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RESEARCH**

APPLICATION NUMBER:
201367Orig1s000

MEDICAL REVIEW(S)

Team Leader Review

Date	2/23/11
From	Norman Hershkowitz, MD, PhD
Subject	Clinical Team Leader Review
NDA/BLA #	201367
Supplement#	
Applicant	Eisai Co., Ltd.
Date of Submission	April 30, 2010
PDUFA Goal Date	March 3, 2011
Proprietary Name / Established (USAN) names	Banzel/rufinamide
Dosage forms / Strength	Oral Suspension (40 mg/ml)
Proposed Indication(s)	Adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS)
Recommended:	Approval

1. Introduction/Background

Rufinamide is approved for adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome in patients 4 years and older. Up to the present time it has been available only in tablet form (100mg, 200mg, and 400mg). The present submission consists of a request for approval of an oral suspension for this drug. The marketing approval is based upon bioequivalence of the oral suspension with that of the marketed tablets

2. CMC/Device

Initial chemistry review (initial review 12/16/10) did not find the application as approvable, later clarification by the Sponsor resolved all issues and , these, however, have been resolved and approval is recommended in an updated review (2/23/11). No post-approval commitments are recommended.

3. Clinical Pharmacology/Biopharmaceutics

As noted above, approval is based upon the demonstration of bioequivalence, The primary data came from a single randomized, open label, 4-period crossover trial that compared the bioavailability of a single 400 mg dose of the marketed tablet with three different suspension formulations (study E2080-E044-003) in healthy volunteers (n = 21). There was a 7 to 10 day washout between each single dose. One such formulation was selected. Clinical pharmacology

has agreed that the study is adequate and justifies approval. No post-approval commitments were recommended.

4. Clinical/Statistical- Efficacy

Efficacy is based upon prior studies and the present bridging bioequivalent study.

5. Safety

Dr. Dinsmore performed the safety evaluation for study E2080-E044-003. While there were some adverse events which are not a part of the present label (paraesthesia, chest discomfort, palpitations, arthralgia and ocular hyperemia), these were mild and there was not adequate evidence to attribute these to drug as a causal factor. Some minor laboratory abnormalities were noted, but again could not be attributed to the drug. Of interest there were 2 cases of urinary track infections, but two such isolated cases, in the background of a previous absence of signal could not be used to determine drug causality. No deaths or serious adverse events were observed. Dr. Dinsmore did not recommend any post-approval commitments.

6. Inspections and Financial Disclosure

Inspections for primary study proved satisfactory. Financial disclosure was obtained, and found satisfactory, for the principal investigator; however such disclosure was not able to be obtained for 4 of the 5 sub-investigators. Dr. Dinsmore pursued the issue of due diligence for the search and the role of these investigators in the final results and determined that there was no compelling conflict of interest.

7. Recommendations/Risk Benefit Assessment

Dr Dinsmore recommends approval, with no added new safety information. I agree. The clinical reviewer does not recommend any post-approval commitments or recommendations.

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/s/

NORMAN HERSHKOWITZ
03/02/2011

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	201367
Priority or Standard	S
Submit Date(s)	April 30, 2010
Received Date(s)	April 30, 2010
PDUFA Goal Date	March 3, 2011
Division / Office	DNP
Reviewer Name(s)	Steven T. Dinsmore, D.O.
Review Completion Date	February 22, 2011
Established Name	Rufinamide
Trade Name	BANZEL
Therapeutic Class	Antiepilepsy
Applicant	Eisai Inc.
Formulation(s)	Oral Suspension
Dosing Regimen	Twice Daily
Indication(s)	adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS)
Intended Population(s)	children 4 years and older and adults

Template Version: March 6, 2009

Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	3
1.1	Recommendation on Regulatory Action	3
2	INTRODUCTION AND REGULATORY BACKGROUND	3
2.1	Product Information	3
3	ETHICS AND GOOD CLINICAL PRACTICES.....	3
3.3	Financial Disclosures.....	3
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	4
4.1	Chemistry Manufacturing and Controls	4
4.4	Clinical Pharmacology	4
4.4.3	Pharmacokinetics.....	4
5	SOURCES OF CLINICAL DATA.....	5
5.1	Tables of Studies/Clinical Trials	5
6	REVIEW OF EFFICACY.....	6
	Efficacy Summary.....	6
6.1	Indication.....	Error! Bookmark not defined.
6.1.1	Methods	Error! Bookmark not defined.
6.1.2	Demographics.....	Error! Bookmark not defined.
7	REVIEW OF SAFETY.....	7
	Safety Summary	7
7.1	Methods.....	7
7.1.1	Studies/Clinical Trials Used to Evaluate Safety	7
7.1.2	Categorization of Adverse Events.....	7
7.1.3	Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence.....	8
7.2	Adequacy of Safety Assessments	8
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations	8
7.2.2	Explorations for Dose Response.....	8
7.2.3	Special Animal and/or In Vitro Testing	8
7.2.4	Routine Clinical Testing	8
7.2.5	Metabolic, Clearance, and Interaction Workup	9
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class	9
7.3	Major Safety Results	9
7.3.1	Deaths.....	9
7.3.2	Nonfatal Serious Adverse Events	9

7.3.3	Dropouts and/or Discontinuations	9
7.3.4	Significant Adverse Events	10
7.3.5	Submission Specific Primary Safety Concerns	10
7.4	Supportive Safety Results	10
7.4.1	Common Adverse Events	10
7.4.2	Laboratory Findings	11
7.4.3	Vital Signs	12
7.4.4	Electrocardiograms (ECGs)	13

*Reviewer Note: With permission of the Division the NDA review template is truncated for relevance of content and ease of reading because this submission is centered on pharmacokinetic and chemistry support.

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approval of this oral suspension dosing form is recommended.

2 Introduction and Regulatory Background

2.1 Product Information

Rufinamide is currently approved for adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome in children 4 years and older and adults. Rufinamide is currently available in tablet form with strengths of 100mg, 200mg, and 400mg. The tablets are scored on both sides and can be cut in half for dosing flexibility. Tablets can be administered whole, as half tablets or crushed. Whole, sub-divided or crushed tablets may be difficult to administer to younger children due to difficulty in swallowing and ease of administration. The purpose of an oral suspension form is to facilitate administration to children and adults who find difficulty in swallowing.

3 Ethics and Good Clinical Practices

3.3 Financial Disclosures

Study E2080-E044-003 was conducted by Quintiles Drug Research Unit at Guys Hospital, London UK. FDA form 3453 indicates there were 6 clinical investigators. The

sponsor indicates that financial conflict of interest was excluded for only two of the investigators.

This was a single site study where the investigators with absence of financial disclosure were working with an investigator that was cleared of financial conflict of interest. The non-cleared sub-investigators were not directly involved in evaluation of research subjects nor was the test formulation administered under their immediate supervision. The bioavailability results were also not obtained under immediate supervision of the non-cleared investigators. The sponsor attests due diligence in their attempts to obtain financial disclosure information from the four investigators in question, however these sub investigators were no longer employed by the study site (Quintiles) and could not be reached. The sponsor also attests that none of those investigators in question have proprietary interests in Eisai nor have received SPOOS from the sponsor.

Reviewer Comment: Financial disclosure is only available for one third of the clinical investigators who carried out study E2080-E044-003, however because the additional details of the sub-investigator duties and the attestation of the sponsor concerning proprietary interests and SPOOS, the study is acceptable.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The chemistry reviewer found the application to be non-approvable due to a need for additional information and clarification on multiple points. These have been resolved except for a pending review of dosing accuracy study, pending at the time of this writing.

4.4 Clinical Pharmacology

4.4.3 Pharmacokinetics

The clinical pharmacology reviewer finds that the oral suspensions manufactured at each of the three homogeneity speeds (1800, 2100 and 3000 rpm) performed in study E2080-E044-003 are bioequivalent to 400mg rufinamide tablets. (b) (4)

The pharmacology reviewer also finds that under fed conditions both the oral suspension and tablet are bioequivalent.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

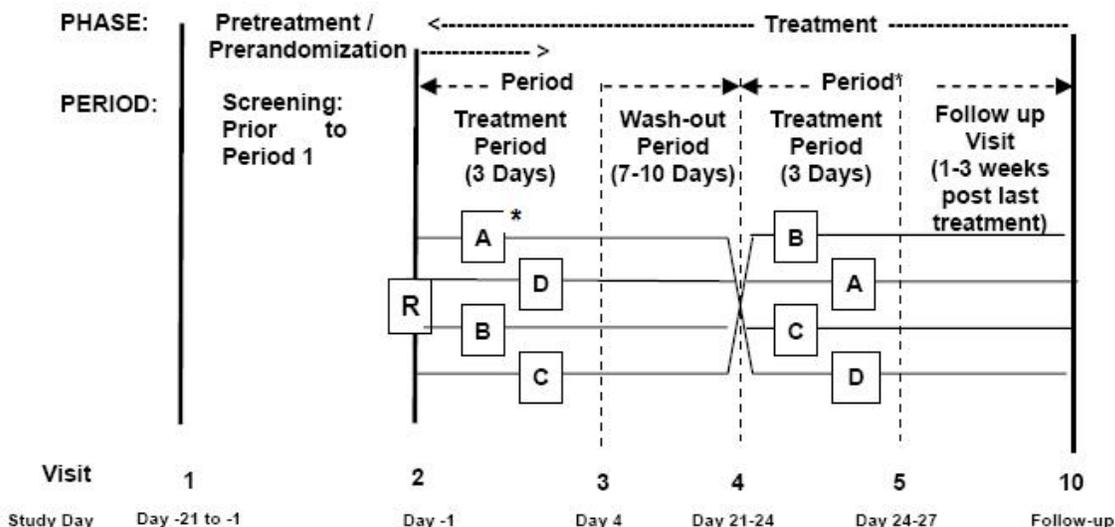
Efficacy and Safety: study E2080-E044-003- “A randomized, open-label, 4-period crossover trial to compare the bioavailability of single 400 mg doses of rufinamide (E2080) administered as the marketed tablet with 3 suspension formulations manufactured using different homogeneity speeds”

Patients were enrolled to one of 4 treatment sequences show below.

Treatment Sequence 1:	400 mg Tablet>-3000 rpm>-1800 rpm>-2100 rpm
Treatment Sequence 2:	1800 rpm>-400 mg Tablet>-2100 rpm>-3000 rpm
Treatment Sequence 3:	2100 rpm>-1800 rpm>-3000 rpm>-400 mg Tablet
Treatment Sequence 4:	3000 rpm>-2100 rpm>-400 mg Tablet >-1800 rpm

These treatment sequences were divided into 4 dose intervals (treatment periods) where the specified dose is directed by the treatment sequence assignment and administered on Day 1 of the treatment period, see study design below. The dose at each treatment point is 400mg of rufinamide formulation. Blood sampling is performed for 72 hours after each dose, safety clinical laboratory samples are obtained on Day 4 of the treatment period. There is a minimum 7 day washout between treatment periods but the interval between treatment periods may be extended to as long as 3 weeks.

Study design Diagram



*Periods and washout repeats for a total of 4 periods and 4 way crossover.

*Letters A-D represent the rufinamide formulations while the connecting lines represent the treatment sequence

6 Review of Efficacy

Efficacy Summary

The primary endpoints are the rufinamide PK parameters $AUC_{(0-72)}$ and C_{max} . The $AUC_{(0-72)}$ and C_{max} values demonstrated bioequivalence to the currently marketed 400mg tablet (ie, 90% CI within 0.8-1.25), see table below.

Statistical Analysis of Pharmacokinetic Parameters: $AUC_{(0-72)}$ and C_{max}						
Parameter	Least square means				Ratio of Treatment Means (Test vs Reference)	90% Confidence Interval
	Test		Reference			
$AUC_{(0-72)}$ (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)

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 {Insert Product Trade and Generic Name}

C _{max} (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)
<p>AUC₍₀₋₇₂₎ = area under the concentration time curve from zero to 72 hours; ng = nanogram;.h = hour; mL = milliliter; C_{max} = maximum observed concentration. Note: Statistical analyses performed on log transformed data using an ANCOVA model including terms for treatment, period and subject. Treatment estimates, ratio of treatment means and 90% confidence intervals presented on the back transformed data of the ANCOVA models.</p>						

7 Review of Safety

Safety Summary

There were no deaths or serious adverse events in the study. There were 3 study withdrawals, two due to urinary tract infection and one due to administrative reasons. One of the urinary tract infection withdrawals had additional notable features of rash and an elevation of serum CK to 537 IU. The CK trended down and rash resolved after study drug discontinued. Abnormalities were noted in the laboratory values and vital signs of some patients, however the limited exposure to the study drug and the measurement of vital signs on day 4 (3 days post dose) cast doubt on the relationship of these observations to rufinamide treatment.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The sponsor submits one phase I study in healthy volunteers to compare the bioavailability of single 400mg doses of rufinamide with 3 suspension formulations manufactured using different homogeneity speeds.

7.1.2 Categorization of Adverse Events

Adverse events were classified by body system/organ class using the Medical Dictionary for Regulatory Activities (MedDRA v11.1) preferred terminology.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

This single phase I study utilized the participation of 24 healthy male and female subjects at a single site thus no pooling of safety data is relevant. This single study is the basis of support for approval of the requested formulation and will be the subject of the safety analysis of sections 7.1 to 7.6.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Each subject who entered the study received a 400mg dose of rufinamide in each of 4 stages of their treatment sequence. Subjects who completed their treatment sequence received a total of 1600mg of rufinamide. Twenty one subjects completed the study with three discontinuations. There were two discontinuations due to adverse events, one each in treatment sequence 3 and 4. There was one discontinuation in treatment sequence 1 noted to be administrative, classified as “other”.

The median age of subjects was 26.5 (range 19 to 50) years, there were 8 male and 16 female subjects. There were 2 non-white subjects enrolled 1 Black and 1 Asian.

7.2.2 Explorations for Dose Response

All subjects received a single 400mg dose of rufinamide at each of 4 treatments.

7.2.3 Special Animal and/or In Vitro Testing

None in this submission

7.2.4 Routine Clinical Testing

Vital signs, 12-lead electrocardiograms (ECGs), blood and urine sample collection for laboratory safety tests were carried out and recorded at the following times: Screening, on admission (Day -1) and prior to discharge (Day 4) for each treatment period, and at Follow-up. A full physical examination was performed during Screening and at Follow-up and an abbreviated examination was performed on Day -1 and at discharge for each treatment period. A physical examination, vital signs, a 12-lead ECG, clinical laboratory, documentation of AEs/concomitant medications and a serum pregnancy test were also carried out at Early Termination (if applicable).

Women of child-bearing potential had a serum pregnancy test at Screening and at Early Termination (if applicable), a urine pregnancy test on Day -1 of each treatment period and at discharge. Medical history and demographic data were recorded at Screening. A urine drug screen and a urine alcohol test were performed at Screening, and on admission to the study center on Day -1 of each treatment period. Blood samples for virology tests were collected at Screening.

Virology tests: Samples taken at Screening for laboratory safety tests were also additionally tested for HIV antibodies type 1 and type 2, hepatitis B surface antigen, and hepatitis C antibodies. Only subjects with negative test results were admitted to the study.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not performed for this phase 1 bioavailability study

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Not performed for this new formulation approval

7.3 Major Safety Results

7.3.1 Deaths

No deaths during this study

7.3.2 Nonfatal Serious Adverse Events

No serious adverse events were reported during the study

7.3.3 Dropouts and/or Discontinuations

There were three withdrawals from this study of 24 subjects. Two were due to TEAE (treatment emergent adverse effects), both were urinary tract infections. One occurred in a subject in period 2 of treatment sequence 3 after dosing with the 1800 rpm suspension and the other in a subject in period 2 of treatment sequence 4 after dosing with the 2100 rpm suspension. The third subject in treatment sequence 1 was withdrawn for administrative reasons

Reviewer Comment: Two urinary tract infections appear to be an unusually high frequency in this small population. In both subjects the infections emerged in period 2 of the study after total exposure to 800mg of rufinamide in a minimum of 11 days. It does

not appear plausible that this low exposure (800mg/11days) was causative of this adverse effect.

7.3.4 Significant Adverse Events

There were 5 adverse events not present in current labeling. These were as follows: Infusion site Paraesthesia, Ocular hyperaemia, chest discomfort, Palpitations and Arthralgia. All of these events were classified as mild and none resulted in withdrawal from the study.

7.3.5 Submission Specific Primary Safety Concerns

none

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

There were 24 adverse events (AE) in the study which occurred in 14 subjects. The most common AE was headache. The clinical trials section of current labeling indicates headache was the also the most common adverse event in all adult double blind trials. The second most frequent event was urinary tract infection. A listing of all adverse events is provided in the table below.

preferred term	# of events
Headache	14
Urinary tract infection	2
Arthralgia	1
Chest discomfort	1
Infusion site paraesthesia	1
Ocular hyperaemia	1
Palpitations	1
Rash	1
Upper respiratory tract infection	1
Vomiting	1

Reviewer Comment: Headache occurred frequently in this study but is also present in labeling due to the frequency in clinical trials. A single case of vomiting is present in the list of adverse events, although frequent in clinical trials for approval; this single case at low exposure is of uncertain causality. The causality of the remainder of the single occurrence adverse events is uncertain.

7.4.2 Laboratory Findings

Definition: day 4 = post treatment, day 1 is day of dosing.

Hematologic

Erythrocytes: There were 9 instances of low day 4 post treatment erythrocyte measurements in 7 patients (2 patients had low events at two treatment periods). In 6 of these 9 instances the erythrocytes were low at baseline, in three baselines were normal. The decline from baseline from among those with normal baseline measurement ranged from -3% to -7%.

In one case (10011037) all day 4 post treatment erythrocyte values remained within normal limits but a follow up value 14 days after final rufinamide dose was observed to drop below the lower limit of normal. An additional follow up obtained 18 days after final dose showed a continued decline with a value 10% below baseline

Hematocrit: there were 12 instances of low hematocrit in 8 subjects. In 9 of these instances the baseline hematocrit was low. Among those where the baseline hematocrit was normal the decline from baseline ranged from -3% to -7%.

In one case (10011037) all day 4 post treatment hematocrit values remained within normal limits but a follow up value 14 days after final rufinamide dose was observed to drop below the lower limit of normal. An additional follow up obtained 18 days after final dose showed a continued decline with a value 10% below baseline

Neutrophils: in a single patient there was a 32% drop in neutrophil count on day 4 of period 1. This subject remained in the study and subsequent day 4 (post treatment) neutrophil values of period 2 to 4 were normal. It is very likely the abnormal value is due to laboratory variability.

Reviewer Comment: These hematologic outliers do not represent a safety signal due to the small changes noted in erythrocytes and hematocrit and the normalization in the case where there was a sudden drop in neutrophil count. In addition based on the prior safety database from approval for rufinamide in LGS, it is unlikely that a 4 dose over 4 week exposure would be adequate to impact hematopoiesis.

Chemistry

CO₂: There were 15 instances of low day 4 blood CO₂ values in 7 patients. In 12 of these instances the baseline CO₂ level was low. In three subjects CO₂ declined from a normal baseline. In two of these subjects the CO₂ values normalized at periods 3 and 4. In the remaining subject the CO₂ value was low at three of the 4 treatment periods, and

reached a nadir during treatment period 4 when the value was 11% below the low normal reference range bound.

Serum Protein: There were 21 instances of low day 4 serum protein in 11 subjects. In six of these instances the baseline was low. The departure from baseline in the remaining 15 instances ranged from -1.5% to -14%. In these 15 instances of low serum protein there was a range of 1.5% to 7.0% below the lower bound of the normal range with a mean of 2.8% below normal. As in the discussion of hematologic parameters, it is unlikely that a 4 dose exposure to the study drug would have an impact on serum protein.

Creatinine kinase (CK): a single case of notably elevated serum CK is noted. This occurred in a patient in period 2, where CK was found to be 537 U/L, a 133% increase over baseline. This patient terminated early due to an additional AE of urinary tract infection. The same patient also had a rash. At follow up the serum CK had dropped to 327 U/L. The subject is noted to have recovered from both the rash and urinary tract infection. It is uncertain if there is a relationship between the infection, rash and elevated serum CK.

Potassium: there were 3 instances of elevated serum potassium which occurred in two subjects. In one subject a two small elevations of 15% and 7% over baseline occurred post treatment in period 1 and 2 respectively then normalized in period 3 and 4. In a second patient there was a 25% increase over baseline post treatment in period 4. The potassium value increased from a baseline of 4.08 mmol/L to 5.1 mmol/L. Although there was a 25% increase over baseline the resulting potassium value of 5.1 mmol/L, only 0.1mmol/L over the upper limit of normal.

Triglycerides: there are 6 instances of post baseline elevation of triglycerides where baseline was normal. These occur in 3 patients. In one patient, every post baseline triglyceride level is elevated. The percent change over baseline ranges from 170% to 257 %. In the remaining two patients the elevations are less prominent and occur in period 3 in one patient and period 4 in the second.

Reviewer Comment: None of these observed chemistry outlier values are of sufficient magnitude to indicate a safety signal.

7.4.3 Vital Signs

Orthostatic Systolic Blood pressure measurement: there were 9 instances in 8 patients of systolic orthostatic blood pressure change ≥ 20 mmHg or lower. This occurred on more than 1 post treatment reading in 1 patient who had a ≥ 20 mmHg change post treatment in period 2 and 3. This same subject (10011014) also had the largest decrease of standing systolic blood pressure.

Systolic blood pressure: There were 5 instances in 4 patients of an increase in supine systolic blood pressure greater than 20mmHg post treatment. The greatest of these values was 45mmHg. There were 3 instances in 2 patient of an increase in standing systolic blood pressure \geq 20mmHg over baseline. The largest of these changes was 60mmHg (subject 10011014); the remaining two instances were 26mmHg and 20mmHg respectively.

Heart Rate: there were 13 instances of standing heart rate increase on day 4, >20 beats/min, in 9 patients. Three of these patients also had an identified orthostatic blood pressure drop <-20 mmHg. In subject (10011011) both the standing tachycardia and a notable orthostatic drop in systolic blood pressure occurred post treatment in period 3.

Reviewer comment: There is a post treatment decline in blood pressure, both orthostatic and systolic standing in a notable number of patients in this study. This is difficult to attribute to rufinamide because the measurements are obtained on day 4 following dose which is greater than 5 half lives. There is also no evidence that rufinamide causes blood pressure elevation based on examination of the vital sign data

7.4.4 Electrocardiograms (ECGs)

Clinically significant ECG changes are not reported.

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/s/

STEVEN T DINSMORE
03/02/2011

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