DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202834/S-014
NDA 208277/S-002

SUPPLEMENT APPROVAL
RELEASE FROM POSTMARKETING REQUIREMENT
NEW POSTMARKETING REQUIREMENT

Eisai, Inc.
Attention: Adi Lampmann, RQAP-GCP
Associate Director, Global Regulatory Strategy
155 Tice Boulevard
Woodcliff Lake, NJ 07677

Dear Ms. Lampmann:

Please refer to your Supplemental New Drug Application (sNDAs), dated and received March 28, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for FYCOMPA (perampanel) tablets and oral suspension.

These Prior Approval supplemental new drug applications provide for the expansion of the use of Fycompa (perampanel) tablets and oral suspension for the treatment of partial onset seizures (POS), with or without secondarily generalized seizures, to include patients 4 years of age and older.

APPROVAL & LABELING

We have completed our review of these supplemental applications. They are 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 Prescribing Information, and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

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/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

RELEASE FROM POSTMARKETING REQUIREMENT

We note that these supplements contain study reports that are responsive to the following postmarketing requirements listed in our October 22, 2012, and April 29, 2016, approval letters, for Fycompa tablets (NDA 202834) and Fycompa oral suspension (NDA 208277), respectively.

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

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:	September 2016
Study Completion:	September 2021
Final Report Submission:	March 2022

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 2017
Trial Completion:	September 2019
Final Report Submission:	March 2020

We have reviewed your submissions and have determined that you are released from the above postmarketing requirements for the following reasons:

1. The Pediatric Research Equity Act (PREA) postmarketing requirements (1932-4 and 3076-1) have been partially addressed by studies conducted with Fycompa tablets and oral suspension in the age group of 4 to less than 12 years and will be reissued for the age group of at least 1 month to less than 4 years for these two dosage forms.

2. The postmarketing requirement (1932-9) is no longer needed because the following language has been added to Section 9.3 (Dependence) of the Fycompa Prescribing Information (per the agreement noted in the December 15, 2017, Preliminary Comments):

   FYCOMPA may cause dependence and withdrawal symptoms that may include anxiety, nervousness, irritability, fatigue, lethargy, asthenia, mood swings, and insomnia.

Postmarketing requirements 1932-4 and 3076-1 are being replaced by the new postmarketing requirements described below. Additionally, with the approval of these supplements (NDA 202834/S-014, NDA 208277/S-002), Fycompa tablets and oral suspension are appropriately labeled for use in pediatric patients aged 4 years to less than 12 years.

REQUIRED PEDIATRIC ASSESSMENTS

Under the 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.

Your deferred pediatric studies required under section 505B(a) of the FDCA 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)(C) of the FDCA. These required studies are listed below.

3496-1 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 < 2 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. In the long term extension component, a minimum of 25 patients must be exposed to perampanel for 6 months at or above the dose or doses identified as effective.

Final Protocol Submission:	March 2021
Core Study Completion:	March 2024
Extension Study Completion:	March 2025
Final Core Report Submission:	December 2024
Final Extension Report Submission:	December 2025

3496-2 A pharmacokinetic (PK) study in children with epilepsy who are 2 years to less than 4 years of age to characterize pharmacokinetic parameters following multiple administrations of oral perampanel. This study should include patients taking perampanel with and without concomitant CYP3A4 inducers.

Final Protocol Submission:	September 2019
Study Completion:	June 2021
Final Report Submission:	December 2021

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDAs 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 REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

Finally, we remind you that there are postmarketing requirements listed in the October 22, 2012, and April 29, 2016, approval letters, for Fycompa tablets (NDA 202834) and Fycompa oral suspension (NDA 208277), respectively, that remain open:

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:	March 2022

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 2017
Trial Completion:	September 2019
Final Report Submission:	March 2020

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the Prescribing Information to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
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).

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. 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.

REPORTING REQUIREMENTS

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

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

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
Prescribing Information
Medication Guide

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WILLIAM H Dunn
09/27/2018