CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208277Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Billy Dunn, MD
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	208277
Applicant Name	Eisai, Inc.
Date of Submission	6/30/15
PDUFA Goal Date	4/30/16
Proprietary Name/ **Established (USAN) Name**	Fycompa/perampanel
Dosage Forms/Strength	Oral suspension/0.5 mg per mL
Proposed Indication(s)	Adjunctive therapy for the treatment of partial-onset seizures with or without secondarily generalized seizures and primary generalized tonic-clonic seizures in patients with epilepsy 12 years of age and older
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Natalie Getzoff, MD
Statistical Review	N/A
Pharmacology Toxicology Review	N/A
CMC/OBP Review	Martha Heimann, PhD
Microbiology Review	N/A
Clinical Pharmacology Review	Xinning Yang, PhD
OPDP	Aline Moukhtara, RN, MPH
OSI	N/A
CDTL Review	Angela Men, MD, PhD
OSE/DMEPA	Deborah Myers, RPh, MBA
OSE/DDRE	N/A
OSE/DRISK	N/A
OMP/DMPP	Sharon Williams, MSN, BSN, RN
PMHS	Donna Snyder, MD; Leyla Sahin, MD
SEALD	N/A
Other	Alicja Lerner, MD, PhD (CSS); Karen Long, PharmD

OND=Office of New Drugs
OPDP=Office of Prescription Drug Promotion
OSE=Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
CDRH=Center for Devices and Radiologic Health
PMHS=Pediatric and Maternal Health Staff
DDRE=Division of Drug Risk Evaluation
DRISK=Division of Risk Management
OMP=Office of Medical Policy
DMPP=Division of Medical Policy Programs
SEALD=Study Endpoints and Labeling Development
CSS=Controlled Substance Staff

1. Introduction

Fycompa (perampanel) is an approved drug product as adjunctive therapy for the treatment of partial-onset seizures (POS) with or without secondarily generalized seizure and primary generalized tonic-clonic seizures (PGTC) in patients with epilepsy aged 12 years and older.

Eisai submitted the current application to support approval of a new oral suspension (0.5 mg per mL) formulation for the same indications and dosages as are currently approved. Tablets are the currently marketed formulation.

The members of the review team recommend approval and I will briefly discuss their major findings.

2. Background

Fycompa was initially approved in 2012. The current marketed and labeled dose is 2 to 12 mg tablets once daily with individual dosing adjusted based on clinical response.

3. CMC/Device

Dr. Heimann recommends approval. I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of no more than 24 months for the unopened bottle and the product should be used within 90 days after opening the bottle or discarded. She notes that a categorical exclusion may be granted. There are no recommended postmarketing commitments or requirements. There are no other CMC issues.

4. Nonclinical Pharmacology/Toxicology

N/A

5. Clinical Pharmacology/Biopharmaceutics

The sponsor submitted the report of study E2007-A001-048, a pharmacokinetic (PK) crossover study intended to demonstrate bioequivalence of 12 mg doses of perampanel given as oral suspension and tablet formulations. Dr. Yang reviewed these data in detail and found that the oral suspension formulation demonstrated bioavailability comparable to the tablet formulation and that the two formulations can be used interchangeably. As summarized by Dr. Norm Hershkowitz, clinical Team Leader, and Dr. Men, Cross-Discipline Team Leader for

this application, fasted Cmax and AUC and fed AUC of the two formulations were bioequivalent, whereas fed Cmax of the oral solution was 23% lower than the tablet after a single dose. As described in detail in Dr. Yang's review, population PK modeling demonstrated that in a multiple-dosing scenario at steady state, Cmax and AUC of the two formulations were bioequivalent when switched from one to the other in the various combinations of fed and fasting, including in the "worst case" scenarios of switching from tablet administered under fasted state to suspension given with food and vice versa. Cmin was also evaluated and there were no clinically meaningful differences. As Dr. Hershkowitz notes, switching comparisons are of greatest relevance when considering maintenance therapy at steady state, as previous determinations regarding efficacy and safety are predominantly based on maintenance dosing at steady state. Dosing initiation involves weekly titration up to maintenance doses and small changes during the treatment initiation period are unlikely to be clinically interpretable. Dr. Yang finds no obstacles to approval. Dr. Hershkowitz and Dr. Men agree. I concur with the conclusions reached by Dr. Yang, Dr. Hershkowitz, and Dr. Men that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

N/A

7. Clinical/Statistical-Efficacy

Efficacy is addressed by extrapolation from the efficacy demonstrated for the approved tablet formulation, supported by the clinical pharmacology information described above.

8. Safety

Safety is addressed primarily by extrapolation from the safety profile of the approved tablet formulation, supported by the clinical pharmacology information described above. Additional safety data were reviewed in detail by Dr. Getzoff and summarized by Dr. Hershkowitz and Dr. Men. When compared with the known safety profile of perampanel as reflected in its approved labeling, they find no evidence of any new or worsened safety issue. Overall, the safety profile of perampanel, as assessed in the clinical pharmacology studies (the study described above along with information from an additional smaller study), is consistent with its known safety profile. Dr. Hershkowitz notes a series of discussions with Dr. Lerner concerning the possibility of withdrawal seizures as a manifestation of perampanel dependence, as discussed in Dr. Lerner's review. As Dr. Hershkowitz notes, he and Dr. Getzoff examined this issue and do not believe these are part of a specific withdrawal syndrome as seizures in epilepsy patients may occur upon withdrawal of treatment. Dr. Hershkowitz also notes that the approved label includes a warning regarding withdrawal of antiepileptic drugs concerning the potential for increased seizure frequency. Dr. Hershkowitz feels the approved labeling adequately addresses this issue at this time. I agree. Dr.

Hershkowitz also describes the results of a postmarketing review performed by Dr. Long of reports of psychosis and delirium. Dr. Long concludes that there is a likely causal relationship with perampanel and that labeling should be updated to reflect this finding. Dr. Hershkowitz agrees and we will discuss this with the sponsor. I concur with the conclusions reached by Dr. Getzoff, Dr. Hershkowitz, and Dr. Men that there are no outstanding safety issues that preclude approval.

9. Advisory Committee Meeting

N/A

10. Pediatrics

As Dr. Snyder notes, perampanel was discussed at a pediatric review committee (PeRC) meeting on February 24, 2016, and PeRC agreed with the Division that the product had been fully assessed for pediatric patients 12 years of age and older for the POS and PGTC indications and on the plan for waivers and deferrals for the younger pediatric populations (b) (4) (b) (4) This plan is consistent with our recent conclusion that extrapolation of efficacy for antiepileptic drugs from successful adult efficacy trials to pediatric patients 4 years and older with POS was acceptable. Although, As Dr. Snyder notes, no new postmarketing requirements are needed for the oral formulation (b) (4) (b) (4) (b) (4) Dr. Snyder's review contains a discussion of the various postmarketing requirements.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

Labeling negotiations with the sponsor have been completed and the sponsor has accepted all recommended changes.

13. Decision/Action/Risk Benefit Assessment

I agree with the review team that this application should be approved.

The sponsor has provided substantial evidence of effectiveness for the use of perampanel oral solution as adjunctive therapy for the treatment of partial-onset seizures with or without secondarily generalized seizures and primary generalized tonic-clonic seizures in patients with epilepsy 12 years of age and older based on extrapolation from the efficacy demonstrated for the approved tablet formulation, as supported by pharmacokinetic assessment. There are no new safety concerns associated with the use of perampanel oral solution in this population. There are no outstanding unresolved issues.

No new postmarketing requirements are needed for the oral formulation. The existing postmarketing requirements will be revised and updated to (b) (4) (b) (4) here are no other necessary postmarketing requirements or commitments.

Specific postmarketing risk management activities are not needed.

We have agreed with the sponsor on product labeling that describes the effectiveness and safety of perampanel oral solution as adjunctive therapy for the treatment of partial-onset seizures with or without secondarily generalized seizures and primary generalized tonic-clonic seizures in patients with epilepsy 12 years of age and older.

For these reasons, I will issue an approval letter for this application, to include the agreed-upon product 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