DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202834

NDA APPROVAL

Eisai, Inc.
Attention: Heather A. Bradley, MPH
Senior Manager, Regulatory Affairs
155 Tice Boulevard
Woodcliff Lake, NJ 07677

Dear Ms. Bradley:

Please refer to your New Drug Application (NDA) dated December 22, 2012, received December 22, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for FYCOMPA (perampanel) Tablets 2mg, 4mg, 6mg, 8mg, 10mg, 12mg.

We acknowledge receipt of your amendments dated: May 25, 2011; June 16, 2011; June 22, 2011; June 27, 2011; June 30, 2011; July 7, 2011; July 12, 2011; July 19, 2011; August 5, 2011; September 12, 2011; October 18, 2011; January 17, 2012 (2); February 6, 2012 (2); February 9, 2012; February 16, 2012; March 21, 2012; March 23, 2012; March 30, 2012; April 11, 2012; April 19, 2012; April 20, 2012; April 30, 2012; May 1, 2012; May 10, 2012; May 21, 2012; June 7, 2012; June 21, 2012 (2); July 2, 2012 (2); July 5, 2012; July 13, 2012 (2); July 16, 2012; July 27, 2012; July 30, 2012; August 6, 2012 (2); August 10, 2012; August 14, 2012; August 20, 2012 (2); August 21, 2012; September 5, 2012; September 10, 2012; September 17, 2012; September 27, 2012; and October 16, 2012.

This new drug application provides for the use of FYCOMPA (perampanel) Tablets for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older.

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

CONTROLLED SUBSTANCE SCHEDULING

The final scheduling of this product under the Controlled Substances Act is currently proceeding, but not yet complete as of the date of this letter. We remind you that on May 25, 2011, and again on December 22, 2011, you agreed not to market this drug until the Drug Enforcement Administration has made a final scheduling decision. We further note that, when the scheduling is finalized, you will need to make appropriate revisions to the package insert, the patient package insert and the carton and immediate-container labels through supplementation of your

NDA. This would include the statements detailing the scheduling of Fycompa in the labeling, as required under 21 CFR 201.57(a)(2) and (c)(10)(i).

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on October 16, 2012, 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 (June 2008)." 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 202834**." Approval of this submission by FDA is not required before the labeling is used.

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.

ADVISORY COMMITTEE

Your application for FYCOMPA (perampanel) Tablets was not referred to an FDA advisory committee because the clinical study design is similar to previously approved products in the class.

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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages birth to one month of age because necessary studies are impossible or highly impracticable. Studying the effects of treatment in neonates with seizures is not feasible due to difficulties in characterizing the type of seizures in neonates and accurately quantifying the frequency of such seizures. Neonatal seizures also have different pathophysiology than seizures that occur in older children and respond differently to antiepileptic drugs.

We are deferring submission of your pediatric study for ages one month to less than 12 years of age for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. The required studies are listed below.

1932-1 A pharmacokinetic study in pediatric patients with partial-onset seizures aged 1 month to < 24 months. At least 2 maintenance dose levels of FYCOMPA (perampanel) should be evaluated to characterize pharmacokinetic parameters following multiple administration of oral perampanel. Pharmacokinetic data can be obtained and analyzed using either conventional pharmacokinetics methods with intensive sampling or using a population PK approach by collecting sparse samples. Subjects should be balanced among age cohorts. Effort should also be made to balance the gender distributions within each age cohort.

Final Protocol Submission:	February 2014
Core Study Completion:	January 2016
Extension Study Completion	November 2016
Final Core Report Submission:	July 2016
Final Extension Report Submission:	May 2017

1932-2 A pharmacokinetic study in pediatric patients with partial-onset seizures aged 2 to < 12 years. At least 2 maintenance dose levels of perampanel should be evaluated to characterize pharmacokinetic parameters following multiple administration of oral FYCOMPA (perampanel). Pharmacokinetic data can be obtained and analyzed using either conventional pharmacokinetic methods with intensive sampling or using a population PK approach by collecting sparse samples.

Subjects should be balanced among age cohorts. Effort should also be made to balance the gender distributions within each age cohort.

Final Protocol Submission:	November 2011
Core Study Completion:	November 2013
Extension Study Completion:	September 2014
Final Core Report Submission:	May 2014
Final Extension Report Submission:	March 2015

1932-3 A prospective, randomized, controlled, double-blind, efficacy and safety study of FYCOMPA (perampanel) in children ages 2 years to < 12 years for the adjunctive treatment of partial onset seizures with a long term safety extension. The primary efficacy endpoint during the controlled phase will examine seizure frequency based upon diary data. Safety will be evaluated during the controlled phase and long term extension.

Final Protocol Submission:	February 2014
Core Study Completion:	February 2017
Extension Study Completion:	September 2017
Final Core Report Submission:	August 2017
Final Extension Report Submission:	March 2018

1932-4 Deferred pediatric study under PREA: A prospective, randomized, controlled, double-blind, efficacy and safety study of FYCOMPA (perampanel) for the adjunctive treatment of partial onset seizures in children ages 1 month to < 4 years with a long term safety extension. The primary efficacy endpoint during the controlled phase will examine seizure frequency based upon Video/EEG data. Safety will be evaluated during the controlled phase and long term extension.

Final Protocol Submission:	April 2016
Core Study Completion:	October 2018
Extension Study Completion:	September 2019
Final Core Report Submission:	July 2019
Final Extension Report Submission:	March 2020

Submit the protocols to your IND 068368, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies 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 submissions "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

We note that you have fulfilled the pediatric study requirement for ages 12 to 17 years for this application.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes 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.

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 an unexpected serious risk of the potential for drug interactions due to the potential for metabolism of perampanel by CYP1A2, 2B6, 2C8, 2C9, 2C19, and 2D6; an unexpected serious risk of the potential for drug interactions due to metabolism of perampanel by non-P450 enzymes; or the unexpected serious risk of the potential for drug interactions due to the effect of perampanel on CYP2B6.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1932-5 *In vitro* study to characterize the contributions of CYP1A2, 2B6, 2C8, 2C9, 2C19 and 2D6 to perampanel metabolism.

The timetable you submitted on October 18, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	January 2013
Study Completion:	June 2013
Final Report Submission:	August 2013

1932-6 *In vitro* study to characterize the contributions of non-CYP enzymes to perampanel metabolism. The non-CYP enzymes to be evaluated should be justified and agreed upon by the Agency prior to initiating the study. The requirement for this study will depend on the results of PMR 1932-5.

The timetable you submitted on October 18, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	August 2013
Study Completion:	April 2014
Final Report Submission:	April 2014

1932-7 An *in vitro* study in human liver microsomes to evaluate the effects of a range of concentrations of perampanel (e.g., up to 30 µM and including a clinically relevant concentration of ~3 µM) on CYP2B6 activity using a recommended CYP2B6 probe substrate per the FDA Guidance for Drug-Drug Interactions.

The timetable you submitted on October 18, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	January 2013
Study Completion:	June 2013
Final Report Submission:	August 2013

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess two important safety concerns: 1) the safety of higher doses needed in patients on enzyme-inducing anti-epileptic drugs, specifically the risk of known serious psychiatric and behavioral adverse effects and neurologic effects, including dizziness, gait disturbance, somnolence, and other effects of FYCOMPA (perampanel) and 2) the potential for serious withdrawal effects when FYCOMPA (perampanel) is withdrawn abruptly.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1932-8 A prospective, multiple dose, randomized, controlled, double-blind, safety and efficacy trial of FYCOMPA (perampanel) as adjunctive treatment of partial onset seizures when high doses of Fycompa are added to concomitant treatments in adults on CYP34A inducing antiepileptic drugs (phenytoin, carbamazepine, and oxcarbazepine). The trial will include a long term safety extension. Safety will be evaluated during the controlled phase and long term extension. Safety endpoints will include serious psychiatric and behavioral reactions, and neurologic effects. The efficacy endpoint during the controlled phase will examine seizure frequency based upon diary data. Trial dosages must be selected to produce exposure similar to that experienced by patients receiving 8 and 12 mg of FYCOMPA (perampanel) daily who were on non-inducing concomitant anti-epileptic drugs.

The timetable you submitted on October 18, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	September 2013
Trial Completion:	March 2017
Final Report Submission:	September 2017

1932-9 A prospective human physical dependence trial in patients. The subjects should be titrated to the approved therapeutic dose of FYCOMPA (perampanel) of 8-12 mg, and maintained at this dose for an appropriate amount of time. At the end of the treatment, the drug should be abruptly withdrawn. The trial should be

adequately designed to allow differentiation of direct drug toxicity from true withdrawal symptoms.

The timetable you submitted on October 18, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	September 2013
Trial Completion:	March 2017
Final Report Submission:	September 2017

Please allow for adequate time for Agency review and comment on the protocols prior to the final protocol submission dates.

Submit the protocols to your IND 068368, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, 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.

REQUESTED PHARMACOVIGALENCE

We request that you provide expedited reporting and quarterly reports on the following post-marketing adverse events: 1) tendon and ligament rupture, 2) cholelithiasis and pancreatitis. The quarterly reporting should include a cumulative analysis of these events with comparison to the expected background rates.

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 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
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, 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 Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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 http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, contact Stephanie N. Parncutt, M.H.A., Regulatory Health Project Manager, at (301) 796-4098.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE(S):
Content of 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
10/22/2012