

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**201367Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## Clinical Pharmacology Review

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PRODUCT (Generic Name):	Rufinamide
PRODUCT (Brand Name):	BANZEL
NDA:	201-367
DOSAGE FORM:	Oral Suspension
DOSAGE STRENGTH:	40 mg/ml
INDICATION:	Lennox-Gastaut Syndrome
NDA TYPE:	New Dosage Form
SUBMISSION DATE:	4/30/2010
SPONSOR:	Eisai
REVIEWER:	Veneeta Tandon, Ph.D.
TEAM LEADER:	Angela Men, M.D, Ph.D.
OCP DIVISION:	DCP I, HFD 860
OND DIVISION:	HFD 120

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## 1.0 EXECUTIVE SUMMARY

Rufinamide (BANZEL), a triazole derivative, was first approved in the United States on November 14, 2008 as a tablet formulation (200 and 400 mg film-coated tablets) for adjunctive treatment of seizures associated with Lennox Gastaut Syndrome in patients 4 years and older. The BANZEL Oral Suspension is intended to be used for treatment of the same indication and at the same dose amounts as tablets (in mg) but affords a more convenient presentation for administration to young children. The oral suspension is also expected to address the needs of older patients who are unable to or would prefer not to swallow a solid oral dosage form.

The BANZEL Oral Suspension formulation has a single strength of 40 mg/mL. One 5 mL spoonful of suspension is equivalent to one 200 mg tablet. This dosage form affords compliance and flexibility of dosing (b) (4)

This application contains data from a primary relative bioavailability study in healthy volunteers (E2080E044- 003) entitled "A randomized, open label, 4-period crossover trial to compare the bioavailability of single 400 mg doses of rufinamide administered as the marketed tablet with three suspension formulations manufactured using different homogeneity speeds (1800, 2100 and 3000 rpm)." The results of this study demonstrate all three rufinamide suspension formulations are bioequivalent to the marketed tablet 400 mg when given at equivalent doses.

The findings from overall clinical pharmacology and biopharmaceutics section are as follows:

- **Relative Bioavailability:** The relative bioavailability was assessed in Study 003. The three rufinamide oral suspension formulations manufactured using different homogeneity speeds (1800, 2100 and 3000 rpm) are bioequivalent to the highest strength of the rufinamide tablets (400 mg) under fed conditions. Rufinamide is recommended to be taken under fed conditions. (b) (4)

A supportive study 102 that was conducted with a suspension formulation manufactured using a homogeneity speed of 2850 also demonstrated that the suspension formulation is bioequivalent to the tablet formulation. This suspension formulation was a prototype formulation that used a different flavor than that proposed to be marketed.

- **Food Effect:** The extent of increase in exposure ( $AUC_{(0\text{ inf})}$ ) with the rufinamide oral suspension is similar to that of the tablet, but the increase in  $C_{\max}$  with the tablet formulation was greater than that with the suspension formulation. A high fat meal increased  $AUC_{(0\text{ inf})}$  and  $C_{\max}$  by 31% and 36%, respectively for a 400 mg suspension formulation, where as high fat meal increased  $AUC_{(0\text{ inf})}$  and  $C_{\max}$  by 34% and 56%, respectively for a 400 mg tablet. These differences seen could be due to inter-subject variability in cross-study comparisons. Under fed conditions both formulations are bioequivalent as assessed in the pivotal relative bioavailability study.

### 1.1 RECOMMENDATION

This application is acceptable from perspective of the Office of Clinical Pharmacology. The labeling recommendations made in this review only pertain to this NDA submission and should be conveyed to the sponsor. A pending PLR labeling conversion is not the subject of this review and should be considered before taking action on this NDA. The DSI inspection for Study 003 was satisfactory.

### 1.2 PHASE IV COMMITMENT/REQUIREMENT

None

Veneeta Tandon, Ph.D.  
Division of Clinical Pharmacology I

Team Leader: Angela Men, M.D., Ph.D. \_\_\_\_\_

## 2.0 QUESTION BASED REVIEW

### 2.1 GENERAL ATTRIBUTES

#### 2.1.1 Drug/Drug Product Information:

**Dosage Form/Strengths/Route:** Rufinamide Oral Suspension contains 40 mg/mL of rufinamide.

**Formulation:** The components and composition are shown in the following Table:

**Table: Components and Composition of Rufinamide Oral Suspension**

Dosage Strength	100 mg	200 mg	400 mg*	Function	Reference to standard
Ingredient	Amount [mg]				
(b) (4)					(b) (4)
Rufinamide					
Sodium laurilsulfate					
(b) (4)					
Hypromellose					
Lactose monohydrate					
Cellulose microcrystalline					
(b) (4)					
(b) (4)					
Croscarmellose sodium					
(b) (4)					
Magnesium stearate					
(b) (4)					
(b) (4)					

Rufinamide Oral Suspension was initially developed by Novartis. The prototype (20 mg/mL) and subsequent formulation manufactured at the intended full scale (40 mg/mL) by Novartis used an orange flavor (b) (4) which was replaced by a similar (b) (4) orange flavor (b) (4) by Eisai. The homogenization speed employed by Novartis was 2850 rpm and that by Eisai was 1800, 2100, 2400 and 3000 rpm. (b) (4)

**Indication:**

Adjunctive treatment of seizures associated with LGS in children 4 years and older

**Dosing regimen:**

Same as that approved for the Tablets.

Starting dose: 10 mg/kg/day for Children 400-800 mg/day for adults

Increments: 10 mg/kg every other day for children or 400-800 mg every other day for adults

Maintenance Dose: 45 mg/kg/day or 3200 mg maximum

## 2.2 GENERAL BIOPHARMACEUTICS

### 2.2.1 Is the proposed to-be-marketed formulation of rufinamide oral suspension bioequivalent to the approved rufinamide tablets?

A 400 mg of the Rufinamide Oral Suspension formulation manufactured with a homogenization speeds of 1800, 2100 and 3000 rpm are bioequivalent to the currently marketed 400 mg tablet formulation. Therefore speed of homogenization and in turn particle size distribution appears to have no discernable effect on systemic exposure within the range evaluated in this study (1800 to 3000 rpm). (b) (4)

The bioequivalence of Rufinamide Oral Suspension to the rufinamide tablets was demonstrated in a 4-way crossover study (Study 003) and a supporting relative bioequivalence study (Study 102). This supportive study was reviewed during the original NDA review.

Adequacy of strength of reference formulation used: The highest strength tablet (400 mg) was used to investigate the relative bioavailability compared to the same dose given as the Rufinamide Oral Suspension (10 mL of 40 mg/mL in suspension) and this is acceptable. The tableting mixture used for the tablets 100, 200 and 400 mg is the same and different tablet strengths are obtained by increasing the core weights accordingly.

Adequacy of a bioequivalence study under fed conditions: The relative bioequivalence study was conducted under fed conditions. The product label for rufinamide tablets recommends to take rufinamide with food to increase exposure to optimize efficacy (For tablets food increased AUC by 34% and C<sub>max</sub> by 56%). All efficacy studies for the Tablets NDA were conducted in the presence of food. There are no major safety concerns due to increased exposure and safety assessment for the approval of the tablet formulation was done in the presence of food with doses higher than the maximum approved dose. The comparison of exposure profiles of the commercial tablets and the Rufinamide Oral Suspension was therefore carried out under fed conditions. This is acceptable based on the Office of Clinical Pharmacology decision chart on when to accept a fed bioequivalence study.

Statistical analysis conducted by the sponsor and the reviewer demonstrated that all suspensions are within the acceptance criteria to show that all rufinamide suspension formulations are bioequivalent to the approved tablets (90% CI 0.8-1.25). The statistical analysis from Study 003 is given in the following Table.

<b>Table: Statistical Analysis of Pharmacokinetic Parameters (Study 003): Pivotal Data</b>				
		<b>Test Suspension Formulations (N= 23)</b>		
<b>Parameter</b>		<b>1800 rpm</b>	<b>2100 rpm</b>	<b>3000 rpm</b>
<b>C<sub>max</sub> (ng/mL)</b>	Suspension least square mean (test)	4254.87	4204.29	4418.44
	Tablet least square mean (reference)	4840.24	4840.24	4840.24
	<b>Ratio of Treatment Means (suspension/tablet)</b>	<b>0.88</b>	<b>0.87</b>	<b>0.91</b>
	<b>90% Confidence Interval of Ratio</b>	<b>(0.84-0.92)</b>	<b>(0.83-0.91)</b>	<b>(0.88-0.95)</b>
<b>AUC<sub>(0-72h)</sub> (ng/mL)</b>	Suspension least square mean (test)	74279.02	73746.03	73701.17
	Tablet least square mean (reference)	75960.48	75960.48	75960.48
	<b>Ratio of Treatment Means (suspension/tablet)</b>	<b>0.98</b>	<b>0.97</b>	<b>0.97</b>
	<b>90% Confidence Interval of Ratio</b>	<b>(0.95-1.00)</b>	<b>(0.95-1.00)</b>	<b>(0.95-0.99)</b>
<b>AUC<sub>(0-inf)</sub> (ng/mL)</b>	Suspension least square mean (test)	74668.44	74101.81	74085.66
	Tablet least square mean (reference)	76374.48	76374.48	76374.48
	<b>Ratio of Treatment Means (suspension/tablet)</b>	<b>0.98</b>	<b>0.97</b>	<b>0.97</b>
	<b>90% Confidence Interval of Ratio</b>	<b>(0.95-1.00)</b>	<b>(0.95-0.99)</b>	<b>(0.95-0.99)</b>

The within-subject co-efficient of variation (CV%) of  $C_{max}$  was estimated to be 8.35% and the within-subject CV% of  $AUC_{(0-72)}$  was estimated to be 4.86%.

Another supportive study (Study 102) that was reviewed in the original review of NDA 21-911 for rufinamide tablets also showed that the suspension was bioequivalent to the tablet. The suspension used in this study was the prototype formulation of the suspension with a homogenization speed of 2850 rpm. The only difference with this prototype formulation is the difference in flavor and the speed of homogenization. This study was also conducted under fed conditions using the highest strength of 400 mg tablet as the reference. Please refer to the following Table for relative bioavailability results.

<b>Table: Statistical Analysis of Pharmacokinetic Parameters (Study 102)* (reviewed for original NDA): Supportive Data</b>		
<b>Parameter</b>		<b>2850 rpm (N=24)</b>
<b><math>C_{max}</math> (ng/mL)</b>	Suspension least square mean (test)	4410
	Tablet least square mean (reference)	4720
	<b>Ratio of Treatment Means (suspension/tablet)</b>	<b>0.93</b>
	<b>90% Confidence Interval of Ratio</b>	<b>(0.88-0.98)</b>
<b><math>AUC_{(0-last)}</math> (ng/mL)</b>	Suspension least square mean (test)	81100
	Tablet least square mean (reference)	82600
	<b>Ratio of Treatment Means (suspension/tablet)</b>	<b>1.02</b>
	<b>90% Confidence Interval of Ratio</b>	<b>(0.99-1.05)</b>
<b><math>AUC_{(0-inf)}</math> (ng/mL)</b>	Suspension least square mean (test)	83800
	Tablet least square mean (reference)	82400
	<b>Ratio of Treatment Means (suspension/tablet)</b>	<b>1.02</b>
	<b>90% Confidence Interval of Ratio</b>	<b>(0.98-1.05)</b>

## 2.2.2 What is the effect of food on the bioavailability of the rufinamide suspension formulation?

A high fat meal increased  $AUC_{(0-inf)}$  and  $C_{max}$  by 31% and 36%, respectively for a dose of 400 mg of the suspension formulation.

The food effect was evaluated in Study 102, a randomized, open label, 3-period crossover trial designed to compare the relative bioavailability of a single 400 mg dose of Rufinamide Oral Suspension with that of a single rufinamide 400 mg tablet. The study demonstrated that the previously observed effect of food on the bioavailability of rufinamide tablets was also present for the rufinamide suspension. The suspension formulation used in this study was a prototype formulation in which the homogenization

speed and flavor were different. Study 003 has shown that the homogenization speed (1800, 2100 and 3000 rpm) did not alter bioavailability. The homogenization speed of 2850 rpm tested in the food effect study is within the speed range used in the pivotal relative bioavailability study, hence the results of Study 102 can be considered acceptable. For both the tablet and the suspension, the presence of food increased the absorption of rufinamide. A high fat meal increased  $AUC_{(0-inf)}$  and  $C_{max}$  by 34% and 56%, respectively for the rufinamide tablets. The extent of absorption is similar with the suspension and tablets, but the peak with the tablet formulation was slightly higher than that of the suspension in the presence of high fat food. This could be due to subject variability in a cross study comparisons. An hour increase of  $T_{max}$  (Fasted: 4hr, Fed: 5.1hr) is within the range of 4-6 hours seen across clinical studies. Under similar fed conditions both formulations are bioequivalent.

The statistical analysis showing the effect of food is summarized in the following Table.

<b>Table: Statistical Analysis of Pharmacokinetic Parameters (Study 102)* (reviewed for original NDA): Food effect (N=24)</b>				
<b>Parameter</b>	<b>Suspension (fasted)</b>	<b>Suspension (fed)</b>	<b>Estimate</b>	<b>90% C.I</b>
<b><math>C_{max}</math> (ng/mL)</b>	3240	4410	1.36	1.29, 1.44
<b><math>AUC_{(0-last)}</math> (ng/mL)</b>	63100	82600	1.31	1.27, 1.36
<b><math>AUC_{(0-inf)}</math> (ng/mL)</b>	64400	83800	1.31	1.26, 1.35
<b><math>T_{max}</math> (hr)</b>	4	5.1	-	-

### 2.2.3 Is the analytical validation adequate?

The analytical validation of the pivotal Study 003 is adequate. Please refer to the individual study review on page 11 for details.

## LABELING RECOMMENDATIONS

Labeling changes to the sections relevant to Clinical Pharmacology are given below. The underlined changes in black are made by the sponsor. The changes in color are made by the reviewer.

### 2 DOSAGE AND ADMINISTRATION

BANZEL should be given with food. Tablets can be administered whole, as half tablets or crushed, for dosing flexibility.

|  (b) (4)

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### 3 DOSAGE FORMS AND STRENGTHS

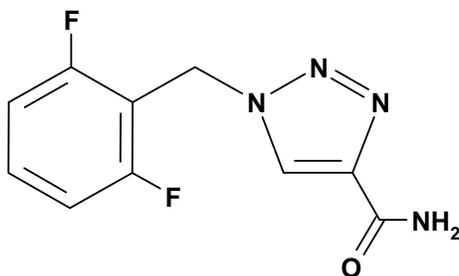
| Film coated Tablets: 200 mg (pink) and 400 mg (pink)  (b) (4) Tablets are scored on both sides.

| Oral Suspension: 40 mg/mL  (b) (4)

| 

### 11 DESCRIPTION

BANZEL (rufinamide) is a triazole derivative structurally unrelated to currently marketed antiepileptic drugs (AEDs). Rufinamide has the chemical name 1-[(2,6-difluorophenyl)methyl]-1*H*-1,2,3-triazole-4 carboxamide. It has an empirical formula of C<sub>10</sub>H<sub>8</sub>F<sub>2</sub>N<sub>4</sub>O and a molecular weight of 238.2. The drug substance is a white, crystalline, odorless and slightly bitter tasting neutral powder. Rufinamide is practically insoluble in water, slightly soluble in tetrahydrofuran and in methanol, and very slightly soluble in ethanol and in acetonitrile.



BANZEL is available for oral administration in film-coated tablets, scored on both sides, containing 200 and 400 mg of rufinamide. Inactive ingredients are colloidal silicon dioxide, corn starch crosscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulphate. The film coating contains hypromellose, iron oxide red, polyethylene glycol, talc, and titanium dioxide.

BANZEL is also available for oral administration as a liquid containing rufinamide at a concentration of 40 mg/mL. Inactive ingredients include microcrystalline cellulose and carboxymethylcellulose sodium, hydroxyethylcellulose, anhydrous citric acid, simeticone emulsion 30%, poloxamer 188, methylparaben, propylparaben, propylene glycol, potassium sorbate, noncrystallizing sorbitol solution 70%, and an orange flavor.

### 12.3 Pharmacokinetics

#### Overview

BANZEL tablets are bioequivalent to BANZEL oral suspension and may be interchanged at equal doses. BANZEL is well absorbed after oral administration. However, the rate of absorption is relatively slow and the extent of absorption is decreased as dose is increased. The pharmacokinetics does not change with multiple dosing. Most elimination of rufinamide is via metabolism, with the primary metabolite resulting from enzymatic hydrolysis of the carboxamide moiety to form the carboxylic acid. This metabolic route is not cytochrome P450 dependent. There are no known active metabolites. Plasma half-life of rufinamide is approximately 6-10 hours.

#### Absorption and Distribution

Following oral administration of BANZEL, peak plasma concentrations occur between 4 and 6 hours ( $T_{max}$ ) both under fed and fasted conditions. BANZEL tablets display decreasing bioavailability with increasing dose after single and multiple dose administration. Based on urinary excretion, the extent of absorption was at least 85% following oral administration of a single dose of 600 mg rufinamide under fed conditions.

Multiple dose pharmacokinetics can be predicted from single dose data for both rufinamide and its metabolite. Given the dosing frequency of every 12 hours and the half-life of 6 to 10 hours, the observed steady-state peak concentration of about two to three times the peak concentration after a single dose is expected.

Food increased the extent of absorption of rufinamide in healthy volunteers by 34% and increased peak exposure by 56% after a single dose of 400 mg tablet, although the  $T_{max}$  was not elevated. Clinical trials were performed under fed conditions and dosing is recommended with food [see *Dosage and Administration (2)*].

Only a small fraction of rufinamide (34%) is bound to human serum proteins, predominantly to albumin (27%), giving little risk of displacement drug-drug interactions. Rufinamide was evenly distributed between erythrocytes and plasma. The apparent volume of distribution is dependent upon dose and varies with body surface area. The apparent volume of distribution was about 50 L at 3200 mg/day.

APPEARS THIS WAY ON ORIGINAL.

## INDIVIDUAL STUDY REVIEW

**Study E2080-E044-003:** 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

The study design is as follows:

Study Design	Randomized, open-label, 4-period, 4-sequence crossover, single study center.
Study Population	N=24 Healthy subjects, 21 completed, 2 discontinued for AEs and 1 for administrative reasons (Subject 10011028 did not get 3000 and tablet and Subject 10011034 did not get 1800 and tablet) <u>Age:</u> 18-55 years (mean 29.8 ± 9.97) <u>Gender:</u> 8 males, 16 females <u>Race:</u> 22 Caucasians, 1 Black, 1 Asian
Treatment Group	Treatment A: Rufinamide, 400 mg single tablet, oral (REFERENCE) Batch No(s): BANZEL Tablets 7401E Treatment B: 10 mL of suspension (40 mg/mL) produced with low homogeneity speed (1800 rpm) (TEST) Batch No(s): C1275A005 Treatment C: 10 mL of suspension (40 mg/mL) produced with intermediate homogeneity speed (2100 rpm) (TEST) Batch No(s): C1275A007 Treatment D: 10 mL of suspension (40 mg/mL) produced with high homogeneity (3000 rpm) (TEST) Batch No(s): C1275A006
Dosage and Administration	<u>Under Fed conditions:</u> Overnight fast, dosing within 30 minutes of high fat breakfast with 240 ml water <u>Washout:</u> 7-10 day
Sampling: Blood	<u>For plasma rufinamide concentrations:</u> Predose, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24, 36, 48 and 72 h after study drug administration.
Urine	none
Feces	none
Analysis	<u>Method:</u> LC/MS/MS method  Linear Range: 20-20000 ng/ml in plasma Lower Limits of Quantitation: 20 ng/ml Quality control concentrations: 50, 500, 4000 and 14000 ng/ml Inter-day precision: % CV: 2.6 % to 5.6 % Inter-day accuracy: 94.5-102.1% of nominal

	Quality control assay validation is acceptable
PK Assessment	AUC <sub>0-72</sub> , AUC <sub>0-∞</sub> , C <sub>max</sub> , T <sub>max</sub> , t <sub>1/2</sub>
Safety Assessment	Vital signs, ECG, Clinical laboratory, AEs
PD Assessment	none

**Pharmacokinetic Results:**

The mean pharmacokinetic parameters from the four treatment arms are given in the following Table:

**Table: Summary of Pharmacokinetic Parameters**

Parameter (units)		400 mg Tablet (N = 22)	1800 rpm (N = 23)	2100 rpm (N = 23)	3000 rpm (N = 23)
AUC <sub>(0-72)</sub> (ng.h/mL)	n	22	23	23	23
	Geometric Mean	74549.86	73383.83	73863.79	73274.56
	CV	25.22	27.34	26.70	27.57
C <sub>max</sub> (ng/mL)	n	22	23	23	23
	Geometric Mean	4768.06	4214.74	4232.64	4396.85
	CV	16.72	20.18	18.58	18.12
AUC <sub>0-inf</sub> (ng.h/mL)	n	22	23	23	23
	Geometric Mean	74954.57	73772.54	74210.93	73651.34
	CV	25.74	27.77	27.08	27.96
t <sub>max</sub> (hours)	n	22	23	23	23
	Median	5.0	5.0	5.0	5.0
	Min-Max	2-10	2-12	2-10	2-10
t <sub>1/2</sub> (hours)	n	22	23	23	23
	Mean	8.54	8.44	8.30	8.39
	Min-Max	6-13.5	5.3-12.5	5.4-12.4	5.6-12.5

The statistical analysis showing the geometric mean ratios and the 90% confidence intervals are given in the following Table:

**Table: Statistical Analysis of Pharmacokinetic Parameters: AUC (0-72) and C<sub>max</sub>**

Parameter	Least Square Means				Ratio of Treatment Means (Test vs Reference)	90% Confidence Interval
	Test		Reference			
AUC <sub>(0-72)</sub> (ng.h/mL)	1800 rpm	74279.02	400 mg Tablet	75960.48	0.98	( 0.95, 1.00)
	2100 rpm	73746.03	400 mg Tablet	75960.48	0.97	( 0.95, 1.00)
	3000 rpm	73701.17	400 mg Tablet	75960.48	0.97	( 0.95, 0.99)
	2100 rpm	73746.03	1800 rpm	74279.02	0.99	( 0.97, 1.02)
	3000 rpm	73701.17	1800 rpm	74279.02	0.99	( 0.97, 1.02)
	3000 rpm	73701.17	2100 rpm	73746.03	1.00	( 0.98, 1.02)
C <sub>max</sub> (ng/mL)	1800 rpm	4254.87	400 mg Tablet	4840.24	0.88	( 0.84, 0.92)
	2100 rpm	4204.29	400 mg Tablet	4840.24	0.87	( 0.83, 0.91)
	3000 rpm	4418.44	400 mg Tablet	4840.24	0.91	( 0.88, 0.95)
	2100 rpm	4204.29	1800 rpm	4254.87	0.99	( 0.95, 1.03)
	3000 rpm	4418.44	1800 rpm	4254.87	1.04	( 1.00, 1.08)
	3000 rpm	4418.44	2100 rpm	4204.29	1.05	( 1.01, 1.10)
AUC <sub>(0-inf)</sub> (ng.h/mL)	1800 rpm	74668.44	400 mg Tablet	76374.48	0.98	( 0.95, 1.00)
	2100 rpm	74101.81	400 mg Tablet	76374.48	0.97	( 0.95, 0.99)
	3000 rpm	74085.66	400 mg Tablet	76374.48	0.97	( 0.95, 0.99)
	2100 rpm	74101.81	1800 rpm	74668.44	0.99	( 0.97, 1.02)
	3000 rpm	74085.66	1800 rpm	74668.44	0.99	( 0.97, 1.02)
	3000 rpm	74085.66	2100 rpm	74101.81	1.00	( 0.98, 1.02)

These results show that the rufinamide suspension formulations made with homogenization speed of 1800, 2100 and 3000 rpm's are bioequivalent to the approved rufinamide tablet formulations as the 90% confidence intervals are between pre-specified limits of 80-120%. The homogenization speed of 3000 rpm was chosen as the homogenization speed of the to-be marketed formulation.

The reviewer's reanalysis gave the same results and therefore the reviewer concurs with the sponsor's conclusion.

The DSI inspection was satisfactory.

### **Conclusion:**

The rufinamide suspension is bioequivalent to the approved tablets.

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/s/  
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VENEETA TANDON  
12/13/2010

YUXIN MEN  
12/31/2010

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

**Office of Clinical Pharmacology**

*New Drug Application Filing and Review Form*

General Information About the Submission

On November 14, 2008, rufinamide tablets were approved for the use as adjunctive therapy of seizures associated with Lennox-Gastaut syndrome in children 4 and older. Rufinamide is currently available as 200 and 400 mg film coated tablets. A Rufinamide Oral Suspension formulation has been developed in order to provide an easy-to-swallow option for young children and those patients who have difficulty swallowing the required number of large tablets (maximum dose is 3200 mg which corresponds to 8 x 400 mg tablets per day). The Rufinamide Oral Suspension formulation has a single strength of 40 mg/mL. The Rufinamide Oral Suspension formulation is intended for use at the same dose amounts as tablets (in mg).

The marketing approval for Rufinamide Oral Suspension is being sought on the basis of bioequivalence with the current marketed tablets. There are no new efficacy studies.

The prototype (20 mg/mL) and subsequent formulation manufactured at the intended full scale (40 mg/mL) used (b) (4)

(b) (4) A Relative BE study under fed conditions (Study 102: Formulation FM-3) was conducted by Novartis comparing the tablets to this suspension formulation. The formulation was optimized with respect to suspending agents and to key product attributes by Eisai. Process qualification studies were successfully completed using four different homogenization speeds. Three of these batches were used in relative bioavailability Study 003: Formulation FM-4 (1800, 2100 and 3000 rpm) under fed conditions. In direct comparison the homogenization speed employed by Novartis in the earlier bioavailability Study 102 was 2850 rpm. The results indicated that particle size and dissolution rate of Rufinamide Oral Suspension are not critical to the bioavailability. (b) (4)

(b) (4). The speed of homogenization is expected to influence the end product particle size distribution and this was thought to potentially impact the rate and/or the extent of absorption of the compound.

	Information		Information
NDA/BLA Number	201-367	Brand Name	Rufinamide
OCP Division (I, II, III, IV, V)	I	Generic Name	BANZEL
Medical Division	520	Drug Class	Antiepileptic
OCP Reviewer	Veneeta Tandon	Indication(s)	Lennox-Gastaut
OCP Team Leader	Angela Men	Dosage Form	Oral Suspension, 40 mg/ml
Pharmacometrics Reviewer	none	Dosing Regimen	200-3200 mg/day (10 ml equivalent to 400 mg tablet)
Date of Submission	4/30/2010	Route of Administration	Oral
Estimated Due Date of OCP Review	1/30/2011	Sponsor	Eisai
Medical Division Due Date	2/11/2011	Priority Classification	Standard
PDUFA Due Date	3/3/2011		

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

<i>Clin. Pharm. and Biopharm. Information</i>				
	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<b>Healthy Volunteers-</b>				
single dose:				
multiple dose:				
<b>Patients-</b>				
single dose:				
multiple dose:				
<b>Dose proportionality -</b>				
fasting / non fasting single dose:				
fasting / non fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
In vivo effects on primary drug:				
In vivo effects of primary drug:				
In vitro:				
<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
<b>PD -</b>				
Phase 2:				
Phase 3:				
<b>PK/PD -</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:	X	2		<b>One pivotal (Study 003) and one supportive (Study 102) which also evaluated food effect for the suspension. This Study 102 has been reviewed in the NDA 21-911 for Tablets</b>
<b>Bioequivalence studies -</b>				

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

traditional design; single / multi dose:				
replicate design; single / multi dose:				
<b>Food-drug interaction studies</b>				
<b>Bio-waiver request based on BCS</b>				
<b>BCS class</b>				
<b>Dissolution study to evaluate alcohol induced dose-dumping</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>				
<b>Total Number of Studies</b>	1	1 New		

**Table 3.2.P.2-1 Formulation History of Rufinamide Oral Suspension**

Component	FM-1 mg/mL	FM-2 mg/mL	FM-3 mg/mL	FM-4 mg/mL
Developer	Novartis	Novartis	Novartis	Eisai
Rufinamide	(b) (4)			
Microcrystalline cellulose and carboxymethylcellulose sodium (Microcrystalline cellulose and carmellose sodium) <sup>a</sup>				
Anhydrous citric acid (Citric acid, anhydrous) <sup>b</sup>				
Simethicone emulsion, 30%				
Poloxamer 188				
(b) (4)				
Hydroxyethyl cellulose (Hydroxyethylcellulose) <sup>b</sup>				
Methylparaben (Methyl parahydroxybenzoate) <sup>b</sup>				
Potassium sorbate				
Propylparaben (Propyl parahydroxybenzoate) <sup>b</sup>				
Propylene glycol				
Noncrystallizing sorbitol solution, 70% (Sorbitol, liquid (non-crystallising)) <sup>b</sup>				
(b) (4)				

<sup>a</sup> Name as listed in BP

<sup>b</sup> Name as listed in Ph. Eur.

(b) (4)

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

## 5.2 Tabular Listing of all Clinical Studies

Type of Study	Study Identifier	Location of Study report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Enrolled/ Completed	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BA	<a href="#">E2080-E044-003</a>	Section 5.3.1.2.1	To compare the bioavailability and pharmacokinetics of rufinamide administered as a tablet formulation with 3 suspension formulations manufactured under different conditions of homogenization speeds	Cross-over, randomized, open label	10 ml oral suspension (40 mg/ml)  400 mg oral tablet	24/21	Healthy male and female subjects (18 to 55 years inclusive); BMI ( $\geq 18$ to $\leq 30$ kg/m <sup>2</sup> inclusive)	4 days Single oral dose on day 1 of Treatment sequences 1, 2, 3, and 4	Complete Full
BA	<a href="#">CRUF3310102</a>	Section 5.3.1.2.2	To assess bioequivalence of the same doses of the rufinamide oral suspension relative to the rufinamide tablet and to assess the food effect on rufinamide oral suspension	Randomized, open-label, three-way crossover study	400 mg oral tablet under fed conditions  400 mg oral suspension (40 mg/ml) under fed and fasted conditions	26/24	Males or sterilized females (18-45 years, inclusive)	9 days	Complete Full

BA: Bioavailability

APPEARS THIS WAY ON ORIGINAL.

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

On initial review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
<b>Criteria for Refusal to File (RTF)</b>					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x			
2	Has the applicant provided metabolism and drug-drug interaction information?			x	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?			x	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>					
<b>Data</b>					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
<b>Studies and Analyses</b>					
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			x	
<b>General</b>					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			

File name: 5\_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA\_BLA or Supplement 090808

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	
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**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?**

**Yes**

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. Please provide proposed labeling with track changes to the current approved label.

Additional Reviewer's Comment (internal only):

1. The pivotal BE study has been done under fed conditions. Although this is not typically ideal, but could be considered a review issue for the application. Rufinamide is instructed to be taken with food and hence the sponsor has conducted the BE study under fed conditions. All clinical trials with the tablet formulation were conducted in the presence of food. The therapeutic index for rufinamide is 400-3200 mg. The results show that the suspension formulation is bioequivalent to the approved tablets under fed conditions.
2. The food effect has not been evaluated with the to-be marketed formulation. The only difference in the two formulations (FM-3 in Study 102 and FM-4 in Study 003) is the change in flavor and the homogenization speed. The homogenization speed in the FM-3 formulation is bracketed by the homogenization speed in the pivotal study. The reviewer finds this acceptable. The food effect study 102 was submitted in the original application and was reviewed already in NDA21-911. The suspension shows an increase in AUC(0-t) and Cmax by 31 and 36%, respectively and the tablet formulation shows an increase in AUC(0-t) and Cmax by 34 and 56%, respectively.
3. DSI inspection should be requested for Study 003.

**Investigator(s):**

Darren Wilbraham, MBBS, DCPSA

**Study Center(s):**

Quintiles Ltd. Guys Drug Research Unit (GDRU)  
6 Newcomen Street  
London SE1 1YR  
United Kingdom

**Analytical Site**

(b) (4)

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Reviewing Clinical Pharmacologist

Date

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Team Leader/Supervisor

Date

File name: 5\_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA\_BLA or Supplement 090808

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-201367

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ORIG-1

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EISAI INC

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RUFINAMIDE ORAL  
SUSPENSION

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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VENEETA TANDON  
06/22/2010

YUXIN MEN  
06/23/2010