported in the original NDA among witch polymorphic (b) (4) was identified as the most thermodynamically stable.

Drug Product

The drug product is an oral suspension for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in children 4 years and older and adults. The proposed trade name of the product is Banzel™ (rufinamide) oral suspension and it is formulated at a strength of 40 mg/m with pharmaceutical grade common compendial excipients. The finished product is orange flavoured, opaque, practically white, and slightly thixotropic. The recommended target doses are 3200 mg/day for adults and 45 mg/kg/day (to a maximum 3200 mg/day) for children, administered in two equally divided doses.

The product development was originally initiated at Novartis but completed by Eisai. Novartis developed a prototype formulation (40mg/ml) based on their prior knowledge and then tested this formulation for bioequivalence with that of the marketed product, Banzel™ Tablets, 400 mg. The result of this BE study met the agency's criteria of bioequivalence. However, after the acquisition of this product by Eisai, minor change was done with the formulation (b) (4). In addition to that, although the Novartis final formulation was found to be bioequivalent, Eisai considered that the physico-chemical characterization of that formulation with respect to relevant biopharmaceutical properties of the suspension was limited to single point dissolution and particle size.

It is to be noted that the solubility of rufinamide is limited and in the original NDA the particle size and bulk density of the API was found to be critical for dissolution. The particle size of the drug substance is also considered critical for any suspension preparation. Therefore, Eisai evaluated extensively the effect of manufacturing process (particularly the homogenization) on the drug substance particle size during the course of development. Based on their study, the sponsor established an in process particle size limit of (b) (4).

Chemistry Assessment Section

(during its homogenization) that showed no significant effect on in vitro dissolution (limit (b) (4) drug release in NMT 15 minutes). Three batches with different homogenization speeds were manufactured and tested for bioequivalence study in healthy human subjects. Regardless of significant differences in dissolution characteristics (and limit in specification) exist between these two different pharmaceutical dosage forms (tablets vs. suspension), all batches of rufinamide orals suspension were found to be bioequivalent to the tablets. Results suggests that the rate of absorption of rufinamide across the GI membrane might be limited and physical characteristics of the product, such as drug substance particle size may not have statistically significant impact on *in vivo* profile (PK parameters) as long as it ((b) (4) of particles) is maintained below the (b) (4)

The drug product was formulated with compendial grade commonly used excipients that are generally used for any suspension preparation. The level of critical formulation components, particularly the preservative systems were thoroughly evaluated and found to be adequate. The physical characteristics, such as rheological property were also evaluated so that product can be easily poured into dosing device by the patients. The product is manufactured by (b) (4)

A risk assessment for all these manufacturing unit operations was performed at the initial stage of the product development and linked with the critical quality attributes of the finished product. Such risk assessment for the manufacturing process was then performed using commercial size batches and established a set of critical process parameters (CPP) with designated risk levels. Based on that, the sponsor has identified the target operating condition with a validated operating range that will be followed for all the future commercial batches. However, no design space or process model was submitted in this application.

The drug product has acceptable specification and all analytical methods used are validated appropriately. Extensive stability studies were conducted including commercial scale batches. All studies showed satisfactory product stability during the period tested. However, (b) (4) potassium sorbate showed a tendency of gradual decrease in its assay over time. The sponsor conducted a detailed statistical analysis on the assay values of (b) (4) based on which they have proposed a product shelf life of (b) (4). However, after evaluating the details on such study, the reviewer found that the extrapolated assay value of the potassium sorbate (b) (4)

Therefore, a product shelf life of 18 months can be granted at this stage and can be extended based on the actual data at post approval stage.

Rufinamide Oral Suspension is packaged in 500 mL oriented-polyethylene terephthalate (o-PET) bottles with child-resistant (CR) (b) (4) closures and (b) (4). Each bottle will contain 460 mL of the suspension. The product will be co-packaged with a set of two (2) 20 mL oral syringe and LDPE press-in-bottle adapter (PIBA). From the given data, the dosing device were found to be acceptable for safe

Chemistry Assessment Section

and accurate dosing. Rufinamide Oral Suspension will be manufactured by [REDACTED] (b) (4)

The sponsor's responses on the CMC deficiencies were found to be acceptable, except for that the estimated assay value for potassium sorbate in drug product formulation [REDACTED] (b) (4)

[REDACTED] the shelf life of the product can be approved for 18 months only. [REDACTED] (b) (4)

In summary, the CMC reviewer found that the level of information and scientific data provided in this application are adequate to support its approvability.

B. Description of How the Drug Product is Intended to be Used

Banzel™ is an aqueous suspension for oral administration in children 4 years and older and adults oral administration for adjunctive treatment of seizures associated with Lennox Gastaut syndrome. The recommended target doses are 3200 mg/day for adults and 45 mg/kg/day (to a maximum 3200 mg/day) for children, administered in two equally divided doses.

C. Basis for Approvability or Not-Approval Recommendation

This new drug application (22-568) **can be approved** from the perspective of chemistry, manufacturing, and controls

Chemistry Assessment Section

III. Administrative**A. Reviewer's Signature**

/s/ A. Khairuzzaman, Ph.D.

B. Endorsement Block

Chemistry Reviewer:
Pharmaceutical Assessment Lead:
Branch Chief:
Project Manager:

Akm Khairuzzaman, Ph.D.
Martha Heiman, Ph.D.
Ramesh Sood, Ph.D.
Teshara G Bouie

C. CC Block

Orig. NDA 201-367
HFD-120/Division File

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/s/

AKM KHAIRUZZAMAN

02/23/2011

This NDA is approvable from CMC point of view

RAMESH K SOOD

02/23/2011

NDA 201-367

**BanzelTM (rufinamide) Oral Suspension
40mg/ml**

Eisai Medical Research Inc.

**Akm Khairuzzaman, Ph.D.
ONDQA/DNDQA1/Branch 1**

Reviewed for the Division of Neurology Products, HFD-120

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Chemistry Review Data Sheet

1. NDA 201-367
2. REVIEW #: 1
3. REVIEW DATE: 15-Dec-2010
Revised:
4. REVIEWER: Akm Khairuzzaman, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	30-April-2010

7. NAME & ADDRESS OF APPLICANT:

Name	Eisai Medical Research
Address	300 Tice Boulevard Woodcliff Lake, NJ 07677, USA.
Representative	Kevin McDnald, Assistant Director, Reg. Affairs
Telephone	(201) 627-2292
FAX Number	(201) 949-4915

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name	Banzel™
Non-Proprietary Name (USAN)	Rufinamide
Code Names	N/A
Chemistry Type	5
Submission Priority	S

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)
10. PHARMACOL. CATEGORY: Anti-epileptic
11. DOSAGE FORM: Suspension
12. STRENGTH/POTENCY: 40mg/ml
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: X Rx OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

 SPOTS product – Form Completed

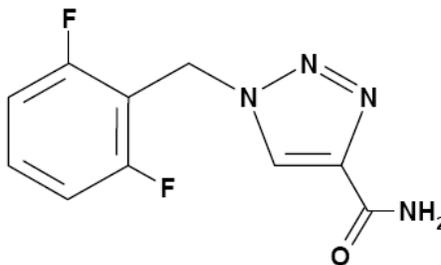
 X Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Names: 1-[(2,6-difluorophenyl)methyl]-1*H*-1,2,3-triazole-4 carboxamide

US Adopted Name (USAN): Rufinamide

Laboratory Codes: N/A



Chemical Formula: $C_{10}H_8F_2N_4O$

Molecular Weight: 238.2

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED
(b) (4)	III		(b) (4)	7	Inadequate	
	III		7	Inadequate		
	III		4	Adequate	07-Sept-2010 (Anamitro Banerjee)	
	III		4	Adequate	17-Nov-2003 (Donald N. Klein)	
	III		4	Adequate	29-Nov-2010 (Akm Khairuzzaman)	
	III		4	Adequate	29-Nov-2010 (Akm Khairuzzaman)	

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

Comments: Sufficient CMC information regarding DMF (b) (4) could not be found to support this NDA.

Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21-911	Banzel Tablets

18. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		
LNC	N/A	----	----
Methods Validation	Not Necessary	----	----
OSE-DMEPA		----	----
EA	Categorical Exclusion: Acceptable	See Review Date Above	A. Khairuzzaman
Microbiology	Acceptable	11/09/2010	Vinayak B Pawar
Biopharmaceutics	Dissolution methods: Acceptable	12/15/2010	Akm Khairuzzaman

The Chemistry Review for NDA 201-367

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This new drug application (201-367) cannot be recommended for approval from the perspective of chemistry, manufacturing, and controls until the deficiencies listed at the end of this review are adequately addressed.

The Office of Compliance has not yet given an acceptable recommendation for the manufacturing and testing facilities.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no Phase 4 commitments.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Rufinamide is not a 'new molecular entity. It is currently available in the market (as immediate release tablets with a proprietary name of Banzel™, 200 mg and 400 mg, ref NDA # 21-911) for the treatments of partial seizures and for seizures associated with Lennox-Gastaut Syndrome. Due to complications associated with tablet swallow in pediatric and senior population, Eisai Medical Research has developed a suspension formulation for the same drug and filed this NDA under the regulatory provision of 505(b)(1). Therefore, all information pertaining to the drug substance is referenced to the sponsor's original NDA # 21-911 and the sponsor is using the same drug substance with same specification in this product as well.

This review primarily captured the critical information pertaining to chemistry, manufacturing and control for the development of drug product, Banzel™ (rufinamide) oral suspension, 40 mg/ml.

Drug Substance

The drug substance, rufinamide (chemical name: 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide) is a triazole derivative structurally unrelated to other currently marketed anti-epileptic drugs. It exist as a white, crystalline, odorless, slightly bitter tasting, neutral powder. Rufinamide is not a new molecular entity and classified as BCS III by the sponsor. The

Executive Summary Section

molecule was well characterized and detail information was submitted in the approved NDA # 21-911 in support of Rufinamide Tablets. Therefore, very limited information on the drug substance has been submitted under this application since it is the same manufacturer with same specification. Rufinamide has no ionizable functionality and is poorly soluble (approximately 27-31 mg/L at 25°C and 40-70 mg/L at 37°C) in water, gastric fluid and intestinal fluid. The critical quality attributes of the drug substance identified in the original NDA for rufinamide were bulk density, polymorphic transition, particle size and shape. These physico chemical attributes of the API could also play a critical role in the ultimate performance of this finished dosage form (suspension) as discussed in details under respective section. There were four (4) polymorphic reported in the original NDA among with polymorphic (b) (4) was identified as the most thermodynamically stable.

Drug Product

The drug product is an oral suspension for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in children 4 years and older and adults. The proposed trade name of the product is Banzel™ (rufinamide) oral suspension and it is formulated at a strength of 40 mg/ml with pharmaceutical grade common compendial excipients. The finished product is orange flavoured, opaque, practically white, and slightly thixotropic. The recommended target doses are 3200 mg/day for adults and 45 mg/kg/day (to a maximum 3200 mg/day) for children, administered in two equally divided doses.

The product development was originally initiated at Novartis but completed by Eisai. Novartis developed a prototype formulation (40mg/ml) based on their prior knowledge and then tested this formulation for bioequivalence with that of the marketed product, Banzel™ Tablets, 400 mg. The result of this BE study met the agency's criteria of bioequivalence. However, after the acquisition of this product by Eisai, minor change was done with the formulation (b) (4). In addition to that, although the Novartis final formulation was found to be bioequivalent, Eisai considered that the physico-chemical characterization of that formulation with respect to relevant biopharmaceutical properties of the suspension was limited to single point dissolution and particle size.

It is to be noted that the solubility of rufinamide is limited and in the original NDA the particle size and bulk density of the API was found to be critical for dissolution. The particle size of the drug substance is also considered critical for any suspension preparation. Therefore, Eisai evaluated extensively the effect of manufacturing process (particularly the homogenization) on the drug substance particle size during the course of development. Based on their study, the sponsor established an in process particle size limit of (b) (4) (during its homogenization) that showed no significant effect on in vitro dissolution (limit (b) (4) drug release in NMT 15 minutes). Three batches with different homogenization speeds were manufactured and tested for bioequivalence study in healthy human subjects. Regardless of significant differences in dissolution characteristics (and limit in specification) exist between these two different pharmaceutical dosage forms (tablets vs. suspension), all batches of rufinamide oral suspension were found to be bioequivalent to the tablets. Results suggests that the rate of absorption of rufinamide across the GI membrane might be limited and physical characteristics of the product, such as drug substance particle size may not have

Executive Summary Section

statistically significant impact on *in vivo* profile (PK parameters) as long as it (b) (4) of particles) is maintained below the (b) (4)

The drug product was formulated with compendial grade commonly used excipients that are generally used for any suspension preparation. The level of critical formulation components, particularly the preservative systems were thoroughly evaluated and found to be adequate. The physical characteristics, such as rheological property were also evaluated so that product can be easily poured into dosing device by the patients. The product is manufactured by (b) (4)

A risk assessment for all these manufacturing unit operations was performed at the initial stage of the product development and linked with the critical quality attributes of the finished product. Such risk assessment for the manufacturing process was then performed using commercial size batches and established a set of critical process parameters (CPP) with designated risk levels. Based on that, the sponsor has identified the target operating condition with a validated operating range that will be followed for all the future commercial batches. However, no design space or process model was submitted in this application.

The drug product has acceptable specification and all analytical methods used are validated appropriately. Extensive stability studies were conducted including commercial scale batches. All studies showed satisfactory product stability during the period tested. However, (b) (4) potassium sorbate showed a tendency of gradual decrease in its assay over time. The sponsor conducted a statistical analysis on the assay values of (b) (4) based on which they have proposed a product shelf life of (b) (4). The sponsor has not provided any details of such statistical analysis and therefore, based on the stability data, a shelf life of one (1) year can be granted at this stage.

Rufinamide Oral Suspension is packaged in 500 mL oriented-polyethylene terephthalate (o-PET) bottles with child-resistant (CR) (b) (4) closures and (b) (4). Each bottle will contain 460 mL of the suspension. The product will be co-packaged with a (b) (4), an LDPE press-in-bottle adapter (PIBA), and (b) (4) Rufinamide Oral Suspension will be manufactured by (b) (4).

In summary, the CMC reviewer found that the level of information and scientific data provided in this application are adequate for most of the part of the drug development. However, there were several deficiencies identified and questions/inquiries were sent to the sponsor on 12/03/2010. This application can be granted approved from CMC point of view once the sponsor provide us satisfactory responses to our questions.

B. Description of How the Drug Product is Intended to be Used

Banzel™ is an aqueous suspension for oral administration in children 4 years and older and adults oral administration for adjunctive treatment of seizures associated with Lennox-

Executive Summary Section

Gastaut syndrome. The recommended target doses are 3200 mg/day for adults and 45 mg/kg/day (to a maximum 3200 mg/day) for children, administered in two equally divided doses.

C. Basis for Approvability or Not-Approval Recommendation

This new drug application (22-568) cannot be approved from the perspective of chemistry, manufacturing, and controls until the sponsor provide satisfactory responses to the list of deficiencies.

APPEARS THIS WAY ON ORIGINAL.

Executive Summary Section

III. Administrative**A. Reviewer's Signature**

/s/ A. Khairuzzaman, Ph.D.

B. Endorsement Block

Chemistry Reviewer:	Akm Khairuzzaman, Ph.D.
Pharmaceutical Assessment Lead:	Martha Heiman, Ph.D.
Branch Chief:	Ramesh Sood, Ph.D.
Project Manager:	Don Henry

C. CC Block

Orig. NDA 22-568
HFD-120/Division File

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/s/

AKM KHAIRUZZAMAN

12/16/2010

Pending for approval

RAMESH K SOOD

12/16/2010

Initial Quality Assessment
Branch I
Division of New Drug Quality Assessment I

OND Division: Division of Neurology Products
NDA: 201367
Applicant: Eisai Medical Research
Stamp Date: 03-May-2010
PDUFA Date: 03-Mar-2011
Trademark: Banzel®
Established Name: Rufinamide
Dosage Form: Suspension
Route of Administration: Oral
Indication:

CMC Lead: Martha R. Heimann, Ph.D.

	Yes	No
ONDQA Fileability:	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Comments for 74-Day Letter	<input checked="" type="checkbox"/>	<input type="checkbox"/>

Summary and Critical Issues:

Summary

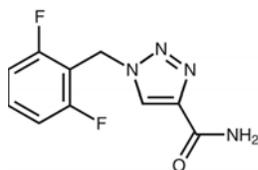
Banzel® (rufinamide) is indicated for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in children 4 years and older and adults. Currently, rufinamide is available as conventional immediate release tablets (NDA 21-911) in two strengths, 200 mg and 400 mg. The recommended target doses are 3200 mg/day for adults and 45 mg/kg/day (to a maximum 3200 mg/day) for children, administered in two equally divided doses.

The current NDA provides for a rufinamide oral suspension formulation to be available in a single strength, 40 mg/mL, for twice daily administration. The product is intended to be used primarily in young children, but may be used by older patients who can not swallow, or prefer not to use, the tablet formulation. The applicant has provided in-vivo bioequivalence data to establish the equivalency of the oral suspension to the approved tablets.

Drug Substance

The active ingredient in Banzel Oral Solution, rufinamide (chemical name: 1-(2,6-difluorobenzyl)-1*H*-1,2,3-triazole-4-carboxamide), is a triazole derivative structurally unrelated to other currently marketed anti-epileptic drugs. It is a well characterized small molecule with molecular formula C₁₀H₈F₂N₄O and a molecular weight of 238.2. The drug substance is a white, crystalline, odorless, slightly bitter tasting, neutral powder. Rufinamide has no ionizable functionality and is poorly soluble (approximately 27-31 mg/L at 25°C and 40-70 mg/L at 37°C) in water, gastric fluid and intestinal fluid. Rufinamide exhibits polymorphism; the approved manufacturing process produces (b) (4) Due to the (b) (4) crystals, rufinamide freely forms

agglomerates and so has a low bulk density and poor flow properties. The chemical structure of rufinamide is:



The bulk drug substance is manufactured under NDA 21-911, which is cross-referenced for CMC information. Information provided in the current NDA is limited to a summary of the manufacturing facilities and drug substance specification approved under NDA 21-911, and a discussion of physicochemical properties relevant to manufacture and performance of the Rufinamide Oral Suspension. [Refer to Module 3.2.P.2.1].

Drug Product

The proposed dosage form is an orange flavored suspension containing 40 mg/mL of rufinamide. The product is described as opaque, practically white, and slightly thixotropic. Components and composition of Rufinamide Oral Suspension are summarized in the applicant's Table 3.2.P.1-1.

Table 3.2.P.1-1 Components and Composition of Rufinamide Oral Suspension

Component	Composition mg/mL	Function	Specification
Rufinamide	40.0	Active ingredient	In-house (E2080)
Microcrystalline cellulose and carboxymethylcellulose sodium (Microcrystalline cellulose and carmellose sodium) ^a			(b) (4)
Anhydrous citric acid (Citric acid, anhydrous) ^b			NF, B.P.
Simethicone emulsion, 30%			USP, Ph.Eur.
Poloxamer 188			USP
(b) (4)			NF, Ph.Eur.
(b) (4)			(b) (4)
Hydroxyethyl cellulose (Hydroxyethylcellulose) ^b			NF, Ph.Eur.
Methylparaben (Methyl parahydroxybenzoate) ^b			NF, Ph.Eur.
Potassium sorbate			NF, Ph.Eur.
Propylparaben (Propyl parahydroxybenzoate) ^b			NF, Ph.Eur.
Propylene glycol			USP, Ph.Eur., B.P.
Noncrystallizing sorbitol solution, 70% (Sorbitol, liquid (non-crystallising)) ^b			NF, Ph.Eur.
(b) (4)			USP, Ph.Eur.

^a Name as listed in B.P.

^b Name as listed in Ph. Eur.

(b) (4)

All components of Rufinamide Oral Suspension except (b) (4) comply with compendial (USP/NF) requirements and are commonly used as excipients in oral dosage forms.

Rufinamide Oral Suspension will be packaged in 500 mL oriented-polyethylene terephthalate (o-PET) bottles with child-resistant (CR) (b) (4) closures and (b) (4). Each bottle will contain 460 mL of the suspension. The product will be co-packaged with a (b) (4) an LDPE press-in-bottle adapter (PIBA), and a (b) (4).

Rufinamide Oral Suspension will be manufactured by (b) (4). The manufacturing process and in-process controls are outlined in the applicant's Figure 3.2.P.3.3-1.

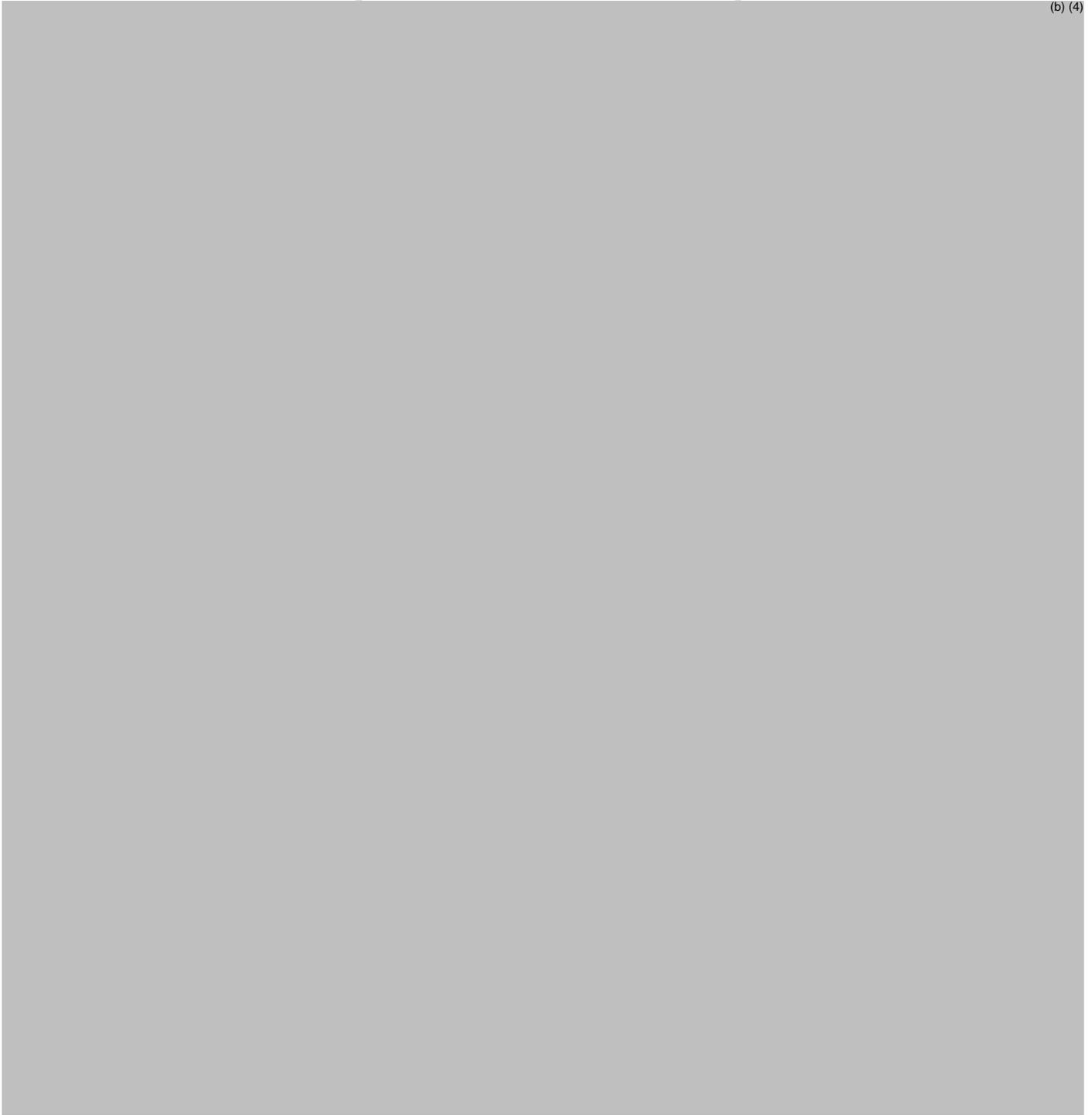


Figure 3.2.P.3.3—1 Manufacturing Process Flow Diagram of Rufinamide Oral Suspension

The proposed regulatory specification for Rufinamide Oral Suspension is shown in the applicant's Table 3.2.P.5.1-1. The proposed analytical procedures are relatively straight-forward. Rufinamide Assay, Related substances, and preservatives content are using determined using related gradient, reverse phase, HPLC methods (b) (4) UV detection at 220 nm for rufinamide assay and related substances and (b) (4) for preservatives]. Dissolution is determined using USP Apparatus II at 50 rpm in 2% aqueous sodium lauryl sulfate solution. Dissolution results are quantitated by HPLC.

Table 3.2.P.5.1-1 Specification for Rufinamide Oral Suspension

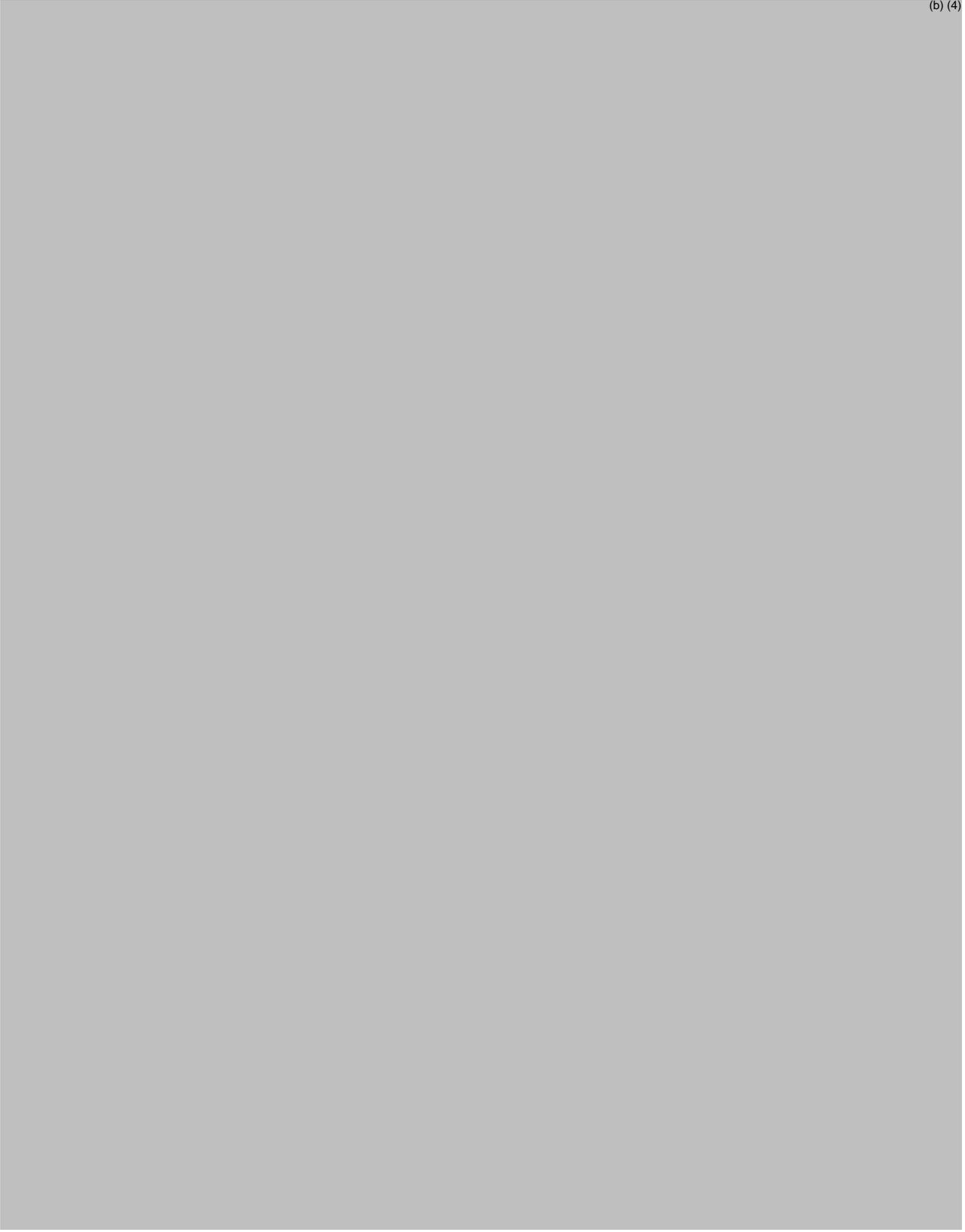
(b) (4)



ATTACHMENT 1

Manufacturing Establishments for Rufinamide Oral Suspension

(b) (4)



ATTACHMENT 1

Manufacturing Establishments for Rufinamide Oral Suspension

(b) (4)



**CHEMICAL MANUFACTURING CONTROLS
FILING CHECKLIST FOR A NEW NDA/BLA**

NDA Numbers: 201367 Applicant: Eisai Inc.

Stamp Date: 03-May-2010

Drug Name: Rufinamide Oral Suspension

NDA Type: Standard

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Content Parameter	Yes	No	Comment
1	Is the section legible, organized, indexed, and paginated adequately?	X		
2	Are ALL of the manufacturing and testing sites (including contract sites) identified with full street addresses (and CFNs, if applicable)?	X		
3	Is a statement provided to indicate whether each manufacturing or testing site is ready for inspection or, if not, when it will be ready?	X		
4	Is a statement on the Environmental Impact provided as required in 21 CFR 314.50(d)(1)(iii)?	X		A claim for categorical exclusion was submitted.
5	Is information on the Drug Substance provided as required in 21 CFR 314.50(d)(1)(i)?	X		
6	Is information on the Drug Product provided as required in 21 CFR 314.50(d)(1)(ii)?	X		
7	If applicable, has all information requested during the IND phases, and at the pre-NDA meetings been included?	NA		
8	Have draft container labels and package insert been provided?	X		
9	Have all DMF References been identified?	X		
10	Is information on the investigational formulations included?	X		
11	Is information on the Methods Validation included?	X		Included but placed under Comparability Protocol heading. Applicant will be asked to correct.
12	If applicable, is documentation on the sterilization process validation included?	NA		

IS THE CMC SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA is not fileable from chemistry, manufacturing, and controls perspective, state the reasons and provide comments to be sent to the Applicant. **NA**

Martha R. Heimann, Ph.D.

Pharmaceutical Assessment Lead, DPA 1, ONDQA

Date

Ramesh Sood, Ph.D.

Branch Chief, DPA 1, ONDQA

Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201367	ORIG-1	EISAI INC	Banzel (rufinamide) Oral Suspension

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

/s/

MARTHA R HEIMANN
05/20/2010

RAMESH K SOOD
05/21/2010