

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-911**

**APPROVABLE LETTER**



NDA 21-911

Eisai Medical Research, Inc.  
Attention: Loretta Robertson, Pharm.D.  
Associate Director Regulatory Affairs  
55 Challenger Road  
Ridgefield Park, NJ 07660

Dear Dr. Robertson:

Please refer to your new drug application (NDA) dated November 17, 2005, received November 17, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for \_\_\_\_\_ (rufinamide) tablets. **b(4)**

We acknowledge receipt of your submissions dated:

March 13, 2006	March 17, 2006	May 23, 2006	June 15, 2006
June 23, 2006	August 17, 2006	August 22, 2006	September 1, 2006

We have completed our review of this application, as amended, and it is approvable. Our reasons follow below.

You have submitted results of 8 controlled trials that appear, by design, capable of demonstrating the effect of an antiepileptic drug, but results are inconsistent, leave the appropriate dose unclear, and with one exception, show either no, or numerically very small effects. While the studies do suggest that rufinamide has activity, we see no good basis for identifying the useful range of doses and even the evidence of efficacy is not reasonably assured. \_\_\_\_\_ **b(4)**

\_\_\_\_\_ The potential exception to this conclusion is the clearly favorable single study, study 22, in Lennox-Gastaut Syndrome (LGS), but, as will be explained below, we do not believe the remaining data adequately support the single study.

Study ET1 compared 4 doses of rufinamide (200, 400, 800, 1600 mg/day) and placebo as adjunctive therapy in patients with partial seizures. Your primary outcome analysis (the linear trend test) was positive and we believe that the study does, overall, provide evidence of an effect, even though the results were not linear, with 800 mg having the largest effect. The results of the dose-finding aspect of the study, however, are hard to interpret. The reductions in seizure frequency compared to baseline were very modest, barely one to 1.5 seizure per month and the percent reductions compared to placebo were -3% 11%, 17% and 12% for the 200, 400, 800 and 1600 mg doses, respectively. We also note that your amended statistical plan for this study called for an analysis of the individual doses using a Poisson regression. The results of this analysis are not presented in your application; we request that you provide these results.

Although we acknowledge that the results of the Wilcoxon analysis that you did present yielded nominal statistical significance for all doses above 200 mg/day, in this reasonably large study (about 125-130 per group) only the 800 mg group attained a nominally statistically significant result when analyzed with a more traditional ANCOVA that included country as a covariate. Thus, the study suggests (but again, with an extremely small effect on seizure frequency), that 800 mg is at least as effective as a larger dose.

The 800 mg dose, however, showed no effect in study 18 in patients with primary generalized tonic-clonic seizures.

Study 21A compared rufinamide 3200 mg/day to placebo in a population similar to study ET1, showing a significant effect on the protocol-specified Wilcoxon rank sums test, but in a study with substantial geographic distribution it is desirable to examine effects of country and other covariates. Our ANCOVA analysis on log transformed 28 day seizure frequency, with baseline frequency and country as covariates, gave a p-value of 0.09. The study thus provides some, but not strong, evidence of an effect and again, the median change compared to baseline is just 20% (15% in US patients), a reduction compared to placebo of about one seizure per month. The dose, moreover, is fully 4 times that of the dose with the greatest treatment effect in study ET1.

The same 3200 mg dose was compared to 300 mg in a monotherapy study, study 16. No difference between doses was seen. This could reflect activity of the 300 mg dose, but in that case, it is difficult to see why a 3200 mg dose would be needed.

Study 38, a pre-surgery study, reported a significant effect of 3200 mg/day on time to meeting exit criteria, the primary endpoint, but showed essentially identical proportions of patients who actually met exit criteria (protocol-specified worst-case scenario), an unusual outcome in our experience. Again, the study supports the existence of some activity, but shows a very small effect that seems of little real value.

Finally, study 21 P, a placebo-controlled study of 45 mg/kg/day in pediatric patients with partial seizures showed no effect at the same dose that was effective in Lennox-Gastaut Syndrome, failing to provide any kind of confirmatory evidence for the positive finding.

In sum, there is a single study showing a clear effect in Lennox-Gastaut \_\_\_\_\_ and great uncertainty as to the dose needed for the modest effect seen, with the two supportive studies suggesting 800 and 3200 mg/day (the latter study examined no other dose).

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We also do not consider the data adequate to support an indication for use of rufinamide in LGS. While study 22 is clearly positive and there is at least some other evidence of activity from the adult studies, we do not at this time consider the evidence sufficient to support approval based on the single study. In the past, approvals based on single studies in LGS have been supported by clear evidence of an effect on partial seizures in adults, generally at least 2 clearly positive studies. We do not find that support here.

For these reasons, we request that you perform at least one additional controlled trial, preferably in patients with partial seizures, that examines the effects of a relevant range of doses. We would be happy to discuss the design of such a study with you.

Because we have fundamental questions about the effectiveness of rufinamide, we do not believe we can draft product labeling at this time. Therefore, we have not included draft labeling with this letter.

### **Additional Clinical Comments**

1. There were a number of patients with clinically notable changes in some laboratory parameters noted at the final visit. The final disposition of such patients was not clear to us. Please re-examine the records for these patients and, for each patient, clearly state whether there was follow-up on the abnormal lab value, the nature of the follow-up if one existed, and the final outcome if known.
2. Also, a clinically more meaningful evaluation of thyroid function tests suggesting a hypothyroid response should be submitted. For the different subgroups of patients in the safety database, please submit re-analyses of the proportions of patients who simultaneously experienced an increase in serum TSH and a decrease in serum thyroxine (T3, T4, free and bound) or vice versa by treatment.
3. We note that across controlled trials, 1% of rufinamide-treated patients experienced status epilepticus while none of the placebo-treated patients experienced SE. We ask that you further address this finding. As part of this discussion, for the 2 groups, please present the proportions of patients with a previous history of SE. Also, to further investigate the possibility that rufinamide might exacerbate epilepsy for a subgroup of patients, we ask that, for all dose groups in each controlled trial, you present graphs of the cumulative distribution functions (CDFs) for percent change in seizure frequency from baseline. Such graphs provide a visual understanding of a drug's efficacy across the range of possible outcomes. We ask that you also create such CDFs for appropriate pooled studies.
4. The theoretical possibility exists that a new AED would be effective only when used concomitantly with certain other AEDs, due to specific pharmacodynamic interactions. For some of your controlled trials, you have provided subgroup analyses of efficacy with concomitant AEDs. We ask that you provide such information for all your controlled trials, including the failed trial.
5. The results of Study E2080-A001-002, which examined QT intervals, found rufinamide to be associated with reduction of the QT interval ranging from approximately 2 to 20 msec. For this study (E2080-A001-002) and for the ECG data collected in the clinical trials, please provide outlier tables summarizing the number and percent of subjects with QT intervals in each of the following categories. We ask that you provide this table for each dose level and stratify by heart rate correction method.

#### Absolute QT:

- < 420 msec
- < 410 msec
- < 400 msec
- < 390 msec
- < 350 msec
- < 300 msec

QT Reduction from Baseline:

QT interval decreases < 5 msec from baseline  
QT interval decreases < 10 msec from baseline  
QT interval decreases < 15 msec from baseline  
QT interval decreases < 20 msec from baseline

**Clinical Pharmacology**

You should evaluate the in vitro P-gp inhibition potential of rufinamide.

**Non-Clinical Comments**

1. We note that the rat carcinogenicity study is inadequate.

As you know, the high dose male and the mid- and high-dose female groups experienced excessive decreases in body weight relative to controls, resulting in reduced ability to detect potential carcinogenic effects. We believe that the body weight effect was likely exacerbated by unpalatability of the feed. Based on estimates of plasma AUCs, we note that the plasma exposures in the low dose females and the mid-dose males (the groups that did not suffer excessive weight loss) were not sufficiently greater than those achieved in humans to provide confidence that the tumorigenic potential of rufinamide has been adequately assessed at clinically relevant exposures. We further note evidence in your application suggesting that similar doses could be administered by gavage without the excessive body weight effects observed with dietary administration.

Were we convinced that rufinamide provides a significant clinical benefit, we might be persuaded that the rat study could be repeated in Phase 4. We do ask that you address the possibility that an adequate 2-year study in rats could be conducted using gavage dosing. The need for and the timing of the conduct of a repeat study will depend upon your response to this letter.

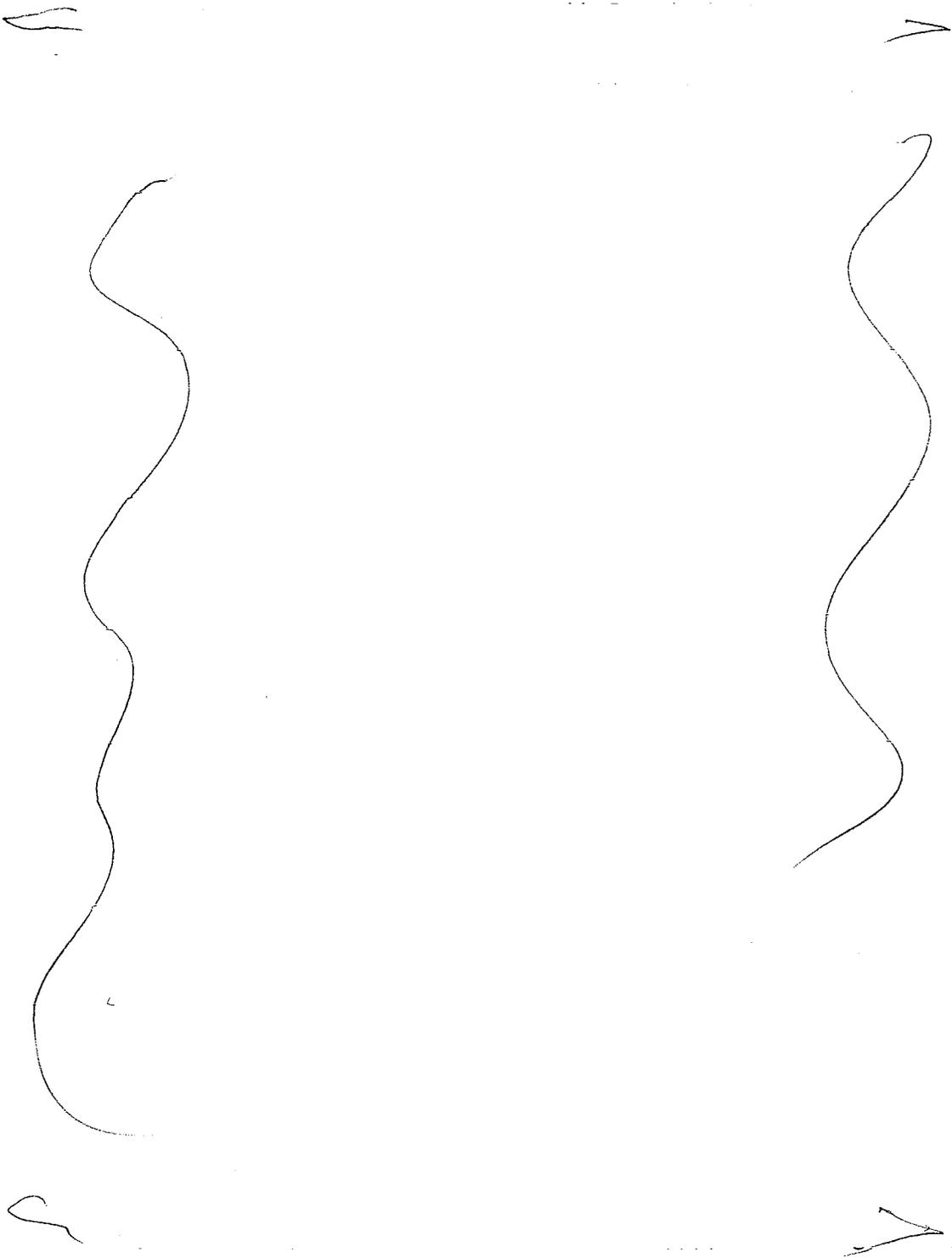
2. Several critical nonclinical studies do not conform to current standards and are, therefore, inadequate: a) the in vivo micronucleus assay in rat did not evaluate the recommended 2000 micronucleated polychromatic erythrocytes per animal, b) the rat fertility study evaluated too few male animals (12/group) and did not employ 1:1 mating, and c) the rabbit embryofetal development study did not evaluate a maternally toxic high dose. These studies need to be repeated (cf. OECD Guidelines for the Testing of Chemicals, Guideline 474; Guideline for Industry: Detection of Toxicity to Reproduction for Medicinal Products ICH-S5A).

3. The finding of decreased whole and regional brain weights in the juvenile rat study should be further investigated, e.g., using expanded neurohistopathology and brain morphometry.

4. The developmental age range studied in juvenile dogs was inadequate. A dog study in which dosing is initiated at an earlier age (corresponding to the clinical age range) needs to be conducted, and bone growth and density and brain development (using expanded neurohistopathology) should be evaluated in addition to the standard toxicity endpoints. There is particular concern regarding developmental effects on bone and brain based on the bone tumor findings in the mouse carcinogenicity study and the

brain weight effects in the juvenile rat study. You are encouraged to submit a protocol for review and comment prior to initiation of the study.

Trade name and Carton/Container Labeling



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A. GENERAL COMMENTS

1. We note that you propose \_\_\_\_\_  
We recommend using contrasting colors, boxing, or other means to differentiate these three strengths.
2. Ensure that the established name is at least 1/2 the size of the proprietary name to be in accordance with 21 CFR 201.10(g)(2).
3. Decrease the prominence of the net quantity statement so that it is less prominent than the strength. Additionally, relocate the net quantity so that it is not in close proximity to the strength. We have seen medication errors resulting from confusion between the net quantity and strength where they are located in close proximity to each other. The proprietary name, established name, and strength should be the most prominent information on the labels and labeling.

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B. CONTAINER LABELS

See GENERAL COMMENTS A1 through A3.

C. UNIT DOSE BLISTER LABELS

See GENERAL COMMENT A1.

D. CARTON LABELING

1. See GENERAL COMMENTS A1 through A3.
2. Revise the net quantity statement \_\_\_\_\_

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When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
  - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

- Present tabulations of the new safety data combined with the original NDA data.
  - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
  - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
  4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
  5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
  6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
  7. Provide English translations of current approved foreign labeling not previously submitted.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact Courtney Calder, PharmD, Regulatory Project Manager, at (301) 796-1050.

Sincerely,

*{See appended electronic signature page}*

Robert Temple, MD  
Office Director  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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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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Robert Temple  
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