

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-911

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-911

NDA APPROVAL

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

Dear Mr. Zuccarini,

Please refer to your new drug application (NDA) dated November 17, 2005, received November 17, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Banzel (rufinamide) Tablets, 100, 200, and 400 mg.

We acknowledge receipt of your submissions dated February 29, April 1 and 11, May 8, July 22 and 25, August 5, 19, 20, 25, and 28, September 10, 15, 22, and 25, October 10, 16, 17, and 23, and November 3, 7, and 10, 2008.

The February 29, 2008 submission constituted a complete response to our September 15, 2006 action letter.

This new drug application provides for the use of Banzel (rufinamide) for adjunctive therapy of seizures associated with Lennox-Gastaut syndrome.

We have completed our review of this application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the FDCA to authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain

purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify the unexpected serious risks of the potential for QT shortening in the setting of concomitant medications that may also have a QT shortening effect, the inhibitory effect of Banzel (rufinamide) on P-gp, and adverse effects on postnatal growth and development.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to identify these unexpected serious risks.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess this unexpected serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following clinical trial.

1. Conduct additional analyses to further examine the effect of Banzel (rufinamide) on the QT interval, specifically studying its effect in patients receiving concomitant medications that may also shorten the QT interval. For clinical trials AE/ET1 and CRUF331-0022 (and any other trials in which patients were treated with medications other than rufinamide and in which QT data was collected), please provide the following:
 - a. The baseline (pre-treatment) mean QT interval (as measured by all three correction methods) in rufinamide-treated patients receiving concomitant drugs believed to shorten the QT interval (listed below) and in patients without such concomitant medications.
 - b. The mean on-treatment QT interval (again by all three correction methods) for rufinamide-treated patients receiving concomitant drugs believed to shorten the QT interval and in patients without such concomitant medications.

Conduct the same analysis for sodium channel blocking drugs. These drugs are also listed below.

QT-SHORTENING DRUGS:

1. Digoxin (Lanoxin ®, Digitek ®, Lanoxicaps ®)
2. Lamotrigine (Lamictal ®)
3. Ranolazine (Ranexa ®)
4. Mexiletine (Mexitil ®)
5. Magnesium

SODIUM CHANNEL BLOCKING DRUGS:

1. Procainamide (Pronestyl ®, Procan ®, Procanbid ®)
2. Disopyramide (Norpace ®)
3. Tocainide (Tonocard ®)
4. Mexiletine (Mexitil ®)
5. Phenytoin (Phenytek ®, Dilantin ®, Eptoin ®, Epanutin ®)
6. Flecainide (Tambocor ®, Almarytm ®, Apocard ®, Ecrinal ®, and Flécaine ®)

7. Propafenone (Rythmol SR ®, Rytmonorm ®)
8. Moricizine
9. Lidocaine
10. Propofol
11. Carbamazepine (Tegreto ®, Biston ®, Calepsin ®, Carbatrol ®, Epitol ®, Equetro ®, Finlepsin ®, Sirtal ®, Stazepine ®, Telesmin ®, Teril ®, Timonil ®, Epimaz ®, Degranol ®)
12. Amitriptyline (Elavil ®, Tryptanol ®, Endep ®, Elatrol ®, Tryptizol ®, Trepiline ®, Laroxy ®, Saroten ®, Triptyl ®)
13. Imipramine (Antideprin ®, Deprenil ®, Deprimin ®, Deprino ®, Depsonil ®, Dynaprin ®, Eupramin ®, Imipramil ®, Irmin ®, Janimine ®, Melipramin ®, Surplix ®, Tofranil ®)
14. Haloperidol (Aloperidin ®, Bioperidolo ®, Brotopon ®, Dozic ®, Duraperidol ®, Einalon ®, Eukystol ®, Haldol ®, Halosten®)
15. Chlorpromazine
16. Digoxin (Lanoxin ®, Digitek ®, Lanoxicaps ®)
17. Metoclopramide (Maxolon ®, Reglan ®, Degan ®, Maxeran ®, Primperan ®, Pylomid ®)
18. Isoproterenol

Final Report Submission: by January 2009

In addition, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following studies.

2. Conduct an *in vitro* metabolism study to characterize the potential serious safety risk of the inhibitory effect of Banzel (rufinamide) on P-gp.

Protocol Submission: by June 2009
Study Start Date: by August 2009
Final Report Submission: by December 2009

3. Conduct a juvenile dog toxicology study to identify the unexpected serious risk of adverse effects on postnatal growth and development.

Protocol Submission: by June 2009
Study Start Date: by September 2009
Final Report Submission: by January 2011

Submit the protocols to your IND 35,534 with a cross-reference letter to this NDA 21-911. Submit all final reports to your NDA 21-911. Use the following designators to prominently label all submissions, including supplements, relating to these postmarketing studies as appropriate:

- **Required Postmarketing Protocol under 505(o)**
- **Required Postmarketing Final Report under 505(o)**
- **Required Postmarketing Correspondence under 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to

report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

Title IX, Subtitle A, Section 901 of FDAAA amends the FDCA to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). This provision took effect on March 25, 2008.

In accordance with section 505-1 of FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Banzel (rufinamide) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Banzel (rufinamide). FDA has determined that Banzel (rufinamide) has serious risks of which patients should be made aware because information concerning the risks could affect patients' decisions to use Banzel (rufinamide). In addition, patient labeling could help prevent serious adverse effects related to the use of these products. Banzel (rufinamide) may increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Banzel (rufinamide).

Your proposed REMS, submitted on October 24, 2008, in an electronic communication, is approved. The REMS consists of the Medication Guide included with this letter and the timetable for submission of assessments of the REMS included in your October 24, 2008 submission.

Your assessment of the REMS should include an evaluation of:

- a. Patients' understanding of the serious risks of Banzel (rufinamide)
- b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
- c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

Prominently identify submissions containing REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission:

- **NDA 21-911 REMS ASSESSEMENT**
- **NEW SUPPLEMENT FOR NDA 21-911**
- **PROPOSED REMS MODIFICATION**

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical to the enclosed labeling (text for the package insert). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 21-911."

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

CARTON AND IMMEDIATE CONTAINER LABELS

Please refer to our correspondence, dated September 3, 2008, requesting that the following revisions be made to the labels:



Submit final printed carton and container labels that are identical to the submitted carton and immediate container labels, except with the revisions listed above, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 21-911.**" Approval of this submission by FDA is not required before the labeling is used.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) 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

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

Rufinamide was not referred to an Advisory Committee for review because it is not the first in its class (antiepileptic drugs), an evaluation of the safety data did not reveal particular safety issues that were unexpected for this class, and the results of the efficacy trial in Lennox-Gastaut Syndrome combined with data from studies in partial seizures did not pose concerns for the use of rufinamide for Lennox-Gastaut Syndrome.

If you have any questions, call Susan Daugherty, Regulatory Project Manager, at (301) 796-0878.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Office Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Labeling

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

/s/

Robert Temple
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