DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208277

NDA APPROVAL

Eisai Inc.
Attention: Heather Bradley, MPH
Director, Global Regulatory Affairs
155 Tice Boulevard
Woodcliff Lake, NJ 07677

Dear Ms. Bradley:

Please refer to your New Drug Application (NDA) dated June 30, 2015, received June 30, 2015, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for FYCOMPA (perampanel) oral suspension.

This new drug application provides for the use of FYCOMPA (perampanel) oral suspension as adjunctive therapy for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy 12 years of age and older and as adjunctive therapy for the treatment of primary generalized tonic-clonic seizures in patients with epilepsy 12 years of age and older.

APPROVAL & LABELING

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.

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 *SPL Standard for Content of Labeling Technical Qs and As*, available 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 immediate container labels that are identical to the carton and immediate container labels submitted on March 10, 2016, 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 *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 208277**." 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.

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.

We are waiving the pediatric study requirement for this application from birth to less than 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 patients with epilepsy from 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 study required by section 505B(a) of the FDCA is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. The required study is listed below.

3076-1 A long-term, open-label, safety study of adjunctive therapy in patients from 1 month to less than 12 years of age with epilepsy. The purpose of this study is to evaluate the long-term safety of FYCOMPA (perampanel) as adjunctive therapy in the treatment of partial-onset seizures (ages 1 month to less than 12 years) or primary generalized tonic-clonic seizures in pediatric patients (ages 2 to less than 12 years). Doses for this study must be at or above those doses determined to be efficacious by Study 1932-4 (patients 1 month to less than 4 years of age with partial-onset seizures), Study 2922-1 (patients 2 to less than 12 years of age with

primary generalized tonic-clonic seizures), and the pharmacokinetic analyses used for the extrapolation of efficacy in pediatric patients 4 to less than 12 years of age with partial-onset seizures. This study may include subjects enrolled in the extension phases of Studies 1932-1, 1932-2, 1932-4, and 2922-1, and may be supplemented as necessary. A minimum of 100 patients must be exposed to study drug for one year at or above the dose or doses identified as effective. Subjects should be balanced among age cohorts to allow for adequate conclusions to be drawn.

Final Protocol Submission:	09/2016
Study Completion:	09/2021
Final Report Submission:	03/2022

We also refer to our approval letters for FYCOMPA (perampanel) tablets (NDA 202834) dated October 22, 2012, containing PREA studies 1932-1, 1932-2, and 1932-4; and dated June 19, 2015, containing PREA study 2922-1. Your deferred pediatric studies required by section 505B(a) of the FDCA for NDA 202834 are required postmarketing studies that also apply to NDA 208277. The required studies are listed below.

1932-1 A pharmacokinetic study in pediatric patients with partial-onset seizures from 1 month to less than 24 months of age. 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.

Extension Study Completion:	11/2016
Final Core Report Submission:	07/2016
Final Extension Report Submission:	05/2017
Deferred Final Extension Report Submission:	03/2022

1932-2 A pharmacokinetic study in pediatric patients with partial-onset seizures from 2 to less than 12 years of age. 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:	11/2011
Core Study Completion:	11/2013
Extension Study Completion:	09/2014

Final Core Report Submission:	05/2014
Final Extension Report Submission:	03/2015
Deferred Final Extension Report Submission:	07/2016

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 from 1 month to less than 4 years of age 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:	04/2016
Core Study Completion:	10/2018
Extension Study Completion:	09/2019
Final Core Report Submission:	07/2019
Final Extension Report Submission:	03/2020

2922-1 Conduct a multiple-dose pharmacokinetic (PK) and tolerability study to explore the range of tolerated doses of FYCOMPA (perampanel) in patients from 2 to less than 12 years of age with epilepsy. A sufficient proportion of subjects must be on background therapy that includes enzyme-inducing AEDs, such as carbamazepine, oxcarbazepine, or phenytoin, which are known to induce perampanel metabolism and decrease its plasma concentrations. PK data will be obtained using a sparse sampling approach. Sufficient PK and tolerability data must be generated from this study before conducting the efficacy and safety study, to inform the dose selection for that study. Sampling must be optimized to ensure adequate characterization of perampanel PK. Using information from the PK study, conduct an adequately powered, controlled, and blinded trial that examines the efficacy and safety of FYCOMPA (perampanel) in the treatment of primary generalized tonic-conic (PGTC) seizures in a pediatric population. Because PGTC seizures are less common in this age group, the study population may include the full range of pediatric patients (e.g., patients less than 17 years old). This study must include a minimum of 60% of patients that are 2 to 12 years of age. Information from the PK/tolerability part of this postmarketing requirement, and its resulting protocol-specified dosing, should be provided to the Division prior to the initiation of the efficacy trial, and agreements on dosing should be reached with the Division before the efficacy trial is initiated.

Final Protocol Submission (PK and tolerability study):	11/2011
Study Completion (PK and tolerability study):	05/2015
Final Report Submission (PK and tolerability study):	06/2016
Final Protocol Submission (Efficacy and safety study)	09/2016
Study Completion (Efficacy and safety study):	09/2020
Final Report Submission (Efficacy and safety study):	03/2021

Submit the protocols to your IND 112515, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as new drug applications (NDAs) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from this study. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

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 assess 1) the safety of higher doses needed in patients on enzyme-inducing antiepileptic drugs, specifically the known risk of serious psychiatric and behavioral adverse effects and neurologic effects, including dizziness, gait disturbance, somnolence, and other effects of FYCOMPA (perampanel); and will not be sufficient to assess 2) the potential for serious withdrawal effects when FYCOMPA (perampanel) is withdrawn abruptly.

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.

Finally, we have determined that only a clinical trial, rather than a nonclinical or observational study, will be sufficient to assess these risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following clinical trials for NDA 208277 for FYCOMPA (perampanel) oral suspension. These required clinical trials are the same as those required under NDA 202834 for FYCOMPA (perampanel) tablets:

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 (perampanel) 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 antiepileptic drugs.

The timetable you submitted to NDA 202834 on October 18, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	09/2013
Trial Completion:	03/2017
Final Report Submission:	09/2017

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 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 to NDA 202834 on October 18, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	09/2013
Trial Completion:	03/2017
Final Report Submission:	09/2017

We refer you to your submission dated April 9, 2014, containing proposed revised milestones for PMR 1932-8 and 1932-9 above. You requested revised milestones because of the time required for you and the Agency to come to agreement on the study design for NDA 202834. The proposed milestones were:

1932-8	Final Protocol Submission:	03/2015
	Trial Completion:	09/2018
	Final Report Submission:	03/2019
1932-9	Final Protocol Submission:	03/2015
	Trial Completion:	09/2018
	Final Report Submission:	03/2019

Additionally, we refer you to your submission dated June 4, 2015, containing proposed revised milestones for PMR 1932-8 and 1932-9 above. You requested revised milestones because of delay in designing, and reaching agreement with FDA on, the final protocol for Study 403 for NDA 202834. The proposed milestones were:

1932-8	Final Protocol Submission:	09/2016
	Trial Completion:	09/2018
	Final Report Submission:	03/2019
1932-9	Final Protocol Submission:	09/2016
	Trial Completion:	09/2018
	Final Report Submission:	03/2019

We acknowledged the proposed milestones in our "Acknowledge Revised Postmarketing Requirement Milestones" letters issued to NDA 202834, dated August 15, 2014, and January 21, 2016.

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.

Please note that the original schedule serves as the basis for defining the status of a postmarketing requirement, even if a revised schedule has been proposed. Your annual progress reports, required under 21 CFR 314.81(b)(2)(vii), must include both the original and revised schedules, and the reason for the revision. Because these submission dates differ from those specified in the milestones listed in the October 22, 2012, approval letter for NDA 202834, we consider these postmarketing requirements delayed. This status is posted on the FDA Postmarketing Requirement and Commitments website: http://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm.

REQUESTED PHARMACOVIGALENCE/PHARMACOVIGILENCE

We request that you provide expedited reporting and quarterly reports on the following postmarketing 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, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

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. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. 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.

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

Sincerely,

{See appended electronic signature page}

Billy Dunn, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation 1
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/

WILLIAM H Dunn
04/29/2016