APPLICATION NUMBER:
201367Orig1s000

CHEMISTRY REVIEW(S)
NDA 201-367

Banzel™ (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.

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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]-1H-1,2,3-triazole-4 carboxamide
   US Adopted Name (USAN): Rufinamide
   Laboratory Codes: N/A

   ![Chemical Structure](attachment:chemical_structure.png)

   Chemical Formula: $\text{C}_{10}\text{H}_8\text{F}_2\text{N}_4\text{O}$
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## 17. RELATED/SUPPORTING DOCUMENTS:

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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 20 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 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 \(^{(b)}\) 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 (40 mg/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 \(^{(b)}\) 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 \(^{(b)}\)
Chemistry Assessment Section

(during its homogenization) that showed no significant effect on in vitro dissolution (limit 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 (of particles) is maintained below the

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

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, 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 based on which they have proposed a product shelf life of However, after evaluating the details on such study, the reviewer found that the extrapolated assay value of the potassium sorbate 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) closures and 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
and accurate dosing. Rufinamide Oral Suspension will be manufactured by [redacted].

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] the shelf life of the product can be approved for 18 months only.

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.
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: Teshara G Bouie

C. CC Block

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

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

/s/

AKM KHARUZZAMAN  
02/23/2011
This NDA is approvable from CMC point of view

RAMESH K SOOD  
02/23/2011

Reference ID: 2909224
NDA 201-367

Banzel™ (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
Table of Contents

Table of Contents .....................................................................................................2

Chemistry Review Data Sheet.................................................................................4

The Executive Summary .........................................................................................8

I. Recommendations .......................................................................................................................8
   A. Recommendation and Conclusion on Approvability.................................................................8
   B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk
      Management Steps, if Approvable ..............................................................................................8

II. Summary of Chemistry Assessments.........................................................................................8
   A. Description of the Drug Product(s) and Drug Substance(s)..........................................................8
   B. Description of How the Drug Product is Intended to be Used ........................................................10
   C. Basis for Approvability or Not-Approval Recommendation .............................................................11

III. Administrative.........................................................................................................................12
   A. Reviewer’s Signature ............................................................................................................................12
   B. Endorsement Block ...............................................................................................................................12
   C. CC Block ........................................................................................................................................12

Chemistry Assessment ...........................................................................................13


S DRUG SUBSTANCE [Rufinamide, Eisai Medical Research]..................................................13
   S.1 General Information [Rufinamide, Eisai Medical Research].......................................................13
   S.2 Manufacture [Rufinamide, Eisai Medical Research]......................................................................13
   S.3 Characterization [Rufinamide, Eisai Medical Research]...............................................................14
   S.4 Control of Drug Substance [Rufinamide, Eisai Medical Research].............................................14
   S.5 Reference Standards or Materials [Rufinamide, Eisai Medical Research].................................16
   S.6 Container Closure System [Rufinamide, Eisai Medical Research]..............................................16
   S.7 Stability [Rufinamide, Eisai Medical Research].............................................................................16

P DRUG PRODUCT [BanzelTM Tablets].................................................................................16
   P.1 Description and Composition of the Drug Product [BanzelTM Oral Suspension].......................16
   P.2 Pharmaceutical Development [BanzelTM Oral Suspension].......................................................17
   P.3 Manufacture [BanzelTM Oral Suspension]....................................................................................44
CHEMISTRY REVIEW

P.4  Control of Excipients [Banzel™ Oral Suspension]................................................................. 47
P.5  Control of Drug Product [Banzel™ Oral Suspension]............................................................ 49
P.6  Reference Standards or Materials [Banzel™ Oral Suspension].............................................. 62
P.7  Container Closure System [Banzel™ Oral Suspension].......................................................... 62
P.8  Stability [Banzel™ Oral Suspension] ..................................................................................... 63

A  APPENDICES .................................................................................................................. 68
A.1  Facilities and Equipment (biotech only).................................................................................. 68
A.2  Adventitious Agents Safety Evaluation.................................................................................... 68
A.3  Novel Excipients .................................................................................................................. 68

R  REGIONAL INFORMATION ............................................................................................. 68
R.1  Executed Batch Records ...................................................................................................... 68
R.2  Comparability Protocols ...................................................................................................... 69
R.3  Methods Validation Package ............................................................................................... 69

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 ..................... 69
A.  Labeling & Package Insert ..................................................................................................... 69
B.  Environmental Assessment Or Claim Of Categorical Exclusion ......................................... 72

III. Establishment Evaluation Report ...................................................................................... 73

IV. List Of Deficiencies ......................................................................................................... 74

Reference ID: 2878838
Chemistry Review Data Sheet

1. NDA 201-367

2. REVIEW #: 1

3. REVIEW DATE: 15-Dec-2010
   Revised:

4. REVIEWER: Akm Khairuzzaman, Ph.D.

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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 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
CHEMISTRY REVIEW

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 which polymorphic  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 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 during its homogenization that showed no significant effect on in vitro dissolution (limit 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 (of particles) is maintained below the.

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.

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, potassium sorbate showed a tendency of gradual decrease in its assay over time. The sponsor conducted a statistical analysis on the assay values of based on which they have proposed a product shelf life of 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) closures and. Each bottle will contain 460 mL of the suspension. The product will be co-packaged with a, an LDPE press-in-bottle adapter (PIBA), and. Rufinamide Oral Suspension will be manufactured by.

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

/s/

AKM KHAIRUZZAMAN
12/16/2010
Pending for approval

RAMESH K SOOD
12/16/2010
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-difluoro-benzyl)-1H-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 crystals, rufinamide freely forms...
agglomerates and so has a low bulk density and poor flow properties. The chemical structure of rufinamide is:

![Chemical Structure of Rufinamide]

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**

<table>
<thead>
<tr>
<th>Component</th>
<th>Composition mg/mL</th>
<th>Function</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rufinamide</td>
<td>40.0</td>
<td>Active ingredient</td>
<td>In-house (E2080)</td>
</tr>
<tr>
<td>Microcrystalline cellulose and carboxymethylcellulose sodium (Microcrystalline cellulose and carmellose sodium) b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anhydrous citric acid (Citric acid, anhydrous) b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simethicone emulsion, 30%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poloxamer 188</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxyethyl cellulose (Hydroxyethylcellulose) b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylparaben (Methyl parahydroxybenzoate) b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium sorbate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propylparaben (Propyl parahydroxybenzoate) b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propylene glycol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noncrystallizing sorbitol solution, 70% (Sorbitol, liquid (non-crystallising)) b</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Name as listed in B.P.

b Name as listed in Ph. Eur.
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 UV detection at 220 nm for rufinamide assay and related substances and 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>
<thead>
<tr>
<th>Table 3.2.P.5.1-1</th>
<th>Specification for Rufinamide Oral Suspension</th>
</tr>
</thead>
</table>

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**Additional issues**

**Administrative:** Rufinamide Oral Suspension is a new dosage form and approval of this application may be expected to increase use of the active moiety. The firm has submitted a claim for categorical exclusion under 25.31(b) which states that use of this product will not cause the concentration of the drug substance active moiety to be one part per billion (1 ppb) or greater at the point of entry into the aquatic environment.

**Establishment Evaluation:** A full list of facilities involved in the manufacture, packaging and testing of Rufinamide Oral Suspension is provided in the submission. The facilities listed in Attachment 1 were entered into EES on 17-May-2010.

**Labeling/Established Name:** Rufinamide is a neutral compound. Therefore, there is no issue of consistency between the established name (rufinamide oral suspension) and the labeled potency.

**Methods Validation:** The methods validation section is included in Module 3.2.R; however, it is indexed under "Comparability Protocol." This is considered a minor deficiency which the applicant will be asked to correct.

**Comments for 74-Day Letter**

You have not provided any assessment of the stability of the drug substance to potential polymorphism once formulated in the product. As rufinamide is a poorly soluble drug substance, changes to the solid state characteristics (e.g., hydrate formation) could adversely impact on bioavailability.

In Module 3.2.R Regional Information, the Methods Validation section is included under the "Comparability Protocol" heading. Please correct this in a future submission.

**Review, Comments and Recommendation:**

The NDA is fileable from a CMC perspective.

The drug substance is manufactured under an approved NDA. The suspension formulation is relatively simple and there are no QbD aspects to the submission. Assignment of the CMC portion of the NDA to a single reviewer is recommended. The ONDQA Biopharmaceutics team should be consulted for review of the dissolution method. It is recommended that the OPS Microbiology Staff be consulted for evaluation of the microbiological controls and preservative effectiveness.

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

Ramesh Sood, Ph.D.
Branch Chief Date
ATTACHMENT 1

Manufacturing Establishments for Rufinamide Oral Suspension

(b)(4)
ATTACHMENT 1

Manufacturing Establishments for Rufinamide Oral Suspension
The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

<table>
<thead>
<tr>
<th>Content Parameter</th>
<th>Yes</th>
<th>No</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Is the section legible, organized, indexed, and paginated adequately?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>2 Are ALL of the manufacturing and testing sites (including contract sites) identified with full street addresses (and CFNs, if applicable)?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>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?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>4 Is a statement on the Environmental Impact provided as required in 21 CFR 314.50(d)(1)(iii)?</td>
<td></td>
<td>X</td>
<td>A claim for categorical exclusion was submitted.</td>
</tr>
<tr>
<td>5 Is information on the Drug Substance provided as required in 21 CFR 314.50(d)(1)(i)?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>6 Is information on the Drug Product provided as required in 21 CFR 314.50(d)(1)(ii)?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>7 If applicable, has all information requested during the IND phases, and at the pre-NDA meetings been included?</td>
<td></td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>8 Have draft container labels and package insert been provided?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>9 Have all DMF References been identified?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>10 Is information on the investigational formulations included?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>11 Is information on the Methods Validation included?</td>
<td></td>
<td>X</td>
<td>Included but placed under Comparability Protocol heading. Applicant will be asked to correct.</td>
</tr>
<tr>
<td>12 If applicable, is documentation on the sterilization process validation included?</td>
<td></td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

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
<table>
<thead>
<tr>
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<th>Submission Type/Number</th>
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<th>Product Name</th>
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<tr>
<td>NDA-201367</td>
<td>ORIG-1</td>
<td>EISAI INC</td>
<td>Banzel (rufinamide) Oral Suspension</td>
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARTHA R HEIMANN  
05/20/2010

RAMESH K SOOD  
05/21/2010