DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST

NDA 021911

Eisai, Inc.
Attention: C. Michael Doroshuk, RAC
Director, Global Regulatory Affairs
300 Tice Boulevard
Woodcliff Lake, NJ 07677

Dear Mr. Doroshuk:

Reference is made to your October 27, 2009 Proposed Pediatric Study Request for Banzel (rufinamide).

This study plan involves the potential use of Banzel® (rufinamide) in the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in pediatric patients of 2 to less than 4 years of age whose seizures are inadequately controlled.

Lennox-Gastaut syndrome (LGS) is one of the most severe forms of childhood epilepsy. The syndrome is rare, with an annual incidence 0.2 to 2.8 per 10,000 births in European countries, but because it persists, LGS has a prevalence that increases to 2.6 per 10,000 children at 10 years of age, when it represents 5-10% of all childhood epilepsies. LGS usually appears in children between the ages of 2 and 8 years (the onset peaks between 3 and 5 years), but occasionally has its onset in older children and some of its symptoms can appear earlier than 2 years. LGS persists into adulthood in a large number of patients and has a significant morbidity and mortality.

The standard of care for the treatment of seizures associated with LGS involves beginning with pharmacological monotherapy and then typically progressing to combination therapy using a variety of well established or newer antiepileptic drugs (AEDs). Pharmacologic agents approved for the treatment of seizures associated with LGS include lamotrigine, rufinamide, topiramate, felbamate, and clonazapam. Other agents are used off-label. Despite the availability of multiple therapeutic options, treatment is usually unsatisfactory and the long-term prognosis for children with LGS is very poor.

Rufinamide has been approved for the adjunctive treatment of seizures associated with LGS in patients aged 4 to 30 years based on a double-blind, placebo-controlled trial (CRUF331 0022) in a population of patients with seizures of LGS despite "optimal" treatment . This study demonstrated significant superiority of rufinamide over placebo for all primary efficacy variables: percentage change in total seizure frequency; percentage change in tonic-atonic seizure frequency; and the seizure severity rating. Subjects in the rufinamide-treatment group experienced a 32.7% median reduction in total seizure frequency per 28 days relative to the Baseline Period, compared to an 11.7% median reduction for the placebo-treatment group (p=0.0015). An improvement in seizure severity was observed in 53.4% of

rufinamide-treated subjects compared to 30.6% of placebo-treated subjects (p=0.0041). The median percentage change in tonic-atonic seizure frequency per 28 days was significantly higher for rufinamide-treated subjects (42.5) than for placebo-treated subjects (1.4) (p<0.0001).

A controlled trial to establish effectiveness in the ≥2 to 4 years old group is not necessary, as the effectiveness demonstrated in the original trial in the older pediatric population can be extrapolated to the younger patients because this disorder is physiologically similar in the younger group. A pharmacokinetic and safety trial is, however, required to support approval in this younger age group. We are not requesting studies in patients with partial onset seizures because the completed clinical trials of partial seizure treatment in adults did not show effectiveness and a controlled study of partial seizure treatment in the pediatric population showed a complete absence of treatment effect.

To obtain needed pediatric information on Banzel, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the study described below.

- *Clinical studies:*

  Study 1: An open-label design, multicenter study to evaluate the safety and pharmacokinetics of adjunctive rufinamide treatment over a six-month period in pediatric patients ≥2 to <4 years of age with inadequately controlled Lennox-Gastaut syndrome (LGS).

- *Objective of the study:*
  - to evaluate the overall safety and tolerability of rufinamide in the target population
  - to evaluate the age group specific pharmacokinetics of rufinamide
  - to establish a tolerable dosage regimen that will produce plasma levels in this population similar to that in the population in whom rufinamide is currently recommended.

- *Patients to be Studied:*

  - *Age group in the study to be performed*: Patients ≥2 to <4 years old, with at least 25% of patients in the age range ≥2 to ≤ 3 years.

  - *Number of patients to be studied:* Enrollment of at least 50 or greater as needed to fulfill pharmacokinetic patient subsets defined by age (see first bullet).

  - *Safety:* At least 50 patients with exposures within the determined therapeutic range.

  - *Pharmacokinetics:* The study must enroll sufficient number of patients to target a 95% confidence interval (CI) within 60% and 140% of the point estimate for the geometric mean estimates of clearance for rufinamide in patients taking concomitant inducers, inhibitors, and neutral antiepileptic drugs (AEDs).

  - *Representation of Ethnic and Racial Minorities:* The study must include adequate (i.e., proportionate to disease population) representation of children of ethnic and racial

minorities. If you are not able to enroll an adequate number of these patients, you must provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- *Study endpoints:*

  - *Pharmacokinetic Endpoints:* Pharmacokinetic parameters such as CL, Vd, AUC, and Cavgss must be evaluated using sparse sampling. The pharmacokinetic parameters must be compared to previous data from patients >4 years of age. The timing of blood samples must be such that the effect of concomitant AEDS on rufinamide pharmacokinetics can be characterized.

  - *Safety Endpoints:* Safety outcomes must include a standard evaluation of safety parameters, to include clinical chemistry, hematology parameters, amylase and lipase, performed on all treated subjects. ECG's must also be performed to monitor for QT shortening and other cardio-electrophysiological effects, one recording at baseline and 3 duplicate at a sampling point corresponding to Cmax after achieving steady state rufinamide levels. Treatment-emergent adverse events must be summarized by presenting incidence of adverse events. Height, weight and head circumference must also be monitored using standardized methodology at baseline and at the end of rufinamide treatment interval. Descriptive summary statistics (mean plus standard deviation, median, and range) of the laboratory, and vital signs, and changes from baseline must be evaluated.

    Plasma concentrations of rufinamide should be checked at the time of significant undesirable effect.

    Review of Adverse Events (AEs) must be performed at each visit (Baseline, week 2, 4, 8, 16, and 24); laboratory tests must be performed at Screening, Baseline, and weeks 2, 4, 8, 16 and 24.

    While all adverse events must be reported, patients must be actively monitored for the following adverse events: pancreatitis, liver toxicity, blood dyscrasias, skin reactions, hypersensitivity reactions, EKG and cardiovascular events, neuropsychiatric effects, and significant changes in growth and development.

- *Known Drug Safety concerns and monitoring:*
  - Somnolence, fatigue and coordination abnormalities
  - QT shortening
  - Multi-Organ Hypersensivity Reactions
  - Leukopenia
  - Pancreatitis

- *Extraordinary results:* In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must

contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- *Drug information:*

  - dosage form: an age appropriate dosage formulation must be used.
  - route of administration: oral
  - regimen: an appropriate regimen, including titration, should be employed to achieve the stated objective of the study. The rate of titration should depend upon tolerability. Dosage may be titrated back based upon tolerability.

    Use an age-appropriate formulation in the study described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

    In accordance with section 505A(e)(2), if

    1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population studied (i.e., receives approval);
    2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
    3) you have not marketed the formulation within one year after the Agency publishes such notice,

    the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

    If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

    Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

- *Labeling that may result from the study*: You must submit proposed pediatric labeling to incorporate the findings of the study. Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that Banzel is safe and effective, or whether such study results are inconclusive in the studied pediatric population or subpopulation, the labeling must include information about the results of the study. Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study.

- *Format and types of reports to be submitted*: You must submit a full study report (which has not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the report must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

  Under section 505A(d)(2)(B) of the Act, when you submit the study report, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

  Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the FDA website at http://www.fda.gov/CDER/REGULATORY/ersr/Studydata.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072349.pdf.

- *Timeframe for submitting the study report:* The above study report must be submitted to the Agency on or before November 14, 2015. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you

are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

  Furthermore, if you agree to conduct the study, but have not submitted the study report on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit the protocol for the above study to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

A report of the study must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORT - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

In accordance with section 505A(k)(1) of the Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric study conducted in response to this Written Request within 210 days of submission of your study report. These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e. complete or partial response);
2. the status of the application (i.e. withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, complete response); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the

submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

If you have any questions, call Jacqueline Ware, Pharm.D., Senior Regulatory Project Manager, at (301) 796-1160.

Sincerely,

{See appended electronic signature page}

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

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
08/05/2011