CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202834Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template for Fycompa
PMR # 1932-1

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: Pediatric Pharmacokinetic (b) (4) Study in Patients 1 month to < 24 months of age

PMR/PMC Schedule Milestones:		
	Final protocol Submission Date:	February 2014
	Core Study Completion Date:	January 2016
	Extension Study Completion Date:	November 2016
	Final Core Report Submission Date:	July 2016
	Final Extension Report Submission Date:	May 2017

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☒ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☒ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

This is a PREA study.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The aim of the study is to characterize the PK of perampanel following multiple administrations in patients with partial-onset seizures aged 1 month to < 24 months old, (b) (4) of perampanel in this pediatric population.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☒ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template for Fycompa
PMR # 1932-2

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: Pediatric Pharmacokinetic (b) (4) Study in Patients aged 2 to <12 years.

PMR/PMC Schedule Milestones:		
	Final protocol Submission Date:	November 2011
	Core Study Completion Date:	November 2013
	Extension Study Completion Date:	September 2014
	Final Core Report Submission Date:	May 2014
	Final Extension Report Submission Date:	March 2015

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☒ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☒ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

This is a PREA study.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The aim of the study is to characterize the PK of perampanel following multiple administrations in patients with partial-onset seizures aged 2 to < 12 years old, (b) (4) of perampanel in this pediatric population.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☒ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template for Fycompa
PMR # 1932-3

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: A prospective, randomized, controlled, double-blind, efficacy and safety study of FYCOMPA (perampanel) in children ages 2 years to < 12 years for the adjunctive the 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.

PMR/PMC Schedule Milestones:		
	Final protocol Submission Date:	February 2014
	Core Study Completion Date:	February 2017
	Extension Study Completion Date	September 2017
	Final Core Report Submission Date:	August 2017
	Other: Final Extension Report Submission Date:	March 2018

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

This is a PREA requirement. A waiver has been given for children under 1 month due to the impractical nature of studying a population that is very small in number. A deferral has been granted for those ages 1 month to< 12 years of age; it is appropriate for a PMR because the drug is about to be approved and the pediatric study has not been completed. It is appropriate for a PMR because the drug is about to be approved for children 12 years and older and adults and pediatric studies in the younger patients have not been performed.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of this study is to evaluate the safety and efficacy of Fycompa for the adjunctive the treatment of partial onset seizures in the ages 2 years to < 12 years. Efficacy and short term safety will be studied in the controlled phase and long term extension.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☒ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A prospective, randomized, controlled, double-blind, efficacy and safety study of FYCOMPA (perampanel) in children ages 2 years to < 12 years for the adjunctive the 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.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
Continuation of Question 4

☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

PMR/PMC Development Template for Fycompa
PMR # 1932-4

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: 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.

PMR/PMC Schedule Milestones:

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

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

This is a PREA requirement. A waiver has been given for children under 1 month due to the impractical nature of studying a population that is very small in number. A deferral has been granted for those patients ages 1 month to< 12 years of age. It is appropriate for a PMR because the drug is about to be approved for children 12 years and older and adults and studies in the younger pediatric population have not been performed. This study examines patients 1 month to <4 years old.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of this study is to evaluate the safety and efficacy of Fycompa in the adjunctive the treatment of partial onset seizures in the ages 1 month < 4 years. Efficacy and short term safety will be studied in the controlled phase, and long term safety will be studied in the long term extension.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☒ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

PMR/PMC Development Template for Fycompa
PMR # 1932-5

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: *In vitro* study to characterize the contributions of CYP1A2, 2B6, 2C8, 2C9, 2C19 and 2D6 to perampanel metabolism.

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	January 2013
Study/Clinical trial Completion Date:	June 2013
Final Report Submission Date:	August 2013
Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☒ Theoretical concern
- ☐ Other

There is a theoretical concern about the contributions of specific non-CYP3A4/5 metabolic enzymes to perampanel metabolism. This request is made based on the FDA guidance "Drug Interaction Studies —Study Design, Data Analysis, and Implications for Dosing and Labeling Recommendations" http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf. It can be conducted post-marketing as the label will refer to the uncertainty regarding the involvement of other P450 enzymes in perampanel metabolism.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

CYP3A4/5 have been shown in vitro to metabolize perampanel, and may be the major enzyme responsible for the formation of several metabolites of perampanel (M1, M3, M4 and M19). In humans ketoconazole, a strong CYP3A inhibitor, only increased perampanel AUC by 20%, suggesting the limited role of CYP3A in perampanel metabolism, although carbamazepine decreased perampanel AUC by 67% with a corresponding 3-fold increase in perampanel clearance, exceeding the anticipated contribution from CYP3A4/5 alone. Carbamazepine is a broad-spectrum enzyme inducer which can induce not only CYP3A but also CYP2C8, CYP2C9, CYP2C19, CYP2B6 and non-CYP enzymes. Overall, the *in vivo* studies indicated that metabolic enzymes other than CYP3A may be involved in perampanel metabolism.

As described above, there was apparent discrepancy between *in vitro* findings and *in vivo* results, although there were some limitations to the in vitro studies, as well as a mass balance study so that the relative contribution of each known metabolite to overall perampanel metabolism remains unknown. Thus, if a metabolic enzyme is responsible for the formation of one or multiple metabolites and represents the major metabolic pathway for perampanel, a potent inhibitor of this enzyme would be expected to significantly increase the plasma perampanel concentrations and lead to adverse drug interactions.

The goal of this study is to elucidate the contributions of CYP enzymes (other than CYP3A4/5) e.g., characterization of the enzymes involved in the formation of all identified metabolites of perampanel (including the oxidative metabolite M5). Pending study results, further in vivo study may be considered.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☒ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☒ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☒ Other
Nonclinical drug metabolism study

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____
(signature line for BLAs)

PMR/PMC Development Template for Fycompa
PMR # 1932-6

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: *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.

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	August 2013
Study/Clinical trial Completion Date:	April 2014
Final Report Submission Date:	April 2014
Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☒ Theoretical concern
- ☐ Other

There is a theoretical concern about the contributions of non-CYP3A4/5 metabolic enzymes, including non-CYP enzymes, to perampanel metabolism. This request is made based on the FDA guidance "Drug Interaction Studies —Study Design, Data Analysis, and Implications for Dosing and Labeling Recommendations"
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

In vivo studies indicate that metabolic enzymes other than CYP3A may be involved in perampanel metabolism. The role of non-P450 enzymes has not yet been evaluated. The goal of this study is to elucidate the contributions of non-CYP enzymes to perampanel metabolism. Pending study results, further in vivo study may be considered.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☒ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☒ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____
(signature line for BLAs)

PMR/PMC Development Template for Fycompa
PMR # 1932-7

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: 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.

PMR/PMC Schedule Milestones:		
	Final protocol Submission Date:	January 2013
	Study/Clinical trial Completion Date:	June 2013
	Final Report Submission Date:	August 2013
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☒ Theoretical concern
- ☐ Other

There is a theoretical concern regarding the potential for perampanel to stimulate CYP2B6 activity at clinically relevant concentrations that have not been previously studied in vitro. This request is based on the FDA guidance "Drug Interaction Studies —Study Design, Data Analysis, and Implications for Dosing and Labeling Recommendations" http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

An in vitro study using human liver microsomes showed that perampanel at a concentration of 30 µM increased CYP2B6 activity to 2.2 ~ 3.6 fold of control. The sponsor did not evaluate other concentrations of perampanel. The steady-state maximum plasma concentration (Cmax,ss) of perampanel at a maintenance dose of 8 mg is projected to be 1.89 µM. If perampanel is shown to significantly stimulate the CYP2B6 activity at this therapeutic concentration, there will be a concern for reduced effectiveness of CYP2B6 substrates (e.g., buproprion) as a result of decreased systemic exposure of these drugs when co-administered with perampanel. The goal of this study is to evaluate effect of perampanel on CYP2B6 activity at clinically relevant concentrations. Based on the results of this *in vitro* study, further *in vivo* study may be needed.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☒ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____
(signature line for BLAs)

PMR/PMC Development Template for Fycompa
PMR # 1932-8

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: Safety and Efficacy trial in patients taking enzyme inducing AEDs

PMR/PMC Schedule Milestones:		
	Final protocol Submission Date:	September 2013
	Study/Clinical trial Completion Date:	March 2017
	Final Report Submission Date:	September 2017
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☒ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

The optimal dose of Fycompa in patients taking enzyme-inducing antiepileptic drugs (AEDs) was not evaluated in the NDA. The labeling will describe the reduced effect on seizure rates in the presence of these drugs and will discuss the need to monitor for clinical response and tolerability when these drugs are introduced or withdrawn.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The optimal dose of Fycompa in patients taking enzyme-inducing antiepileptic drugs (AEDs) was not evaluated in the NDA. The risk is that enzyme inducing drugs decrease exposure to perampanel relative to exposure as well as effect on seizure rates observed in patients taking non-enzyme inducing antiepileptic drugs. If doses are increased to compensate for this, there is a possibility that adverse events could occur, either due to formation of an as yet uncharacterized metabolites or due to increased and unpredicted exposure to perampanel without a complete understanding of the doses that are safe or effective.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☒ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
Continuation of Question 4

☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)
A prospective human physical dependence study in healthy volunteers

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template for Fycompa
PMR # 1932-9

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: A prospective human physical dependence trial in patients.

PMR/PMC Schedule Milestones:		
	Final protocol Submission Date:	September 2013
	Study/Clinical trial Completion Date:	March 2017
	Final Report Submission Date:	September 2017
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☒ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☒ Theoretical concern
   - ☐ Other

The abuse potential of the drug is part of the drug's safety assessment. According to 21 CFR 314.50(d)(5)(vii), if the drug has a potential for abuse, the sponsor must submit a description and analysis of studies or information related to abuse of the drug. FYCOMPA is a new molecular entity (NME). The Sponsor has not provided or adequately collected organized withdrawal symptoms data in order to perform a complete assessment of physical dependency of FYCOMPA. Although a withdrawal syndrome is suggested by the data provided in the NDA, this data is flawed. While this will likely not effect the scheduling of the drug, this information is needed to better inform prescribers of this potential adverse reaction.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

There is a risk for withdrawal after abrupt discontinuation of Fycompa. In the submitted NDA, withdrawal symptom questionnaires were not given to all patients who were participating in clinical trials. Therefore it is requested that a prospective physical dependency trial in patients be conducted.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☒ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)
A prospective human physical dependence study in healthy volunteers

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SALLY U YASUDA
10/22/2012

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	**FYCOMPA (perampanel) tablets for oral use**
Applicant	Eisai
Application/Supplement Number	NDA 202834 S1
Type of Application	Original NDA
Indication	"Adjunctive therapy for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older"
Established Pharmacologic Class[1]	non-competitive AMPA glutamate receptor antagonist
Office/Division	ODEI/DNP
Division Project Manager	Stephanie Parncutt
Date FDA Received Application	December 22, 2011
Goal Date	October 22, 2012
Date PI Received by SEALD	October 22, 2012
SEALD Review Date	October 22, 2012
SEALD Labeling Reviewer	Eric Brodsky
SEALD Division Director	Laurie Burke

PI = prescribing information

[1] The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO:** The PI **does not meet** the requirement for this item **(deficiency)**.
- **YES:** The PI **meets** the requirement for this item **(not a deficiency)**.
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Highlights (HL)

GENERAL FORMAT

YES 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

YES 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

NO 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment: *Contraindications header is shifted to the right.*

YES 4. White space must be present before each major heading in HL.

Comment:

NO 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment: *Neurologic Effects in Warnings and Precaution, Boxed Warning.*

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*****

Selected Requirements of Prescribing Information

• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment:

Product Title

YES 10. Product title in HL must be **bolded.**

Comment:

Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning

YES 12. All text must be **bolded**.

Comment:

YES 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

Selected Requirements of Prescribing Information

YES 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." in *italics* and centered immediately beneath the heading.

Comment:

YES 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

YES 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths

YES 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

Comment:

N/A 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement

YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment:

Revision Date

YES 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.

Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment:

YES 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

NO 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

NO 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)

12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

YES 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, "*[see Warnings and Precautions (5.2)]*".

Comment:

N/A 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

YES 42. All text is **bolded**.

Comment:

YES 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

YES 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

YES 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

YES 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

Comment:

N/A 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Patient Counseling Information

YES 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment:

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/s/

ERIC R BRODSKY
10/22/2012

LAURIE B BURKE
10/22/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

M E M O R A N D U M

October 18, 2012

From:	Nadia Hejazi, M.D., Medical Officer Pediatric and Maternal Health Staff
Through:	Hari Cheryl Sachs, M.D., Team Leader Lynne Yao, MD, OND Acting Associate Director Pediatric and Maternal Health Staff
Document ID Number:	NDA 202834
Sponsor:	Eisai Inc.
Drug:	FYCOMPA (perampanel)
Proposed Indication:	Adjunctive therapy in patients 12 years and older with partial seizures with or without secondarily generalizated seizures
Dosage form and route of administration:	Oral tablets 2, 4, 6, 8, 10 and 12 mg
Dosing regimen:	Once daily
PeRC Date:	August 29, 2012
Consult Question:	The Division of Neurology is requesting PMHS assistance with PeRC review preparation.

PMHS worked with DNP in preparing paperwork for the review of the pediatric plan by the Pediatric Review Committee (PeRC) which took place on August 29, 2012. Perampanel is a new molecular entity that is a selective non-competitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor antagonist which will be indicated for the treatment of partial onset seizures in patients 12 years and older based on three randomized double blind, placebo-controlled trials. These trials included approximately 100 adolescent patients exposed to perampanel.

PeRC agreed with the Division's plan to waive the required studies under PREA in pediatric patients less than 1 month because studies are impossible or highly impractical, and to defer studies in patients 1 month to < 12 years of age because the product is ready for approval in adults and adolescents (see Appendix 1 for PeRC minutes).

PMHS has also participated in labeling meetings for perampanel and provided comments for the Pediatric Use Section 8.4. Please refer to the final labeling negotiated with the sponsor for specific details.

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/s/

HARI C SACHS
10/19/2012

LYNNE P YAO
10/22/2012

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: October 22, 2012

To: Stephanie Parncutt
Regulatory Project Manager
Division of Neurology Products (DNP)

From: Quynh-Van Tran, PharmD, BCPP
Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)

cc: Meeta Patel, PharmD
Regulatory Review Officer
Division of Consumer Drug Promotion

Mathilda Fienkeng, PharmD
Acting Team Leader
DPDP

Subject: OPDP's comment for NDA 202834
Fycompa (perampanel) tablets

Background

Thank you for the opportunity to review the proposed Prescribing Information (PI) for Fycompa (perampanel) tablets (FDA dated version 10/17/2012). Please see attached PI with our comments incorporated therein. If you have any questions, please contact Quynh-Van Tran at (301) 796-0185 or Quynh-Van.Tran@fda.hhs.gov.

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/s/

QUYNH-VAN TRAN
10/22/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Memorandum

Date:	October 17, 2012
Reviewer:	Loretta Holmes, BSN, PharmD Division of Medication Error Prevention and Analysis
Team Leader:	Irene Z. Chan, PharmD, BCPS Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Fycompa (Perampanel) Tablets 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg
Application Type/Number:	NDA 202834
Applicant:	Eisai, Inc.
OSE RCM #:	2012-82

***** This document contains proprietary and confidential information that should not be released to the public.*****

Contents

1 INTRODUCTION

This review evaluates the revised container labels, professional sample blister pack labeling and professional sample carton labeling for Fycompa (Perampanel) Tablets submitted on October 16, 2012 (see Appendix A). The Division of Medication Error Prevention and Analysis (DMEPA) previously reviewed the revised container labels, professional sample blister pack labeling and professional sample carton labeling under OSE Review 2012-82, dated October 9, 2012.

2 MATERIALS REVIEWED

DMEPA reviewed the following labels and labeling.

- Revised container labels submitted on October 16, 2012
- Professional sample blister pack labeling submitted on October 16, 2012
- Professional sample carton labeling submitted on October 16, 2012

Additionally, our recommendations in OSE Review 2012-82, dated October 9, 2012 were reviewed to assess whether the aforementioned labels and labeling adequately address our concerns from a medication error perspective.

3 CONCLUSION AND RECOMMENDATIONS

Review of the revised documents show that the Applicant implemented our recommendations and we find the revisions acceptable. Therefore, we have no further recommendations.

If you have further questions or need clarifications, please contact Laurie Kelley, OSE Project Manager, at 301-796-5068.

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/s/

LORETTA HOLMES
10/17/2012

IRENE Z CHAN
10/18/2012

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Consumer Drug Promotion

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: October 11, 2012

To: Stephanie Parncutt
Regulatory Project Manager
Division of Neurology Products (DNP)

From: Meeta Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion, Division of Consumer Drug Promotion (formerly known as Division of Drug Marketing, Advertising, and Communications [DDMAC])

Subject: NDA 202834
DCDP Comments for draft MG for FYCOMPA (perampanel) tablets for oral administration

DCDP has reviewed the proposed Medication Guide (MG) for FYCOMPA (perampanel) tablets. We have reviewed DMPP's comments from 10/03/12 and agree with those changes. We offer the following additional comments at this time.

Thank you for the opportunity to comment on the proposed MG.

If you have any questions or concerns, please contact Meeta Patel at 301-796-4284 or meeta.patel@fda.hhs.gov.

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/s/

MEETA N PATEL
10/18/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Memorandum

Date:	October 9, 2012
Reviewer:	Loretta Holmes, BSN, PharmD Division of Medication Error Prevention and Analysis
Team Leader:	Irene Z. Chan, PharmD, BCPS Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Fycompa (Perampanel) Tablets 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg
Application Type/Number:	NDA 202834
Applicant:	Eisai, Inc.
OSE RCM #:	2012-82

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Contents

1 INTRODUCTION

This review evaluates the revised container labels and professional blister pack and carton labeling for Fycompa (Perampanel) Tablets submitted on July 2, 2012 (see Appendix A). The Division of Medication Error Prevention and Analysis (DMEPA) previously reviewed the proposed container labels and professional sample blister pack and carton labeling under OSE Review 2012-82, dated June 19, 2012.

2 MATERIALS REVIEWED

- Revised container labels submitted on July 2, 2012
- Professional sample blister pack labeling submitted on July 2, 2012
- Professional sample carton labeling submitted on July 2, 2012
- Sample (hand mock-up) of the professional sample blister card and carton

Additionally, our recommendations in OSE Review 2012-82 were reviewed to assess whether the aforementioned labels and labeling adequately address our concerns from a medication error perspective.

3 CONCLUSIONS AND RECOMMENDATIONS

Review of the revised documents show that the Applicant implemented our recommendations. However, additional changes were made to the container labels, blister pack and carton labeling that were not requested by DMEPA. Some of these changes included the use of two font colors in the proprietary name and a new layout for the tablets in the professional sample blister pack. We have identified vulnerabilities in the revised labels and labeling that may lead to medication errors. Therefore, we have the following recommendations which should be conveyed to the Applicant and implemented prior to approval.

3.1 COMMENTS TO THE APPLICANT

A. Container Labels and Professional Sample Blister Pack and Carton Labeling

1. The proprietary name is presented in two different font colors “Fyc” in red and “compa” in green. Consequently, the use of two colors highlights and may bring prominence to only a portion of the name. Additionally, the use of two colors in the proprietary name incorporates similar principles of TallMan lettering which is typically reserved for differentiating known look-alike established name pairs or in rare circumstances proprietary name pairs to help reduce the risk of name confusion resulting in medication error. Since Fycompa is not a name that has been involved in name confusion, the differentiating color of the “Fyc” portion and the “compa” portion is inappropriately applied. Therefore, the name should be presented with the use of one unique color, preferably not one of the colors utilized for strength differentiation.
2. In the proprietary name, the bottom of the letter “c” is extended with the use of a sweeping graphic line that intersects the letter “o” and sweeps above the

letters that follow. The graphic line represents intervening matter that decreases the readability of the proprietary name. Remove this sweeping graphic line from the proprietary name.

3. The "Rx Only" statement is too prominent. Debold the "Rx Only" statement.
4. The "CV" symbol is too prominent. Decrease the size of the "CV" symbol.

B. Professional Sample Blister Pack

We find the original layout of the tablets in a straight line to be less confusing and less error-prone as compared [redacted] (b) (4) We recommend the use of the original layout. However, if that is not feasible, we provide the following recommendations for the revised presentation.

1. Revise the statement [redacted] (b) (4) " to read "Take one tablet orally once daily at bedtime" for increased clarity.
2. The light green font used for the days of the week lack sufficient contrast against the green background. For days 1 through 7 font color, consider using the same light orange color that used for the 2 mg strength. For days 8 through 14 font color, consider using the same dark orange color that is used for the 4 mg strength. This may help to improve contrast and further help to differentiate the Week 1 and Week 2 regimens.
3. Add the instructions for removing the tablets from the blister pack to the left inside panel in order to have the instructions where they are more readily seen.
4. The 2-D artwork shows brackets around the tablets. Please clarify whether or not these represent actual physical barriers on the blister pack.

If you have further questions or need clarifications, please contact Laurie Kelley, OSE Regulatory Project Manager, at 301-796-5068.

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/s/

LORETTA HOLMES
10/09/2012

IRENE Z CHAN
10/09/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	October 03, 2012
To:	Russell Katz, MD, Director **Division of Neurology Products (DNP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Robin Duer, MBA, RN Patient Labeling Reviewer **Division of Medical Policy Programs, (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Review of Patient Labeling: Medication Guide
Drug Name (established name):	FYCOMPA (perampanel)
Dosage Form and Route:	Tablets for Oral Use
Application Type/Number:	NDA 202-834
Applicant:	Eisai, Inc.

1 INTRODUCTION

On December 22, 2011, Eisai Inc., re-submitted for the Agency's review a New Drug Application (NDA 202834) for FYCOMPA (perampanel) Tablets, indicated for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy, aged 12 years and older. NDA 202834 was originally submitted on May 25, 2011, but on July 21, 2011, the Agency issued a Refuse to File (RTF) letter.

This review is written in response to a January 02, 2012 request by the Division of Neurology Products (DNP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Medication Guide (MG) for FYCOMPA (perampanel) Tablets.

2 MATERIAL REVIEWED

- Draft FYCOMPA (perampanel) Medication Guide (MG) received on December 22, 2011, revised by the review division throughout the current review cycle, and received by DMPP on September 27, 2012
- Draft FYCOMPA (perampanel) Prescribing Information (PI) received on December 22, 2011, revised by the Review Division throughout the current review cycle, and received by DMPP on September 27, 2012
- Approved POTIGA (ezogabine) comparator labeling dated March 19, 2012

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the MG is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHAWNA L HUTCHINS
10/03/2012

LASHAWN M GRIFFITHS
10/03/2012

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: September 18, 2012

TO: Stephanie N. Parncutt, Regulatory Project Manager
Martin Rusinowitz, M.D., Medical Officer
Division of Neurology Products

FROM: Antoine El-Hage, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Leibenhaut, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 202-834

APPLICANT: Eisai, Inc.

DRUG: Fycompa® (Perampanel)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard review
INDICATION: Treatment of patients with partial–onset seizures
CONSULTATION REQUEST DATE: March 27, 2012
DIVISION ACTION GOAL DATE: October 22, 2012
PDUFA DATE: Not listed /assume to be October 22, 2012

I. BACKGROUND:

The Applicant, Eisai Inc., submitted a New Drug Application for the use of oral perampanel, an antiepileptic drug (AED), as an adjunctive therapy for the treatment of partial seizures in adults. A partial seizure is an episode of abnormal electrical activity that is the product of a lesion in some part of the cerebral cortex. These lesions may have been present since birth or earlier, or they may develop following head trauma, infections, stroke, and certain other conditions. Perampanel is not approved in the U.S. The sponsor claims that this antiepileptic drug is effective as adjunctive therapy for the treatment of partial seizure in patients, aged 12 years and above.

Investigational Drug

Perampanel, also known as E20007, is a first-in-class, highly selective noncompetitive antagonist for alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA). Clinical evidence suggests that AMPA receptors play a key role in several neurodegenerative disorders. Most epilepsy drugs target channel activity, but AMPA uses a different approach and focuses on excitatory damage. It is known that excessive activation of AMPA receptors damages brain cells by increasing the flow of calcium into the brain. This condition leads to seizures in patients. Perampanel works by inhibiting the excess activity of AMPA receptors, thus reducing the excitatory-inhibitory nerve imbalance caused in the brains of epilepsy patients which in turn helps in reducing damage to the brain cells and preventing seizures. The Applicant states that clinical studies do not suggest any significant safety concerns for the use of up to 12 mg/day of perampanel.

The Applicant submitted a new formulation for approval of perampanel as adjunctive therapy at 8 and 12 mg tablets in subjects with a diagnosis of simple partial seizures and complex partial seizures with or without secondarily generalized seizures. The Applicant is seeking approval of the new product by submitting data from two pivotal Protocols E2007-G000-304 and E2007-G000-305 to support approval of the pending application. The 2 doses of perampanel used in the two pivotal studies were 8 mg and 12 mg. Subjects took a maximum of six tablets daily for the duration of treatment. Subjects were up-titrated weekly in 2-mg increments to their randomized dose of 8 mg or 12 mg perampanel or placebo for 24 weeks.

Protocols E2007-G000-304 & E2007-G000-305 are essentially the same; therefore, a single description of key design features is presented.

Protocol E2007-G000-304 was a randomized, double-blind, placebo-controlled, parallel group phase 3 study with 3 treatment arms:

Placebo arm enrolled 125 subjects
8 mg perampanel arm enrolled 125 subjects
12 mg perampanel arm enrolled 125 subjects

The study consisted of three phases: pre-randomization phase, double-blind phase (titration period + maintenance period), and follow-up phase.

The primary objective of Study E2007-G000-304 entitled "A Double-Blind, Placebo-Controlled, Dose-Escalation, Parallel-Group to Evaluate the Efficacy and Safety of E2007 (perampanel) Given as Adjunctive Therapy in Subjects with Refractory Partial Seizure." was to evaluate the efficacy of 2 doses of perampanel (8 mg and 12 mg) in comparison to placebo given as adjunctive therapy in subjects with refractory partial seizures.

The secondary objectives were: 1) to assess safety and tolerability of adjunctive perampanel vs placebo in subjects with refractory partial seizures, and 2) to assess potential withdrawal symptoms of perampanel vs. placebo in subjects with refractory partial seizures.

The review division requested inspection of four clinical investigators (one domestic site and three foreign sites) for the pivotal protocols Study E2007-G000-304 and E2007-G000-305 because data from the protocols are considered essential to the approval process. These sites were targeted for inspection due to: 1) enrollment of a relatively large number of subjects and, for Dr. Batista's site, a large treatment effect and larger number of protocol violations, 2) domestic and foreign data show conflicting results pertinent to decision-making, and 3) the need to determine if sites conducted the trial ethically and were in compliance with GCP and local regulations.

II. RESULTS (by protocol/site):

Name of CI, site # and location	**Protocol and # of subjects**	**Inspection Dates**	**Final Classification**
Ramon Batista, M.D., MBA Dept. of Neurology University of Florida HSC/Jacksonville Tower one, Ninth floor 580 West Eight Street Jacksonville, FL 32209 Site# 5128	Protocol E2007-G000-304 Number of subjects: 13	5/21-29/2012	Pending (Preliminary classification VAI)
Jorge W. Lasso, M.D. Penafiel, Chief of Neurology Hospital Padre Alberto Hurtado Esperanza 2150 Santiago, Chile Site#1701	Protocol E2007-G000-304 Number of subjects: 22	8/6-8/2012	Pending (Preliminary classification NAI)
Wim Van Paesschen, M.D., Ph.D Neurologist, Chief of Clinic UZ Gasthuisberg (UZ Leuven) Neurology Herestraat 49 Leuven 3000, Belgium Site# 1303	Protocol E2007-G000-305 Number of subjects: 8	7/30-8/2/2012	Pending (Preliminary classification NAI)
Elinor Ben-Menachem, M.D., Ph.D Dept. of Clinical Neuroscience Division of Neurology Sahlgrenska Academy Sahlgren University Hospital 413 45 Göteborg, Sweden Site# 4501	Protocol E2007-G000-305 Number of Subjects 14	7/31-8/3/2012	Pending (preliminary classification NAI)

Key to Classifications
NAI = No deviations
VAI = Deviation(s) from regulations
OAI = Significant deviations for regulations. Data unreliable.
Pending = Preliminary classification based on e-mail communication from the field; the EIR has not been received from the field and complete review of EIR is pending.

Note: Observations noted below for the four sites are based on an e-mail communication from the field; the Establishment Inspection Report (EIR) has not been received from the field and complete review of the EIR is pending. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

1. **Ramon Batista, M.D.**
   Jacksonville, FL 32209

   a. What Was Inspected: This inspection was performed as a data audit for NDA 202-834. Study protocol E2007-G000-304: At this site, a total of 18 subjects were screened, and five subjects were reported as screen failures. Thirteen (13) subjects were randomized and eleven subjects completed the study. Review of the Informed Consent Documents, for 13 subjects verified that subjects signed informed consent prior to enrollment.

   The medical records/source data for 13 subjects enrolled were reviewed including drug accountability records, inclusion/exclusion criteria, vital signs, laboratory results, and adverse events. Source documents were compared to case report forms and data listings for primary efficacy endpoints and adverse events.

   b. **General observations/commentary:** At the conclusion of the inspection, a one item Form FDA 483 was issued to Dr. Batista. Our investigation found that the clinical investigator did not follow the protocol inclusion criteria.

   The protocol for Study E2007-G000-304 required that during the 6 week pre-randomization period, subjects must have had greater than or equal to 5 seizures per 6 week period, with 2 or more of the seizures per each 3 week period. Although Subject 51284005 met the criteria for the total number of seizures over the 6 week period, the subject had no seizures documented for the last 3 weeks of the pre-randomization period. The clinical investigator agreed with the inspectional finding in a letter dated June 6, 2012, in which he promised corrective measures to prevent recurrence of the situation. OSI finds his response acceptable

   The medical records reviewed disclosed no other adverse findings that would negatively impact the reliability of the data. With the exception of the item noted above, the records reviewed were found to be organized and the data verifiable. There were no known limitations to this inspection.

   c. Assessment of Data Integrity: Although regulatory violation was noted at Dr. Batista's site, the finding is not likely to significantly affect overall data integrity or

subject safety as they are considered isolated in nature. The data from Dr. Batista's site are considered reliable in support of the application.

2. **Jorge W. Lasso, M.D.**
   Santiago, Chile

   a. What Was Inspected: This inspection was performed as a data audit for NDA 202-834. Study E2007-G000-304: At this site, a total of 28 were screened, and six subjects were reported as screen failures. Twenty (22) subjects were randomized into the study, and 19 subjects completed the study. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed consent forms prior to enrollment.

   The medical records/source data for all subjects were reviewed including drug accountability records, vital signs, laboratory results, IRB records, prior and current medications, and inclusion/exclusion criteria. Source documents for 14 subjects were compared to data listings for primary efficacy endpoints and adverse events listing. In addition, the files for six subjects were reviewed in detail. There was no evidence of under-reporting of adverse events at this site. There were no known limitations to the inspection.

   b. General Observations/Commentary: At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Lasso. However, inspectional finding such as lack of telephone calls to subjects in-between visits were discussed with the clinical investigator at the conclusion of the inspection. The clinical investigator agreed that this was probably an oversight and sometimes the site staff were unable to contact the subjects.

   The medical records reviewed were verifiable based on the information available at the site. There were no known limitations to the inspection. There were no deaths and no evidence of under-reporting of adverse events. The study appears to have been conducted adequately, and the data generated by this site can be used to support the pending application.

   c. Assessment of Data Integrity: Although deviations were noted they are considered minor concerns and discrepancies. Thus, the data in support of clinical efficacy and safety at Dr. Lasso's site are considered reliable and appear acceptable in support of the pending application.

3. **Elinor Ben-Menachem, M.D., Ph.D.**
   413 45 Göteborg, Sweden

   a. What Was Inspected: This inspection was performed as a data audit for NDA 202-834. Study Protocol E2007-G000-305: At this site, a total 18 subjects were screened, two subjects reported as screen failures. Fourteen subjects were randomized into the study, and 12 subjects completed the study. Review of the Informed Consent Documents, for all subjects records reviewed, verified that all subjects signed consent forms prior to enrollment.

The medical records/source documents for 16 subjects were reviewed in depth, including drug accountability records, vital signs, IRB files, laboratory test results, inclusion/exclusion criteria, and use of concomitant medications. Source documents for subjects were compared to case report forms and data listings, to include primary efficacy endpoints and adverse events

b. General Observations/Commentary: The medical records reviewed were found to be in order and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Ben-Menachem. However the following items were discussed with the clinical investigator. The investigation found minor transcription errors in recording the number of seizures for Subject 45-5006 (3 vs 13). Subject 45-5016 had a Type–B seizure instead of Type-C. In addition, Subjects 4501-5010 and 4501-5012 signed the informed consent prior to IRB approval due to subsequently revised consent form document with minor changes, and the two subjects later signed the revised version. The review team considered the observations to be minor and to have had no impact on data acceptability. There were no known limitations to the inspection.

c. Assessment of Data Integrity: The data, in support of the clinical efficacy and safety at Dr. Menachem's site are considered reliable and appear acceptable in support of the pending application.

4. **W. Van Paesschen, M.D., Ph.D.**
Leuven, 3000 Belgium

a. What was Inspected: This inspection was performed as a data audit for NDA 202834. Study Protocol E2007-G000-305: At this site, a total nine subjects were screened and one subject was reported as a screen failure. Eight subjects were randomized into the study, four subjects completed the 1st phase of the study, and three subjects entered the extension phase of the study. Subjects withdrew from the study due to side effects (nausea and dizziness indicating that it reduced their quality of life). Review of the Informed Consent Documents, for all subjects records reviewed, verified that all subjects signed consent forms prior to enrollment.

The medical records/source documents for all subjects were reviewed including drug accountability records, vital signs, IRB files, laboratory test results, patient diaries, quality of life questionnaires, inclusion/exclusion criteria, and use of concomitant medications. Source documents were compared to case report forms and data listings, to include primary efficacy endpoint and adverse events.

b. General Observations/Commentary: At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Paesschen. The medical records reviewed were found to be in order, organized and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were no known limitations to the inspection. Our investigation found that Subjects 2 and 6 experienced clusters of seizures and both were withdrawn from the study.

c. Assessment of Data Integrity: The data generated in support of the clinical efficacy and safety at Dr. Van Paesschen's site are considered reliable and appear acceptable in support of the pending application.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Four clinical investigator sites were inspected in support of this application. The inspection of Drs. Lasso, Ben-Menachem, and Van Paesschen revealed no regulatory violations, and the pending classification for these inspections is No Action Indicated (NAI). The final classification for the above three clinical investigators will be determined upon review of the establishment inspection report (EIR). An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR. While regulatory violations were identified during the inspection of Dr. Batista, the findings are not likely to critically impact primary efficacy and safety analyses; therefore, OSI does not consider the effect on overall data integrity to be significant. The pending classification for the inspection of Dr. Batista is Voluntary Action Indicated (VAI). Overall, the data submitted from these four sites are considered reliable in support of the pending application.

{*See appended electronic signature page}*

Antoine El-Hage, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{*See appended electronic signature page}*

Susan Leibenhaut, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

{*See appended electronic signature page*}

Susan Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/s/

ANTOINE N EL HAGE
09/19/2012

SUSAN LEIBENHAUT
09/19/2012

SUSAN D THOMPSON
09/19/2012

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: Aug 30, 2012

To: Russell Katz, M.D., Director
Division of Neurology Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: Alicja Lerner, M.D., Ph.D., Medical Officer
Controlled Substance Staff

Subject: **NDA 202-834** Perampanel (Fycompa)
Indication: Treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older
Dosages: 2-, 4-, 6-, 8-, 10-, and 12-mg oral tablets
Sponsor: Eisai Medical Research, Inc.

Materials reviewed: NDA 202-834 re-submission is located in EDR (Dec 22, 2011)
Previous IND 68368

Table of Contents

I. Summary

A. Background

Perampanel, also known as E2007, (Fycompa) is an AMPA glutamate receptor antagonist and indirect antagonist of NMDA receptor and partial direct antagonist on NMDA receptors, first-in-

class, that is being developed for treatment of partial-onset seizures. The Sponsor performed 38 studies, 27 Phase 1, and 11 Phase 2, 3, and open-label extensions. The drug was also studied for Parkinson diseases, diabetic and post-herpetic neuropathic pain, migraine headache and multiple sclerosis. The application was initially refused-to-file, on July 21 2012.

Perampanel has a mechanism of action involving antagonism at an unknown allosteric site of the AMPA glutamate receptor and is now developed for treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy, aged 12 years and older.

Perampanel is a New Molecular Entity (NME), therefore, its abuse potential has to be fully characterized.

B. Conclusions:

(b) (4)

C. Recommendations:

(b) (4)

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/s/

ALICJA LERNER
08/30/2012

MICHAEL KLEIN
08/30/2012

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 28, 2012

TO: Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I

FROM: Sripal R. Mada, Ph.D.
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

Niraj Mehta, Ph.D.
GLP Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance (DBGC)
Office of Scientific Investigations (OSI)

William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIRs Covering NDA 202-834 FYCOMPA® (E2007 or Perampanel), 2 mg and 12 mg Tablets from Eisai, Inc., USA

At the request of the Division of Neurology Products (DNP), the Division of Bioequivalence and GLP Compliance inspected the following bioequivalence study:

E2007-A001-040: "A Randomized, open-label, crossover study to demonstrate bioequivalence between 6 × 2-mg tablets of perampanel and a single 12-mg tablet of perampanel in healthy subjects"

Clinical:

The inspection of the clinical portions of this study was conducted at **Cetero Research, Fargo, ND**, by Darren D. Holaday of ORA. Following the inspection (b) (4), no Form FDA-483 was issued.

Analytical:

The inspection of the analytical portions of this study was conducted at (b) (4) by (b) (4) (OSI), (b) (4) (OSI), and (b) (4) (ORA). Following the inspection (b) (4), Form FDA-483 was issued (**Attachment 1**). The firm's response was received at OSI on June 1, 2012 (**Attachment 2**).

The Form FDA-483 observation, (b) (4) response to the observations and our evaluation follow:

1. **Failure to document details of fresh calibrator sample preparation in the raw data during -20 and -70 degrees freezer stability studies in validation of the perampanel analytical method.**

In their response to the observation, (b) (4) explained that during the validation in November 2008, laboratory operations were documented as running entries in the chemist's notebook. (b) (4) practice used a "check-box" notation in the chemist's notebook, which referred to an SOP. However, (b) (4) failed to document complete sample processing events on their sample processing forms, and the detailed processing steps were not described in the SOP. Currently, (b) (4) documents all sample processing events in detail on forms.

In the opinion of the reviewers, accuracy of data generated from the -20^{0}C and -70^{0}C freeze-thaw stability experiment cannot be assured since (b) (4) failed to document complete details of sample processing. The "check-box" notation in the chemist's notebook does not confirm that the chemist followed SOP exactly.

2. **The identity of quality control (QC) samples used in the -20 and -70 degrees freeze-thaw stability experiment was not maintained by batch ID after QC sample preparation. All of the QC samples were handled by preparation dates, resulting in failure to record the QC sample batches used in validation of perampanel stability.**

(b) (4) acknowledged that the identity of the QC samples was not maintained by batch ID. Since several batches of QC samples were prepared on the same day and maintained in the same freezer, the freeze-thaw data cannot be related to specific batches of QCs and their handling.

In the opinion of the reviewers, accuracy of the data generated from the -20^{0}C and -70^{0}C freeze-thaw stability experiment cannot be assured.

3. Failure to maintain a freezer-log to record the sample removal and return from the freezer. Thus, identity and condition of QC samples used during stability experiments could not be verified.

In their response to Form FDA-483, (b) (4) acknowledged that QC sample retrieval and placement from freezer was not documented in a freezer log during these experiments. (b) (4) has since implemented a system to log all sample movements for future experiments.

Conclusion:

Following evaluation of the inspectional findings and (b) (4) response, the DBGC reviewers recommend the following:

- The accuracy of the data from the -20^{0}C and -70^{0}C freeze-thaw stability experiment cannot be assured since (b) (4) failed to document complete details of sample processing (see **Form FDA-483, items 1, 2, and 3**). (b) (4) needs to confirm the freeze-thaw stability at -20^{0}C and -70^{0}C by conducting a systematic study.

- The clinical and other analytical data from this study are acceptable for your review.

Sripal R. Mada, Ph.D.
Bioequivalence Branch, DBGC, OSI

Niraj Mehta, Ph.D.
GLP Branch, DBGC, OSI

Final Classifications:

NAI – Cetero Research, Fargo, ND
FEI: 1720861

(b) (4)

cc:
OSI/ (b) (4)
OSI/DBGC/ (b) (4)
OSI/DBGC/BB/ (b) (4)
OSI/DBGC/GLPB/Mehta
OND/ODE1/DNP/Katz/Parncutt
OCP/ (b) (4)
ORA/ (b) (4)
ORA/ (b) (4)
Draft: SRM 08/21/2012
Edit: NM 08/21/2012, MFS 08/22/2012
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/s/

SRIPAL R MADA
08/28/2012

NIRAJ MEHTA
08/28/2012

WILLIAM H TAYLOR
08/29/2012

Executive CAC
Date of Meeting: July 3, 2012

Committee: Abby Jacobs, Ph.D., OND IO, Acting Chair
Paul Brown, Ph.D., OND IO, Member
Linda Fossom, Ph.D., DPP, Alternate Member
Lois Freed, Ph.D., DNP, Supervisor
Christopher D. Toscano, Ph.D., DNP, Presenting Reviewer

Author of Draft: Christopher D. Toscano, Ph.D., DABT

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA #:	202-834
Drug Name:	FYCOMPA (perampanel, E2007)
Sponsor:	Eisai, Inc.; Woodcliff Lake, NJ

Background: FYCOMPA (perampanel, E2007) is an AMPA receptor antagonist being developed by Eisai for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older. Perampanel was negative in a battery of genetic toxicology studies (*in vitro* bacterial reverse mutation assay, *in vitro* mouse lymphoma *tk* assay, *in vivo* micronucleus assay in rat).

Executive CAC recommendations on the mouse and rat carcinogenicity study protocols were communicated to the sponsor on December 18, 2003 under IND 68368.

Mouse Carcinogenicity Study: ICR mice (60/sex/group) were dosed for up to 2 years with daily oral (gavage) doses of 0, 1, 3, 10, or 30 mg/kg E2007 in 0.5% methylcellulose. Due to excessive mortality, dosing was discontinued at Week 87 and 85 in males receiving 10 and 30 mg/kg, respectively, at Week 101 in females receiving 3 and 10 mg/kg, and at Week 92 in females dosed with 30 mg/kg. All surviving animals were sacrificed at Week 104 (males) or Week 103 (females). The increased rate of mortality was associated with self-injury secondary to excessive grooming in both sexes. There was no evidence of drug-related neoplasms in this study.

Rat Carcinogenicity Study: Sprague-Dawley rats (60/sex/group) were dosed for up to 2 years with daily oral (gavage) doses of E2007 in 0.5% methylcellulose (M= 0, 10, 30, 100 mg/kg; F= 0, 3, 10, 30 mg/kg). There was no apparent drug-related effect on survival. Abnormal gait, decreased activity, and prostration/ lateral recumbence were the most common clinical signs observed in E2007-treated animals; convulsion occurred most frequently at the low dose. All surviving animals were sacrificed at Week 104. There was no evidence of drug-related neoplasms in this study.

Executive CAC Recommendations and Conclusions:

Mouse:

- The Committee agreed that the study was adequate.
- The Committee concurred that there were no drug-related neoplasms.

Rat:

- The Committee agreed that the study was adequate.
- The Committee concurred that there were no drug-related neoplasms.

Abigail Jacobs, Ph.D.
Acting Chair, Executive CAC

cc:\
/Division File, DNP
/LFreed, DNP
/CToscano, DNP
/SParncutt, DNP
/ASeifried, OND IO

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/s/

ADELE S SEIFRIED
07/05/2012

ABIGAIL C JACOBS
07/05/2012

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: July 27, 2012

From: Mónica L. Fiszman M.D., Ph.D.
CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Staphanie Parncutt, RPM
DNP

Subject: QT-IRT Consult to NDA 202834

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated June 11, 2012 regarding 120- Day Safety Update. The QT-IRT received and reviewed the following materials:

- Your consult
- TQT review for study report 013 (December 2011)
- Study e2007-g000-227
- Study e2007-g000-218
- ISS-Cardiac Safety Report (120-Day Safety Update, Appendix 4, by Independent Cardiologist Dr. Borje Darpo)

QT-IRT Comments for DNP

We review the material submitted and concluded that it is unlikely that changes from baseline of QTc reported in study 228 after 12 months of treatment in the 8- to 12- mg dose group are a QT signal for the following reasons:

- In the TQT study reviewed by QT-IRT, QTcF did not exceed the threshold of regulatory concern after a 12-mg dose.

- The 12-mg dose was tested during peranpamel clinical program and data obtained from ECG monitoring in controlled trials in patients with epilepsy, Parkinson's disease and neuropathic pain do not show clinically relevant mean QTc values (i.e., QTcF > 500 ms).
- Incidence of TEAEs of concern as per ICH E14 Guidance did not differ significantly from placebo arms and no dose-dependent trend in QTc prolongation was observed in any of the studies.
- It is more likely that results from study 228 are related to variability/changes within the studied population (i.e., disease outcome, concomitant medication, etc.) difficult to elucidate without a comparator group.

BACKGROUND

Perampanel is a highly-selective AMPA-type glutamate receptor antagonist with potential for therapeutic use in patients with various neurological diseases.

Perampanel is indicated in the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older. QT-IRT reviewed TQT study report 013 for this drug and concluded that there was no significant QT prolongation effect and concluded that perampanel did not prolong the QTc interval above the threshold of concern (10 ms).

In an uncontrolled open label extension study with patients with painful diabetic neuropathy and patients with post herpetic neuralgia (Study E2007-A001-228), QTc prolongation was observed after 12 months of treatment in the smaller subset of patients treated with perampanel 8 to 12 mg daily. The mean change from baseline of QTcF was 12.6 ms (median 15.0). The sponsor concludes that this QT signal was not caused by perampanel treatment.

The review division is asking for our review and comments on the Cardiac Safety Report (CSR) contained in the 120-Day Safety Update Report that analyzed ECG results for study E2007-A001-228. The review division is requesting our input in the context of the other ECG data and comment on the Sponsor's conclusion.

Clinical

From 120-Safety Update

This document is the 120-day Safety Update of the Integrated Summary of Safety (ISS) included in New Drug Application (NDA) 202834 for perampanel. The cutoff date for the ISS was 01 Dec 2010, and the cutoff date for this Safety Update was 01 Oct 2011. The new safety data included in this update come from Phase 2 Study 235 and open-label extension (OLE) studies (Studies 207, 233, and 307) that were ongoing as of the ISS cutoff date.

ECG results were summarized through descriptive statistics (mean, median, SD, minimum, maximum) and shift tables of normal/abnormal findings based on the investigator's assessment. In addition, QT intervals were corrected for heart rate using Bazett's formula (QTcB) and Fridericia's formula (QTcF) and tables were generated showing the following:

Markedly abnormal QTcB and QTcF values are summarized in Table 35. There were no clinically significant results. No perampanel-treated subject had a maximum QTcB or QTcF value > 500 msec. Values > 450 msec occurred in 2.8% and 1.3% of the subjects, respectively. The percentages of subjects with changes from baseline of > 60 msec were low (0.7% and 0.3%, for QTcB and QTcF, respectively).

Table 1. Summary of Abnormal QTcB and QTcF Results During Treatment Period - Epilepsy All Treated Pool (Safety Analysis Set)

Parameter	ISS Total Perampanel[a] (N=1639) n (%)	120-day Safety Update Total Perampanel[a] (N=1651) n (%)
Maximum QTcB Category		
n	1480	1517
Normal (< 430 msec)	1042 (70.4)	1015 (66.9)
Borderline (430-450 msec)	396 (26.8)	459 (30.3)
Abnormal (> 450 msec)	42 (2.8)	43 (2.8)
Highly Abnormal (> 500 msec)	0	0
Maximum QTcB Increment from Baseline		
n	1480	1517
Increment of < 30 msec from Baseline	1291 (87.2)	1281 (84.4)
Increment of 30-60 msec from Baseline	182 (12.3)	225 (14.8)
Increment of > 60 msec from Baseline	7 (0.5)	11 (0.7)
Maximum QTcF Category		
n	1480	1517
Normal (< 430 msec)	1327 (89.7)	1338 (88.2)
Borderline (430-450 msec)	137 (9.3)	159 (10.5)
Abnormal (> 450 msec)	16 (1.1)	20 (1.3)
Highly Abnormal (> 500 msec)	0	0
Maximum QTcF Increment from Baseline		
n	1480	1517
Increment of < 30 msec from Baseline	1389 (93.9)	1402 (92.4)
Increment of 30-60 msec from Baseline	88 (5.9)	111 (7.3)
Increment of > 60 msec from Baseline	3 (0.2)	4 (0.3)

Subjects are counted in each applicable category. Percentages are based on the number of subjects in the Safety Analysis Set per treatment group with data during the treatment period.
QTcB = QT interval corrected for heart rate using Bazett's formula, QTcF = QT interval corrected for heart rate using Fridericia's formula
a: Subjects treated with perampanel in any study.
Source: ISS Table 206 and Table 20.13-55.1

Source: 120-day Safety Report, Section 9.3, Table 35, page 147

Reviewer's comments: no subject had a QTcF > 500 ms, the incidence of post-baseline increase in QTcF > 60 ms is low in both, ISS and the 120-day Safety Update.

Cardiac and ECG-related Adverse Events

All cardiac and ECG TEAEs are summarized in Table 26 for the epilepsy all treated pool. When Safety Update rates for cardiac and ECG TEAEs are compared with the ISS rates, there is a slight increase in the incidence rate of such events (5.9% vs. 4.1% in the ISS). No individual event (preferred term) occurred in 1.0% or more of the subjects.

Table 2: Treatment-emergent Adverse Events (Selected Preferred Terms for Cardiac and ECG Adverse Events) by Decreasing Frequency - Epilepsy All Treated Pool (Safety Analysis Set)

MedDRA System Organ Class Preferred Term	ISS Total Perampanel[a] (N=1639) n (%)	120-day Safety Update Total Perampanel[a] (N=1651) n (%)
Subjects with any TEAE	67 (4.1)	97 (5.9)
Cardiac Disorders	50 (3.1)	76 (4.6)
Bradycardia	10 (0.6)	12 (0.7)
Sinus Bradycardia	7 (0.4)	12 (0.7)
Palpitations	5 (0.3)	7 (0.4)
Angina Pectoris	5 (0.3)	9 (0.5)
Tachycardia	4 (0.2)	7 (0.4)
Atrioventricular Block First Degree	4 (0.2)	4 (0.2)
Atrial Fibrillation	3 (0.2)	3 (0.2)
Conduction Disorder	2 (0.1)	3 (0.2)
Acute Coronary Syndrome	1 (0.1)	1 (0.1)
Angina Unstable	1 (0.1)	1 (0.1)
Arrhythmia	1 (0.1)	3 (0.2)
Atrial Flutter	1 (0.1)	1 (0.1)
Atrioventricular Dissociation	1 (0.1)	1 (0.1)
Bradyarrhythmia	1 (0.1)	1 (0.1)

Bundle Branch Block Left	1 (0.1)	1 (0.1)
Cardiac Arrest	1 (0.1)	1 (0.1)
Cardiac Hypertrophy	1 (0.1)	1 (0.1)
Coronary Artery Disease	1 (0.1)	1 (0.1)
Coronary Artery Stenosis	1 (0.1)	1 (0.1)
Dilatation Atrial	1 (0.1)	1 (0.1)
Hypertrophic Cardiomyopathy	1 (0.1)	1 (0.1)
Left Ventricular Hypertrophy	1 (0.1)	2 (0.1)
Myocardial Infarction	1 (0.1)	1 (0.1)
Myocardial Ischaemia	1 (0.1)	2 (0.1)
Sick Sinus Syndrome	1 (0.1)	1 (0.1)
Supraventricular Tachycardia	1 (0.1)	1 (0.1)
Tachycardia Paroxysmal	1 (0.1)	1 (0.1)
Ventricular Arrhythmia	1 (0.1)	1 (0.1)
Sinus Arrhythmia	0	2 (0.1)
Sinus Tachycardia	0	1 (0.1)
Bundle Branch Block Right	0	1 (0.1)
Cardiac Aneurysm	0	1 (0.1)
Cardiac Failure	0	1 (0.1)
Cardiovascular Disorder	0	1 (0.1)
Cardiovascular Insufficiency	0	1 (0.1)
Heart Valve Incompetence	0	1 (0.1)
Mitral Valve Incompetence	0	1 (0.1)
Right Ventricular Hypertrophy	0	1 (0.1)
Tricuspid Valve Incompetence	0	1 (0.1)
Ventricular Extrasystoles	0	1 (0.1)
Congenital, Familial and Genetic Disorders	0	1 (0.1)
Atrial Septal Defect	0	1 (0.1)
Investigations	20 (1.2)	25 (1.5)
Electrocardiogram Abnormal	4 (0.2)	5 (0.3)
Electrocardiogram QT Prolonged	4 (0.2)	4 (0.2)
Blood Pressure Diastolic Decreased	3 (0.2)	3 (0.2)
Electrocardiogram T Wave Abnormal	2 (0.1)	2 (0.1)
Heart Rate Decreased	2 (0.1)	2 (0.1)
Electrocardiogram QRS Complex Prolonged	1 (0.1)	2 (0.1)
Electrocardiogram Normal	1 (0.1)	1 (0.1)
Electrocardiogram QT Shortened	1 (0.1)	1 (0.1)
Electrocardiogram ST Segment Elevation	1 (0.1)	1 (0.1)
Electrocardiogram ST-T Segment Abnormal	1 (0.1)	1 (0.1)
Heart Rate Increased	1 (0.1)	1 (0.1)
Heart Rate Irregular	1 (0.1)	1 (0.1)
ECG Signs of Myocardial Ischaemia	0	1 (0.1)
Electrocardiogram PR Shortened	0	1 (0.1)
QRS Axis Abnormal	0	1 (0.1)

A TEAE is defined as an adverse event that either begins on or after the first dose date and up to 30 days after the last dose date of study drug; or begins before the first dose date and increases in severity during the treatment period.
Subject with two or more adverse events with the same preferred term is counted only once for that preferred term.
ECG = electrocardiogram, MedDRA = Medical Dictionary for Regulatory Activities, TEAE = treatment-emergent adverse event
a: Subjects treated with perampanel in any study.
Source: ISS Table 155, ISS Table 20.9-33, and Table 20.9-165.1

Source: ISS 120-day update, Table 26.

Reviewer's comments: In the epilepsy all treated pool, incidence of TEAEs of interest as per ICH E14 guidance is low in both the 120-days safety update and ISS (< 0.4%). Similar results were seen for other cardiac AEs.

Table 3: Treatment-Emergent Cardiac Adverse Events and ECG Adverse Events by Modal Dose of Perampanel - All Treated Subjects with Partial Seizures (Safety Analysis Set)

MedDRA System Organ Class Preferred Term	Placebo[a] (N=510) n(%)	Perampanel[b] <4 mg/day (N=153) n(%)	4 mg/day (N=192) n(%)	>4-8 mg/day (N=354) n(%)	>8-12 mg/day (N=952) n(%)	Total (N=1651) n(%)
Subjects with any Cardiac/ECG TEAE	15 (2.9)	5 (3.3)	11 (5.7)	22 (6.2)	59 (6.2)	97 (5.9)
Cardiac Disorders	12 (2.4)	5 (3.3)	7 (3.6)	20 (5.6)	44 (4.6)	76 (4.6)
Bradycardia	3 (0.6)	0	0	3 (0.8)	9 (0.9)	12 (0.7)
Sinus Bradycardia	3 (0.6)	1 (0.7)	0	2 (0.6)	9 (0.9)	12 (0.7)
Angina Pectoris	0	1 (0.7)	0	5 (1.4)	3 (0.3)	9 (0.5)
Palpitations	2 (0.4)	0	0	3 (0.8)	4 (0.4)	7 (0.4)
Tachycardia	2 (0.4)	1 (0.7)	1 (0.5)	1 (0.3)	4 (0.4)	7 (0.4)
Atrioventricular Block First Degree	1 (0.2)	0	1 (0.5)	0	3 (0.3)	4 (0.2)
Arrhythmia	0	0	1 (0.5)	1 (0.3)	1 (0.1)	3 (0.2)
Atrial Fibrillation	0	0	1 (0.5)	1 (0.3)	1 (0.1)	3 (0.2)
Conduction Disorder	0	0	1 (0.5)	1 (0.3)	1 (0.1)	3 (0.2)
Left Ventricular Hypertrophy	0	0	1 (0.5)	0	1 (0.1)	2 (0.1)
Myocardial Ischaemia	0	0	0	1 (0.3)	1 (0.1)	2 (0.1)
Sinus Arrhythmia	0	0	0	0	2 (0.2)	2 (0.1)
Sinus Tachycardia	1 (0.2)	0	0	0	1 (0.1)	1 (0.1)
Acute Coronary Syndrome	0	0	0	0	1 (0.1)	1 (0.1)
Angina Unstable	0	0	0	0	1 (0.1)	1 (0.1)
Atrial Flutter	0	0	0	0	1 (0.1)	1 (0.1)
Atrioventricular Dissociation	0	0	0	1 (0.3)	0	1 (0.1)
Bradyarrhythmia	0	0	0	0	1 (0.1)	1 (0.1)
Bundle Branch Block Left	0	0	0	0	1 (0.1)	1 (0.1)
Bundle Branch Block Right	0	0	0	0	1 (0.1)	1 (0.1)
Cardiac Aneurysm	0	0	0	0	1 (0.1)	1 (0.1)
Cardiac Arrest	0	0	0	0	1 (0.1)	1 (0.1)
Cardiac Failure	0	0	0	1 (0.3)	0	1 (0.1)
Cardiac Hypertrophy	0	0	1 (0.5)	0	0	1 (0.1)
Cardiovascular Disorder	0	0	0	0	1 (0.1)	1 (0.1)
Cardiovascular Insufficiency	0	0	0	0	1 (0.1)	1 (0.1)
Coronary Artery Disease	0	0	0	1 (0.3)	0	1 (0.1)
Coronary Artery Stenosis	0	0	0	1 (0.3)	0	1 (0.1)
Dilatation Atrial	0	1 (0.7)	0	0	0	1 (0.1)
Heart Valve Incompetence	0	0	0	0	1 (0.1)	1 (0.1)
Hypertrophic Cardiomyopathy	0	0	0	1 (0.3)	0	1 (0.1)
Mitral Valve Incompetence	0	0	0	0	1 (0.1)	1 (0.1)

A TEAE is defined as an adverse event that either begins on or after the first dose date and up to 30 days after the last dose date of study drug; or begins before the first dose date and increases in severity during the treatment period.
Subject with two or more events in the same system organ class (or with the same preferred term) is counted only once for that system organ class (or preferred term).
a: Subjects treated with placebo during the double-blind study.
b: Subjects treated with perampanel in any study. Dose is the modal dose received.

Cardiac Disorders	12	(2.4)	5	(3.3)	7	(3.6)	20	(5.6)	44	(4.6)	76	(4.6)
Myocardial Infarction	0		0		0		1	(0.3)	0		1	(0.1)
Right Ventricular Hypertrophy	0		0		0		0		1	(0.1)	1	(0.1)
Sick Sinus Syndrome	0		0		0		0		1	(0.1)	1	(0.1)
Supraventricular Tachycardia	0		0		1	(0.5)	0		0		1	(0.1)
Tachycardia Paroxysmal	0		0		0		0		1	(0.1)	1	(0.1)
Tricuspid Valve Incompetence	0		0		0		0		1	(0.1)	1	(0.1)
Ventricular Arrhythmia	0		1	(0.7)	0		0		0		1	(0.1)
Ventricular Extrasystoles	0		0		0		0		1	(0.1)	1	(0.1)
Congenital, Familial And Genetic Disorders	0		0		0		0		1	(0.1)	1	(0.1)
Atrial Septal Defect	0		0		0		0		1	(0.1)	1	(0.1)
Investigations	3	(0.6)	0		5	(2.6)	3	(0.8)	17	(1.8)	25	(1.5)
Electrocardiogram Abnormal	0		0		1	(0.5)	0		4	(0.4)	5	(0.3)
Electrocardiogram Qt Prolonged	0		0		1	(0.5)	1	(0.3)	2	(0.2)	4	(0.2)
Blood Pressure Diastolic Decreased	2	(0.4)	0		1	(0.5)	0		2	(0.2)	3	(0.2)
Electrocardiogram Qrs Complex Prolonged	1	(0.2)	0		0		0		2	(0.2)	2	(0.1)
Electrocardiogram T Wave Abnormal	0		0		1	(0.5)	0		1	(0.1)	2	(0.1)

Investigations	3	(0.6)	0		5	(2.6)	3	(0.8)	17	(1.8)	25	(1.5)
Heart Rate Decreased	0		0		0		0		2	(0.2)	2	(0.1)
Ecg Signs Of Myocardial Ischaemia	0		0		0		0		1	(0.1)	1	(0.1)
Electrocardiogram Normal	0		0		1	(0.5)	0		0		1	(0.1)
Electrocardiogram Pr Shortened	0		0		0		0		1	(0.1)	1	(0.1)
Electrocardiogram Qt Shortened	0		0		0		1	(0.3)	0		1	(0.1)
Electrocardiogram St Segment Elevation	0		0		0		0		1	(0.1)	1	(0.1)
Electrocardiogram St-T Segment Abnormal	0		0		0		0		1	(0.1)	1	(0.1)
Heart Rate Increased	0		0		0		0		1	(0.1)	1	(0.1)
Heart Rate Irregular	0		0		0		1	(0.3)	0		1	(0.1)
Qrs Axis Abnormal	0		0		0		0		1	(0.1)	1	(0.1)

Source: Table 20.9-165.1, 120-days safety update

Reviewer's comments: In the analysis of treatment emergent-cardiac adverse events of the epilepsy all treated pool, there were no apparent dose-related trends including no dose-related effects on QT interval. Rates were similar to those reported in the placebo arm.

Similar trends were reported in Parkinson's disease double-blind pool (ISS Table 156, page 335) and in the neuropathic pain double-blind pool (ISS Table 157, page 336).

Study E2007-A001-228

The primary objective of this study was to evaluate the long-term (1-year) safety of perampanel. A total of 262 subjects were enrolled in this study. These subjects had completed 1 of 2 preceding double-blind studies, Study E2007-G000-227 in subjects with painful diabetic neuropathy (PDN), or Study E2007- A001-218 in subjects with post herpetic neuralgia (PHN). Of the 262 enrolled subjects, 84 had received placebo in the preceding double-blind studies and 178 had received perampanel in the preceding double-blind studies.

Over 20% of subjects received the maximum possible dose of 12 mg and over 10% were receiving 12 mg at the end of the study.

-12-Lead Electrocardiograms

All 12-lead ECGs were complete, standardized recordings. The subject rested in a semi-recumbent position for ≥5 minutes before the ECG was obtained. The ECG was reviewed by the Investigator (paper or electronic tracing) and was available for comparison with subsequent ECGs by the Investigator. Electrocardiograms were performed at Visit 1 (baseline), Visit 14 (week 24), Visit 15 (week 36), and EOT Visit (Visit 16-week 48), or Early Discontinuation Visit (if applicable). An ECG was permitted at Unscheduled Visits at the Investigator's discretion.

Digital electrocardiogram (ECG) data were read by (b) (4) .

Table 4: Summary of Change from Baseline in QTcF and QTcB by OLE Study Visit and Actual Dose of Perampanel - All Treated Subjects from OLE Study 228

Visit Parameter (Unit) Statistic	Perampanel[a] <4 mg/day (N=243)	 4 mg/day (N=235)	 >4-8 mg/day (N=205)	 >8-12 mg/day (N=90)	 Total (N=243)
OLE Month 6					
QTcF (msec)					
n	27	41	63	32	163
Mean (SD)	411.6 (17.70)	408.3 (18.81)	404.6 (17.52)	403.5 (21.11)	406.5 (18.68)
Median	416.0	407.0	406.0	406.0	407.0
90% CI	(405.82, 417.44)	(403.32, 413.22)	(400.87, 408.24)	(397.20, 409.86)	(404.04, 408.88)
Min, Max	377, 447	368, 447	362, 453	351, 454	351, 454
Change from Baseline					
n	26	41	62	32	161
Mean (SD)	1.9 (16.33)	2.5 (16.38)	3.1 (16.44)	2.5 (19.23)	2.6 (16.84)
Median	2.5	4.0	3.0	3.5	3.0
90% CI	(-3.55, 7.39)	(-1.82, 6.80)	(-0.39, 6.58)	(-3.23, 8.30)	(0.44, 4.84)
Min, Max	-27, 38	-50, 49	-28, 41	-52, 41	-52, 49

Visit Parameter (Unit) Statistic	Perampanel[a] <4 mg/day (N=243)	 4 mg/day (N=235)	 >4-8 mg/day (N=205)	 >8-12 mg/day (N=90)	 Total (N=243)
OLE Month 12					
QTcF (msec)					
n	26	39	55	29	149
Mean (SD)	408.2 (17.90)	407.4 (19.49)	407.1 (16.96)	412.0 (19.00)	408.5 (18.07)
Median	406.0	410.0	407.0	414.0	408.0
90% CI	(402.16, 414.15)	(402.17, 412.70)	(402.87, 411.42)	(407.00, 419.00)	(405.98, 411.10)
Min, Max	376, 429	269, 429	358, 452	372, 462	358, 462
Change from Baseline					
n	25	38	55	29	147
Mean (SD)	-1.5 (16.96)	3.2 (20.81)	5.1 (16.70)	12.6 (17.67)	5.0 (18.14)
Median	-1.0	4.0	3.0	15.0	4.0
90% CI	(-6.98, 3.94)	(-2.82, 9.30)	(1.34, 8.88)	(7.04, 18.20)	(2.50, 7.46)
Min, Max	-29, 32	-84, 85	-38, 40	-32, 42	-84, 42

a: Subjects treated with perampanel in study 228. Dose is the actual dose received. Subjects are counted in each dose group they exposed to.

Source: ISS, 120 Day Update, Table 20.13-59

Reviewer's comments: After open-label treatment for 6 months, ΔQTcF was 1.9 ms (CI: -3.6 to 7.4 ms), 2.5 ms (CI: -1.8 to 6.8 ms), 3.1 ms (CI: -0.4 to 6.6 ms) and 2.5 ms (CI: -3.2 to 8.3 ms) in the 4 treatment groups (<4 mg 4 mg, >4 to 8 mg and >8 to 12 mg).

At the last visit, after 12 months of treatment, values were largely unchanged in the lower 3 groups: < 4 mg: -1.5 ms (CI: -7.0 to 3.9 ms); 4 mg: 3.2 ms (CI: -2.3 to 8.8 ms); >4 to 8 mg: 5.1 ms (CI: 1.3 to 8.9 ms) but higher in the >8 to 12 mg group: 12.6 ms (CI: 7.0 to 18.2 ms).

Table 5: 12-Lead Electrocardiogram Clinically Notable Results for QTc (Fredericia) Safety Population

	Placebo (N=84)				
	Baseline (1)				
	<=450 msec	>450 to <=500 msec	>500 msec	Total	Missing n
Number of subjects with any post-baseline data, n	83	1	0	84	0
Subjects with no values outside notable range, n (%)	82 (97.6)	0	0	82 (97.6)	0
Subjects with at least one post-baseline notable value (increase of >60 msec from baseline or post-baseline value of >450 msec), n (%)	1 (1.2)	1 (1.2)	0	2 (2.4)	0
Subjects with at least one post-baseline increase of >60 msec, n (%)	0	0	0	0	0
Subjects with at least one post-baseline value of >450 msec and <=500 msec, n (%)	1 (1.2)	1 (1.2)	0	2 (2.4)	0
Subjects with at least one post-baseline value of >500 msec, n (%)	0	0	0	0	0

	Perampanel (N=178)				
	Baseline (1)				
	<=450 msec	>450 to <=500 msec	>500 msec	Total	Missing n
Number of subjects with any post-baseline data, n	177	1	0	178	0
Subjects with no values outside notable range, n (%)	167 (93.8)	1 (0.6)	0	168 (94.4)	0
Subjects with at least one post-baseline notable value (increase of >60 msec from baseline or post-baseline value of >450 msec), n (%)	10 (5.6)	0	0	10 (5.6)	0
Subjects with at least one post-baseline increase of >60 msec, n (%)	0	0	0	0	0
Subjects with at least one post-baseline value of >450 msec and <=500 msec, n (%)	10 (5.6)	0	0	10 (5.6)	0
Subjects with at least one post-baseline value of >500 msec, n (%)	0	0	0	0	0

Percentages are based on the number in the Safety Population who have non-missing data at baseline and at least one non-missing value post-baseline.
(1) Baseline has been defined as the core baseline for subjects who were on active treatment during the preceding double-blind studies and has been defined as Visit 1 of the extension trial (or EOT visit of the preceding double-blind studies, if applicable) for subjects who were on placebo during the preceding double-blind studies.

Source: CSR, Table 14.3.6.3.2

Reviewer's comments: No subject in this study had a post-baseline QTcF >500 ms or an increase over baseline > 60 ms.

-Adverse Events

Table 6: Treatment-emergent Serious Adverse Events – Safety Population

System Organ Class Preferred Term	Prior Double-blind Treatment Group Placebo (N=84) n (%)	 Perampanel (N=178) n (%)
Subjects with at least 1 treatment-emergent SAE	**11 (13.1)**	**25 (14.0)**
Cardiac disorders	**4 (4.8)**	**9 (5.1)**
Acute myocardial infarction	0	1 (0.6)
Arrhythmia	1 (1.2)	0
Atrial fibrillation	0	2 (1.1)
Atrial flutter	1 (1.2)	0
Bradycardia	1 (1.2)	0
Cardiac failure	0	1 (0.6)
Cardiac failure congestive	0	1 (0.6)
Cor pulmonale	1 (1.2)	0
Coronary artery disease	0	2 (1.1)
Myocardial infarction	0	1 (0.6)
Supraventricular tachycardia	0	1 (0.6)
Tachycardia paroxysmal	0	1 (0.6)

Source: CSR, Table 22

Reviewer's comments: No treatment-emergent SAEs of concern as per ICH E14 guidance were reported. No meaningful difference in incidence of serious cardiac AEs between perampanel and placebo arm was reported in this study. One report of atrial fibrillation and another of atrial flutter were considered to be related to study drug.

There were 7 SAEs related to ECG abnormalities. These were arrhythmia (Subject 14071002), atrial fibrillation (Subjects 20261002 and 20421008), atrial flutter (Subject 14071012), bradycardia (Subject 14001007), supraventricular tachycardia (Subject 14061003), and tachycardia paroxysmal (Subject 18051003). The atrial fibrillation in Subject 20421008 and atrial flutter in Subject 14071012 also led to discontinuation.

Reviewer's comment: Subject 14071002: This subject was a 61-year old White female. She received her first dose of open-label perampanel in Study E2007-G000-228 on 03 April 2008. On 24 of June, 2008 subject stopped taking perampanel. On [redacted] *the subject experienced an arrhythmia that was severe, serious, and fatal. Medical history included hypertension, coronary artery disease, angina, coronary artery bypass, varicose veins (both legs), type II diabetes mellitus, obesity, hypercholesterolemia, frequent diarrhea. It seems unlikely that this serious adverse event leading to death is related to study drug.*

Thank you for requesting our input into the development of this product under NDA. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

MONICA L FISZMAN
07/27/2012

NORMAN L STOCKBRIDGE
07/27/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	June 19, 2012
Reviewer:	Loretta Holmes, BSN, PharmD Division of Medication Error Prevention and Analysis
Team Leader:	Irene Z. Chan, PharmD, BCPS Division of Medication Error Prevention and Analysis
Division Director:	Carol A. Holquist, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Fycompa (Perampanel) Tablets 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg
Application Type/Number:	NDA 202834
Applicant:	Eisai Inc.
OSE RCM #:	2012-82

***** This document contains proprietary and confidential information that should not be released to the public.*****

Contents

1 INTRODUCTION

This review evaluates the proposed container labels, professional sample blister pack labeling, professional sample carton labeling, and insert labeling for Fycompa (Perampanel) Tablets, NDA 202834, for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

Fycompa (Perampanel) is a new molecular entity (NME) not approved in any country. NDA 202834 for Fycompa (Perampanel) was originally submitted on May 25, 2011. On July 21, 2011, the Agency issued a Refusal to File (RTF) letter to the Applicant. The NDA was resubmitted on December 22, 2011.

The proprietary name for this product is Fycompa, which we evaluated under separate cover (OSE Review # 2012-170).

1.2 PRODUCT INFORMATION

The following product information is provided in the March 21, 2012 submission.

- **Active Ingredient:** Perampanel
- **Indication of Use:** Treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older
- **Route of Administration:** Oral
- **Dosage Form:** Tablets
- **Strengths:** 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg
- **Controlled Substance Schedule:** (b) (4)
- **Dose and Frequency:** Perampanel should be taken orally once daily before bedtime. Treatment should be initiated with a dose of 2 mg per day. The dose may be increased based on clinical response and tolerability by 2 mg per day increments to a dose of 4 mg to 12 mg per day. The maximum recommended daily dose is 12 mg. Dose increases should occur no more frequently than at weekly intervals.
- **How Supplied:**
  Commercial Distribution: 30-count and 90-count bottles
  Professional Sample: 14-count blister pack
- **Storage:** Store at 25ºC (77ºF); excursions permitted to 15ºC to 30ºC (59ºF to 86ºF).
- **Container and Closure System:**
  Bottle: White high-density polyethylene (HDPE) bottles with a child-resistant (b) (4) closure
  Blister Pack: Packaged in (b) (4) forming film and sealed by

push through or peel-push aluminum lidding foil. The description does not state the blister packs are child-resistant.

2 METHODS AND MATERIALS REVIEWED

Using the principals of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container labels (electronic submission) submitted January 17, 2012 (Appendix A)
- Professional sample blister pack and carton labeling (electronic submission) submitted January 17, 2012 (Appendix B)
- Professional sample blister pack and carton mock-ups sent to the Agency on March 26, 2012 (Appendix C)
- Insert labeling submitted on March 21, 2012 (no image)
- Medication Guide submitted on March 21, 2012 (no image)

3 MEDICATION ERROR RISK ASSESSMENT

The following section describes our risk assessment of the Fycompa (Perampanel) labels and labeling.

3.1 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

The strengths and dosage form proposed for Fycompa are reasonable given the proposed indication, dosage and administration for this product. However, DMEPA identified deficiencies in the container labels, professional sample blister pack, professional sample blister carton, and the insert labeling. These deficiencies include:

- Inadequate prominence of important information
- Layout and format of information that can be optimized
- Unclear label and labeling statements
- Inadequate strength differentiation

We provide recommendations in Section 5 to correct these deficiencies and minimize the risk of medication errors. We did not identify any safety concerns with the Medication Guide (MG) and, therefore, have no recommendations for the MG.

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

4 CONCLUSIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase the readability and prominence of important information on the labels to promote the safe use of the product, to mitigate any confusion, and to clarify information.

5 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. Container Labels (2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg)

1. All of the labels contain a green color block at the top of the label which increases the look-alike similarity between the different strengths. Delete the green color block from the labels in order to improve strength differentiation.
2. The established name does not appear to be at least ½ the height of the proprietary name. Ensure the established name is printed in letters that are at least ½ the height of the letters comprising the proprietary name [21 CFR 201.10(g)(2)].
3. The (b) (4) symbol appears in the middle of the principal display panel (PDP) and is too close to the established name. Relocate the (b) (4) symbol so that it appears further away from the proprietary name and established name.
4. The oval color block surrounding the statement of strength has a yellowish green border which increases the look-alike similarity between the different strengths. Delete the yellowish green border.
5. The statement of strength is located above the product identifying information. This is not the customary location and may hinder a provider's ability to quickly and easily identify this information on the label. Relocate the statement of strength to a position below the established name and dosage form as follows:

   Proprietary Name
   Established Name
   Strength

   To accomplish this move, reposition the proprietary name, established name, and dosage form higher on the PDP.
6. We note the statement of strength is backed by an oval color block that matches the corresponding tablet color. However, the 8 mg strength is difficult to read because it appears in a white font on a light purple background which does not provide sufficient color contrast. Consider using a black font for the 8 mg statement of strength or increasing the saturation of the light purple background in order to improve contrast.
7. The net quantity statement is backed by a color block which increases the prominence of the statement. Additionally, the net quantity statement is in the middle of the principal display panel and is too prominent in this location.

Remove the color block and relocate the net quantity statement to the upper right corner or lower right corner of the PDP, away from the statement of strength.

8. The medication guide statement is on the left side panel and lacks prominence in that location. Additionally, it is not optimally worded. Relocate the Medication Guide statement to the bottom section of the PDP. In order to accomplish this move, relocate the "Manufactured by" statement, "Marketed by" statement, as well as the "Esai" logo to the bottom of the left side panel. We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton.

    a. "Attention Pharmacist: Dispense the enclosed Medication Guide to each patient." or

    b. "Attention Pharmacist: Dispense the accompanying Medication Guide to each patient."

9. The "Esai" logo it too prominent. Decrease the size of the "Esai" logo.

10. The NDC numbers only contain the first five numbers (i.e., 62856-XXX-XX) and are, therefore, not complete. Include the entire NDC number on all labels.

B. Professional Sample Blister Pack

1. Outside Folder Card

a. The regimens for Week 1 and Week 2 are not well separated from one another. Use a heavy bold line, bar or other means to separate Week 1 from Week 2.

b. See Comment A.3 above.

c. The net quantity statement can be improved for clarity. Revise the net quantity statement to read: "This package contains: Seven 2 mg tablets and seven 4 mg tablets".

d. The "Esai" logo is too prominent. Decrease the size of the "Esai" logo.

e. The Agency does not consider starter packs to be drug samples; therefore, the use of the term (b) (4) on drug sample labeling is inappropriate and should not be used. Delete the statement (b) (4) per 21 CFR 203.38 (c) and 64 FR 67720 at 67741.

2. Inside Folder Card

a. The proprietary name and established name are not on the portion of the blister pack that contains the tablets. Place the proprietary name and established name on the right inside panel in order that the product identifying information will be on the portion of the blister that contains the tablets in case the two sides get separated.

b. There are no instructions that state how the tablets should be removed from the blister pack. Provide brief instructions for removing the tablets from the blister pack.

c. On the right inside panel, the statement of strength is not preceded by the statement "Each tablet contains". This statement may help to prevent patients from confusing an entire week's worth of tablets as a 2 mg or 4 mg dose. Therefore, revise the statements of strength to read: "Each tablet contains 2 mg" and "Each tablet contains 4 mg".

d. See Comment B.1.a. above.

e. See Comment A.3 above.

C. Professional Sample Blister Pack Carton

We note there are some slight differences in information layout between the professional sample blister pack carton electronic submission and the mock-up mailed to the Agency. The following comments are based on the electronic submission dated January 17, 2012.

1. The net quantity statement is on the back panel. Relocate the net quantity statement to the PDP.
2. The net quantity statement is not optimally worded. See Comment B.1.c. above.

D. Insert Labeling

The dangerous symbol "/" is used when expressing the daily dose (e.g., 4 mg/day) in Dosage and Administration, Section 2.1 *Partial-Onset Seizures*. Replace the symbol "/" with the word "per" when referring to the total daily dose (e.g., 4 mg per day).

If you have further questions or need clarifications, please contact Laurie Kelley, Project Manager, at 301-796-5068.

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

LORETTA HOLMES
06/19/2012

IRENE Z CHAN
06/19/2012

CAROL A HOLQUIST
06/19/2012

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: April 20, 2012

To: Russell Katz, M.D., Director
Division of Neurology Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: Alicja Lerner, M.D., Ph.D., Medical Officer
Controlled Substance Staff

Subject: **NDA 202-834** Perampanel (Fycompa)
Indication: Treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older
Dosages: 2-, 4-, 6-, 8-, 10-, and 12-mg oral tablets
Sponsor: Eisai Medical Research, Inc.

Materials reviewed: NDA 202-834 re-submission is located in EDR (Dec 22, 2011)
Previous IND 68368

Background

CSS reviewed abuse-related data submitted in NDA 202-834 for perampanel and prepared an 8 factor analysis and recommendation for placing perampanel under the Controlled Substances Act (CSA). The draft recommendation is currently being reviewed by the Office of Chief Counsel (OCC/HHS).

Conclusions:

1. (b) (4)
2.

Recommendation (to be conveyed to the Sponsor):

CSS recommends that Fycompa (Perampanel) be scheduled in (b) (4) of the CSA.

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/s/

ALICJA LERNER
04/20/2012

MICHAEL KLEIN
04/20/2012

DSI CONSULT: Request for Clinical Inspections

Date: March 27, 2012

To: Tejashri Purohit-Sheth, M.D., Branch Chief
Susan Thompson, M.D. Team Leader
Antoine El Hage, Ph.D.
Office of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: *Martin Rusinowitz, Medical Officer, DNP*
Norman Hershkowitz, M.D., Neurology Team Leader, DNP
Russell Katz, M.D., Director, DNP

From: *Stephanie N. Parncutt, Regulatory Health Project Manager/DNP*

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA-202834
Applicant/ Applicant contact information (to include phone/email): Eisai, Inc. 155 Tice Boulevard Woodcliff Lake, NJ 07677
Contact: Heather A. Bradley, MPH; Tel: 201-949-4691; Email: Heather_Bradley@Eisai.com
Drug Proprietary Name: Fycompa (perampanel)
NME or Original BLA (Yes/No): YES
Review Priority (Standard or Priority): Standard

Study Population includes < 17 years of age (Yes/No): YES
Is this for Pediatric Exclusivity (Yes/No): NO

Proposed New Indication(s): Treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older.

PDUFA:
Action Goal Date: October 22, 2012
Inspection Summary Goal Date: August 22, 2012

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site #: 5128 Principal Investigator: Ramon Bautista, M.D., M.B.A. Department of Neurology University of Florida HSC/Jacksonville Tower One, Ninth Floor 580 West Eighth Street Jacksonville, FL 32209 Tel: (904) 244-9190 Fax: (904) 244-9493	E2007-G000-304	13	1. large sample size 2. high number of protocol violations 3. large treatment effect
Site #: 1701 Principal Investigator: Jorge Washington Lasso Penafiel, Chief of Neurology Address: Hospital Padre Alberto Hurtado Esperanza 2150 Santiago, Chile Phone Number: +56-2-379-6295	E2007-G000-304	22	1. large sample size 2. high number of adverse events

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site #: 4501 Principal Investigator: Elinor Ben-Menachem, M.D., Ph.D. Department of Clinical Neurosciene Division of Neurology Sahlgrenska Academy Sahlgren University Hospital 413 45 Goteorg Sweden Phone Number: +46-31-342-1000	E2007-G000-305	14	1. large sample size 2. large treatment effect
Site #: 1303 Principal Investigator: Wim Van Paesschen, M.D., Ph.D. Neurologist, Chief of Clinic UZ Gasthuisberg (UZ Leuven), Neurology Herestraat 49 Leuven, 3000 Belgium Phone Number: +32-16-344-280	E2007-G000-305	8	1. large sample size 2. large treatment effect 3. high number of discontinuations

III. Site Selection/Rationale

Summarize the reason for requesting DSI consult and then complete the checklist that follows your rationale for site selection. Medical Officers may choose to consider the following in providing their summary for site selection.

Rationale for DSI Audits
Domestic Inspections:

Reasons for inspections (please check all that apply):

____ Enrollment of large numbers of study subjects
__X__ High treatment responders (specify): ***In study 304 the treatment effect is significant in US sites but not in Central and South America***
____ Significant primary efficacy results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
__X__ Other (specify): ***High number of protocol violations in study 304.***

International Inspections:

Reasons for inspections (please check all that apply):

____ There are insufficient domestic data
____ Only foreign data are submitted to support an application
__X__ Domestic and foreign data show conflicting results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
__X__ Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study). ***All the foreign sites selected have large sample sizes and also include those with a greater treatment effect than US sites.***

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.

IV. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact *Stephanie N. Parncutt, RPM,* at *301-796-4098 or Martin Rusinowitz, M.D.,* at 301-796-0158.

Concurrence: (as needed)

_____*X*_____ Medical Team Leader
_____*X*_____ Medical Reviewer
_____X_____ Division Director (for foreign inspection requests or requests for 5 or more sites only)

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/s/

STEPHANIE N PARNCUTT
03/29/2012

MARTIN S RUSINOWITZ
04/17/2012

NORMAN HERSHKOWITZ
04/17/2012

RUSSELL G KATZ
04/18/2012

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 06, 2012

TO: Director, Investigations Branch
(b) (4)

Director, Investigations Branch
(b) (4)

FROM: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Investigations Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: FY 2012, **High Priority CDER User Fee NDA Pre-Approval Data Validation Inspection**, Bioresearch Monitoring, Human Drugs, CP 7348.001

RE: NDA 202-834
DRUG: FYCOMPA® (E2007 or Perampanel), 2 mg and 12 mg Tablets
SPONSOR: Eisai, Inc., USA

This memo requests inspections of the clinical and analytical portions of the following bioequivalence study. **At the request of the Review Division, this inspection should be completed before July 22, 2012.**

Study Number: E2007-A001-040

Study Title: "A Randomized, open-label, crossover study to demonstrate bioequivalence between 6 × 2-mg tablets of perampanel and a single 12-mg tablet of perampanel in healthy subjects"

Clinical Site: Cetero Research
4801 Amber Valley Parkway
Fargo, ND, 58104

Clinical Investigator: Robert I. Cooper, M.D.

The data in the NDA submission should be compared to the original documents at the firm. In addition to the standard investigation involving the source documents, drug accountability, etc., the files of communication during the study conduct should be examined for their content. Please check the batch numbers of the test and reference formulations used in the study with the descriptions in documents submitted to the Agency. The site conducting the above bioequivalence study is responsible for randomly selecting and retaining reserve samples from the shipments of drug product provided for subject dosing. Please confirm whether reserve samples were retained as required by 21 CFR 320.38 and 320.63. Samples of the test and reference drug formulations should be collected and mailed to the Division of Drug Analysis, St. Louis, MO, for screening at the following address:

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis (DPA)
Center for Drug Analysis (HFH-300)
US Courthouse and Customhouse Bldg
1114 Market Street, Room 1002
St. Louis, MO 63101, USA

Please obtain a written assurance from the clinical investigator (CI) or the responsible person at the CI's site that the reserve samples are representative of those used in the specific bioequivalence study, and that they were stored under conditions specified in accompanying records. Document the CI’s signed and dated statement (21 CFR 320.38(d, e, g) on the facility's letterhead, or Form FDA 463a, Affidavit. Include the written statement in Sample Collection Report (CR) as a DOC sample.

Please have the records of all subjects in the study audited. The subject records in the submission should be compared to the original documents at the firm. The protocol and actual study conduct, IRB approval, drug accountability, as well as the source documents and case report forms for dosing, clinical and laboratory evaluations related to the primary endpoint, adverse events, concomitant medications, inclusion/exclusion criteria and number of evaluable subjects should be examined. The SOPs for the various procedures need to be scrutinized. Dosing logs must be checked to confirm that correct drug products were administered to the subjects. Please verify that the subjects

were compliant with the trial regimen and confirm the presence of 100% of the signed and dated consent forms, and comment on this informed consent check in the EIR. In addition to the standard investigation involving source documents, the correspondence files should be examined for sponsor-requested changes, if any, to the study data or report. Relevant exhibits should be collected for all findings, including discussion items at closeout, to assess the impact of the findings. Also, please determine if the subjects met the protocol inclusion/exclusion criteria.

Analytical Site: (b) (4)

Analytical Investigator: (b) (4)

Analytical Method: LC-MS/MS

All pertinent items related to the analytical method for the measurement of perampanel concentrations should be examined and the sponsor's data should be audited. The analytical data provided in the NDA submission should be compared with the original documents at the firm. The method validation and the actual assay of the subject plasma samples, as well as the variability between and within runs, QC, stability, the number of repeat assays of the subject plasma samples, and the reason for such repetitions, if any, should be examined. The SOP(s) for repeat assays and other relevant procedures must also be scrutinized. In addition to the standard investigation involving the source documents, the files of communication between the analytical site and the sponsor should be examined for their content.

Following identification of the investigator background material will be forwarded directly. **A scientist from DBGC, OSI with specialized knowledge may participate in the analytical inspection to provide scientific and technical expertise.** Please contact DBGC upon receipt of this assignment to arrange scheduling of the inspection.

Headquarters Contact Person: Sripal R. Mada, Ph.D.
(301)-796-4112

cc:
CDER OSI PM TRACK
OSI/DBGC/BB/Haidar/Skelly/Mada/Dejernett
OND/DNP/Parncutt
OTS/OCP/DCP1/Yang/Men
HFR-CE8590/Richard-Math (BIMO)
HFR-CE850/Bigham/Beacot (DIB)
HFR-CE1515/Tammariello (BIMO)
HFR-CE100/Campbell/Sooter (DIB)
Draft: SRM 03/06/2012
Edit: MFS 03/06/2012
DSI: 6320; O:\BE\assigns\bio202834.doc
FACTS: 1389832

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/s/

SRIPAL R MADA
03/06/2012

MICHAEL F SKELLY
03/06/2012
Skelly signing on behalf of Dr. Haidar

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 202834 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Fycompa Established/Proper Name: perampanel Dosage Form: tablets Strengths: 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg		
Applicant: Eisai, Inc. Agent for Applicant (if applicable): Heather A. Bradley, MPH		
Date of Application: December 22, 2011 Date of Receipt: December 22, 2011 Date clock started after UN:		
PDUFA Goal Date: October 22, 2012	Action Goal Date (if different):	
Filing Date: February 20, 2012	Date of Filing Meeting: January 26, 2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): Treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older.		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.***	☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☒
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system ☐ Pre-filled biologic delivery device/system ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Drug/Biologic ☐ Separate products requiring cross-labeling ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 068368	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			X	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**			X	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs***			X	
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:			X	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***		X		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 5 ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		Confirmed with Lyudmila Soldatova
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			X	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	NA			
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	**X**			
Index: Does the submission contain an accurate comprehensive index?	**X**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	**X**			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			**X**	
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			In 5/25/11 submission
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			In 5/25/11 submission
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	X			In 5/25/11 paper submission
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature?	X			In 5/25/11 submission

Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications]. ***Note:*** *Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*				
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	X			In 5/25/11 and 12/22/11 submissions

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* **December 28, 2011** <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:	**X**			

Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X			

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?		X		
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	X			PPSR submitted on April 30, 2010 to IND 68,368. Confirmed with Millie Wright
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***		X		Confirmed with Millie Wright
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		X		Confirmed with Millie Wright
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	X			Submitted 1/17/12
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox***		X		Confirmed with Kelly
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☐ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	X			
Is the PI submitted in PLR format?[4]	X			

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			Sent on 12/28/11
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***			X	
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***			X	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***			X	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			X	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:*** ***CAC Consult (12/28/11)*** ***CSS Consult (12/28/11)*** ***PMHS Consult (12/28/11)*** ***QT-IRT Consult (7/7/11)***	X			QT-IRT Review in DARRTS on 12/6/11

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

DDMAC (12/28/11)				
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** 1/9/2008 ***If yes, distribute minutes before filing meeting***	X			

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***		X		Sponsor sent in preNDA meeting request but we felt it was premature. See 9/12/10 correspondance.
Any Special Protocol Assessments (SPAs)? **Date(s): CAC Report 12/18/2003; Clinical Review of SPA 5/26/2005; SPA No Agreement 12/2/2009;** ***If yes, distribute letter and/or relevant minutes before filing meeting***	X			Sponsor submitted: 11/6/2003 (SPA's 1 & 2); 10/28/2009 (SPA 3)

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 26, 2012

BLA/NDA/Supp #: 202834

PROPRIETARY NAME: perampanel

ESTABLISHED/PROPER NAME: FYCOMPA

DOSAGE FORM/STRENGTH: tablets

APPLICANT: Eisai, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older.

BACKGROUND: Perampanel is a first-in-class selective, non-competitive antagonist of the ionotropic AMPA glutamate receptor on post-synaptic neurons. Glutamate is the primary excitatory neurotransmitter in the central nervous system and is implicated in a number of neurological disorders caused by neuronal overexcitation. Activation of AMPA receptors by glutamate is thought to be responsible for most fast excitatory synaptic transmission in the brain. In in vitro studies, perampanel inhibited AMPA-induced increase in intracellular calcium.
Perampanel is an orally active, noncompetitive, and highly selective α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist that has been developed as adjunctive treatment for patients with partial-onset seizures. AMPA receptors play a key role in mediating cortical glutamatergic transmission. AMPA antagonists could potentially reduce excessive excitatory activity and excitotoxicity, and thus exhibit anticonvulsant and potentially antiepileptogenic effects. Perampanel has shown anticonvulsant activity in seizure models in rodents. In a rat model of partial seizures, oral perampanel elevated "after discharge threshold" at a dose of 10 mg/kg, and reduced seizure severity at 5 mg/kg and 10 mg/kg, while a significant effect on "after discharge duration" was observed at 10 mg/kg. The results in these animal models suggest that perampanel could be effective in the treatment of partial-onset seizures, with or without secondary generalization

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Stephanie N. Parncutt	Y
Cross-Discipline Team Leader (CDTL)	Norman Hershkowitz		Y

Clinical	Reviewer:	Martin Rusinowitz	Y
	TL:	Norman Hershkowitz	Y
Clinical Pharmacology	Reviewer:	Xinning Yang	Y
	TL:	Angela Men	Y
Biostatistics	Reviewer:	Ququyan (Cherry) Liu	Y
	TL:	Kun Jin	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Christopher Toscano	Y
	TL:	Lois Freed	Y
Statistics (carcinogenicity)	Reviewer:	Matthew Jackson	N
	TL:	Karl Lin	N
Product Quality (CMC)	Reviewer:	Lyudmila Soldatova	Y
	TL:	Martha Heimann	Y
OSE/DMEPA (proprietary name)	Reviewer:	Loretta Holmes	Y
	TL:	Irene Z. Chan	Y
OSE/DRISK (REMS)	Reviewer:	Kendra Worthy	N
OC/DCRMS (REMS)	Reviewer:	Jenny Qin	Y
	TL:	Derek Smith	Y
Bioresearch Monitoring (DSI)	Reviewer:	Tony El Hage, Janice Pohlman	Y
	TL:	Tejashri Purohit-Sheth	N
Controlled Substance Staff (CSS)	Reviewer:	Alicja Lerner	Y
	TL:	Michael Klein	N
Safety	Mary Doi, Sally Yasuda		Y
PEDS	Nadia Hejazi, Courtney Suggs, Millie Wright		Y

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☒ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: Will discuss upon re-filing ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined o Reason: ***the application did not raise significant safety or efficacy issues.*** o ***this drug/biologic is not the first in its class***
• Abuse Liability/Potential **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the	☒ Not Applicable

division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☐ YES ☐ NO
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☐ FILE ☒ REFUSE TO FILE ☒ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO

Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT
Signatory Authority: Ellis Unger **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:

REGULATORY CONCLUSIONS/DEFICIENCIES	
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).

N/A	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
N/A	BLA/BLA supplements: If filed, send 60-day filing letter
N/A	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74 **(Sent on 3/5/12)**
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter. **SRPI entered in to DARRTS**
N/A	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STEPHANIE N PARNCUTT
03/06/2012

OSI CONSULT
Request for Biopharmaceutical Inspections

DATE: February 21st, 2012

TO: Associate Director for Bioequivalence
Office of Scientific Investigations, HFD-48

THROUGH: Xinning Yang, Ph.D. Clinical Pharmacology Reviewer, OCP
Angela Yuxin Men, M.D., Ph.D., Clinical Pharmacology Team Leader, OCP
Office of Clinical Pharmacology

FROM: Stephanie Parncutt, Regulatory Health Project Manager/DNP

SUBJECT: **Request for Biopharmaceutical Inspections**
NDA 202,834
FYCOMPA®, Tablet, 2 mg and 12 mg

Study/Site Identification:

As discussed with you, the following studies/sites pivotal to approval (OR, raise question regarding the quality or integrity of the data submitted and) have been identified for inspection:

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
E2007-A001-040	**Study Center:** Cetero Research 4801 Amber Valley Parkway Fargo, ND, 58104 (701) 239-4750 **Investigator:** Robert I. Cooper, M.D. Initiation Date: (b) (4) Completion Date: (b) (4) Date of Report: (b) (4)	**Test Facility:** (b) (4) **Responsible Scientist:** (b) (4) **Personnel Involved**: (b) (4) First Sample Receipt Date (b) (4) Experimental Start Date (b) (4)

		Experimental End Date	(b) (4)

International Inspections:

(Please note: International inspections require sign-off by the ORM Division Director or DPE Division Director.)

We have requested an international inspection because:

_____ There is a lack of domestic data that solely supports approval;

_____ Other (please explain):

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by **earliest possible date**. We intend to issue an action letter on this application by **October 22, 2012**.

Should you require any additional information, please contact *Stephanie Parncutt, RPM,* at *301-796-4098 or Xinning Yang, Ph.D.,* at *301-796-7412.*

Concurrence: (Optional)
Xinning Yang, Ph.D., Clinical Pharmacology Reviewer, OCP
Angela Yuxin Men, M.D., Ph.D., Clinical Pharmacology Team Leader, OCP

Appendix.

EDR Location: \\CDSESUB1\EVSPROD\NDA202834\202834.ENX

EDR Location: \\Cdsesub1\evsprod\NDA202834

356H Form: \\Cdsesub1\evsprod\NDA202834\0000\m1\us\11-forms\356h.pdf

Cover Letter: \\Cdsesub1\evsprod\NDA202834\0000\m1\us\12-cov-let\cover.pdf

Application Type/Number: nda202834
Incoming Document Category/Sub Category: Electronic Gateway
Incoming Document Category/Sub Category Number:
Letter Date: 12/22/2011 (Re-submission)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STEPHANIE N PARNCUTT
03/05/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 202834 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Fycompa Established/Proper Name: perampanel Dosage Form: tablets Strengths: 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg		
Applicant: Eisai, Inc. Agent for Applicant (if applicable): Heather A. Bradley, MPH		
Date of Application: May 25, 2011 Date of Receipt: May 25, 2011 Date clock started after UN:		
PDUFA Goal Date: March 25, 2012	Action Goal Date (if different):	
Filing Date: July 24, 2011	Date of Filing Meeting: July 14, 2011	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): Treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older.		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.***	☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted

Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐

Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system ☐ Pre-filled biologic delivery device/system ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Drug/Biologic ☐ Separate products requiring cross-labeling ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 068368	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			X	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**			X	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs***			X	
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:			X	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***		X		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 5 ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		Confirmed with Lyudmila Soldatova
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			X	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	NA			
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	**X**			
Index: Does the submission contain an accurate comprehensive index?	**X**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	**X**			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			**X**	
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature?	X			

Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications]. ***Note:*** *Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*				
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	X			

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* **June 6, 2011** <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:	**X**			

Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X			

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?		X		
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	X			PPSR submitted on April 30, 2010 to IND 68,368. Confirmed with Millie Wright
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***		X		Confirmed with Millie Wright
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		X		Confirmed with Millie Wright
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	X			Submitted 6/16/11
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox***		X		Confirmed with Kelly
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☐ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***				Defer to sponsors response to RTF communication.
Is the PI submitted in PLR format?[4]				Defer to sponsors response to RTF communication.

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***				Defer to sponsors response to RTF communication.
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			Sent on date of Filing Meeting.
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☒ Immediate container label ☒ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***			X	
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***			X	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***			X	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			X	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:*** ***CAC Consult (6/6/11)*** ***CSS Consult (6/6/11)*** ***PMHS Consult (6/6/11)*** ***QT-IRT Consult (7/7/11)***	X			

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

DDMAC (7/14/11)				
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** 1/9/2008 ***If yes, distribute minutes before filing meeting***	X			

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***		X		Sponsor sent in preNDA meeting request but we felt it was premature. See 9/12/10 correspondance.
Any Special Protocol Assessments (SPAs)? **Date(s): CAC Report 12/18/2003; Clinical Review of SPA 5/26/2005; SPA No Agreement 12/2/2009;** ***If yes, distribute letter and/or relevant minutes before filing meeting***	X			Sponsor submitted: 11/6/2003 (SPA's 1 & 2); 10/28/2009 (SPA 3)

ATTACHMENT

MEMO OF FILING MEETING

DATE: July 14, 2011

BLA/NDA/Supp #: 202834

PROPRIETARY NAME: perampanel

ESTABLISHED/PROPER NAME: FYCOMPA

DOSAGE FORM/STRENGTH: tablets

APPLICANT: Eisai, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older.

BACKGROUND: Perampanel is a first-in-class selective, non-competitive antagonist of the ionotropic AMPA glutamate receptor on post-synaptic neurons. Glutamate is the primary excitatory neurotransmitter in the central nervous system and is implicated in a number of neurological disorders caused by neuronal overexcitation. Activation of AMPA receptors by glutamate is thought to be responsible for most fast excitatory synaptic transmission in the brain. In in vitro studies, perampanel inhibited AMPA-induced increase in intracellular calcium.
Perampanel is an orally active, noncompetitive, and highly selective α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist that has been developed as adjunctive treatment for patients with partial-onset seizures. AMPA receptors play a key role in mediating cortical glutamatergic transmission. AMPA antagonists could potentially reduce excessive excitatory activity and excitotoxicity, and thus exhibit anticonvulsant and potentially antiepileptogenic effects. Perampanel has shown anticonvulsant activity in seizure models in rodents. In a rat model of partial seizures, oral perampanel elevated "after discharge threshold" at a dose of 10 mg/kg, and reduced seizure severity at 5 mg/kg and 10 mg/kg, while a significant effect on "after discharge duration" was observed at 10 mg/kg. The results in these animal models suggest that perampanel could be effective in the treatment of partial-onset seizures, with or without secondary generalization

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Stephanie N. Parncutt	Y
Cross-Discipline Team Leader (CDTL)	Norman Hershkowitz		Y

Clinical	Reviewer:	Martin Rusinowitz	Y
	TL:	Norman Hershkowitz	Y
Clinical Pharmacology	Reviewer:	Xinning Yang	Y
	TL:	Angela Men	N
Biostatistics	Reviewer:	Ququyan (Cherry) Liu	Y
	TL:	Kun Jin	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Christopher Toscano	Y
	TL:	Lois Freed	N
Statistics (carcinogenicity)	Reviewer:	Matthew Jackson	Y
	TL:	Karl Lin	N
Product Quality (CMC)	Reviewer:	Lyudmila Soldatova	Y
	TL:	Martha Heimann	N
OSE/DMEPA (proprietary name)	Reviewer:	Teresa MacMillan	Y
	TL:	Zach Oleszczuk	Y
OSE/DRISK (REMS)	Reviewer:	Melissa Hulett, Robin Duer, Mary Demspey, LaShawn Griffiths	Y
OC/DCRMS (REMS)	Reviewer:	Jenny Qin	Y
	TL:	Derek Smith	Y
Bioresearch Monitoring (DSI)	Reviewer:	Tony El Hage	Y
	TL:	Tejashri Purohit-Sheth	Y
Controlled Substance Staff (CSS)	Reviewer:	Alicja Lerner	Y
	TL:	Michael Klein	N
Safety	Mary Doi, Sally Yasuda		Y
PEDS	Virgina Elgin, Courtney Suggs, Millie Wright		Y

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☐ Not Applicable ☐ YES ☒ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☒ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: Will discuss upon re-filing ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☐ NO ☒ To be determined Reason:
• Abuse Liability/Potential **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☐ FILE ☒ REFUSE TO FILE ☒ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO

Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
CMC Labeling Review **Comments**:	☒ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT
Signatory Authority: Robert Temple **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:

REGULATORY CONCLUSIONS/DEFICIENCIES	
☒	The application is unsuitable for filing. Explain why: **Please see RTF letter in DARRTS dated 7/21/11.**
ACTIONS ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☒	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
N/A	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
N/A	BLA/BLA supplements: If filed, send 60-day filing letter
N/A	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74 **(Sent on 7/21/11)**

No	Conduct a PLR format labeling review and include labeling issues in the 74-day letter. **SEALD stated a SRPI did not need to be completed for RTF actions.**
N/A	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STEPHANIE N PARNCUTT
12/28/2011

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

NDA	202834
Brand Name	FYCOMPA (perampanel) Tablets
Generic Name	Perampanel (E2007)
Sponsor	Eisai Inc.
Indication	Treatment of partial-onset seizures with or without secondarily generalized in patients with epilepsy
Dosage Form	Tablets (2, 4, 6, 8, 10, 12 mg)
Drug Class	AMPA glutamate receptor antagonist
Therapeutic Dosing Regimen	6 mg/day
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	12 mg/day
Submission Number and Date	SDN 001/ 25 May, 2011
Review Division	DNP / HFD 120

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effect of perampanel (6 mg and 12 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean differences between perampanel (6 mg and 12 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the 2-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 3, indicating that assay sensitivity was established.

In this randomized, double-blinded, active- and placebo-controlled, combined fixed sequence, three-arm parallel group study, 196 healthy subjects received perampanel 6 mg, perampanel 12 mg, placebo, and moxifloxacin 400 mg. Overall summary of findings is presented in **Table 1**

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bound for Perampanel 6 mg, Perampanel 12 mg and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
Perampanel 6 mg	1.5	2.5	(-0.3, 5.3)
Perampanel 12 mg	0.5	3.7	(0.6, 6.9)
Moxifloxacin 400 mg*	4	11.9	(8.8, 14.9)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points is 7.7 ms.

The 'supratherapeutic' dose (12 mg) produces mean C_{max} values less than twice the mean C_{max} for the therapeutic dose (6 mg). The highest expected clinical exposure is considered to occur after multiple daily doses of 12 mg/day (without concomitant administration of CYP3A4 inducers). At these concentrations, there are no detectable prolongations of the QT-interval.

As perampanel is primarily cleared by the CYP3A4 pathway, there is the potential for hepatic dysfunction or concomitant use of CYP3A4 inhibitors to increase perampanel exposure. The effect of mild and moderate hepatic impairment 2 and 4% decrease in clearance, respectively, compared to matched controls. Drug-drug interaction with CYP3A4 inhibitors (i.e., ketoconazole) causes an approximate 20% increase in perampanel exposure, with no effect on C_{max}. It is predicted that concentrations achieved from a 12-mg once daily dose in healthy subjects will, on average, exceed those from use of 4 mg once daily in almost all individuals.

Of note, the dosing of 12 mg once daily at steady state for healthy individuals would not cover the predicted exposures for subjects with mild or moderate hepatic impairment receiving ≥6 mg/day. There are no dosing adjustments proposed for patients with hepatic impairment.

2 PROPOSED LABEL

2.1 SPONSOR'S PROPOSED LABEL

The sponsor proposed the following language in the package insert:

(b) (4)

3 BACKGROUND

3.1 PRODUCT INFORMATION

Perampanel is a selective, non-competitive antagonist of the ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid (AMPA) glutamate receptor on post-synaptic neurons developed for treating partial-onset seizures in patients with epilepsy aged 12 years and older.

3.2 MARKET APPROVAL STATUS

Perampanel is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

From eCTD 2.4.2

"In the hERG assay, effects of perampanel (1 – 30 μmol/L) were evaluated on tail currents recorded from human embryonic kidney 293 (HEK 293) cells stably transfected with hERG cDNA (Study No. DJNR1008). Perampanel inhibited hERG tail currents at concentrations of 10 μmol/L and above, and the estimated IC50 value was 15.8 μmol/L (5.5 μg/mL). No significant inhibition of tail current was observed at concentration of 1 and 3 μmol/L perampanel when compared to vehicle-treated cells.

"Effects of perampanel on cardiovascular (CV) parameters including heart rate, mean blood pressure and the electrocardiogram (ECG) were assessed in unrestrained conscious male and female beagle dogs using a telemetry system (Study No. G00006). Perampanel was administered orally once to dogs at doses of 1 and 10 mg/kg. No adverse effects on heart rate, mean blood pressure or ECG parameters were observed with perampanel up to 10 mg/kg in dogs."

3.4 PREVIOUS CLINICAL EXPERIENCE

From eCTD 2.7.4

"For double-blind, adjunctive therapy, phase 3 studies in all subjects with refractory partial seizures a summary statistics for all quantitative ECG parameters are presented in 5.3.5.3.1, Table 20.13-1 is provided. There were no clinically important changes in mean

ECG parameters from baseline to the end of treatment for any group. Shifts from baseline to end of treatment in ECG interpretation are summarized in 5.3.5.3.1, Table 20.13-2. The analysis revealed no shift of clinical concern.

"Markedly abnormal QTcB and QTcF values are summarized in 5.3.5.3.1, Table 20.13-3. There were no clinically significant results. No subject had a maximum QTcB or QTcF value > 500 msec, and the percentages of subjects with values > 450 msec were similar with placebo and perampanel for QTcB (1.4% and 1.3%, respectively) and for QTcF (0.5% and 0.8%, respectively). The percentages of subjects with changes from baseline of > 60 msec were low and were comparable with placebo and perampanel for QTcB (0.2% and 0.2%, respectively) and for QTcF (0.5% and 0.2%, respectively). There was no dose-dependent increase in the proportion of subjects with either abnormal results or large incremental changes from baseline in QTcB or QTcF.

"For all treated subjects with partial seizures summary statistics for all quantitative ECG parameters are presented in 5.3.5.3.1, Table 20.13-4. There were no clinically important changes in mean ECG parameters from baseline to the end of treatment.

"Shifts from baseline to end of treatment in ECG interpretation are summarized in 5.3.5.3.1, Table 20.13-5. The analysis revealed no shift of clinical concern.

"Markedly abnormal QTcB and QTcF values are summarized in 5.3.5.3.1, Table 20.13-6. There were no clinically significant results. The only subject who had a maximum QTcB or QTcF value > 500 msec was treated with placebo. The percentages of subjects with values > 450 msec were similar with placebo and perampanel for QTcB (3.4% and 2.8%, respectively) and for QTcF (1.0% and 1.1%, respectively). The percentages of subjects with changes from baseline of > 60 msec were low and were comparable with placebo and perampanel for QTcB (1.1% and 0.6%, respectively) and for QTcF (0.8% and 0.3%, respectively). There was no dose-dependent increase in the proportion of subjects with either abnormal results or large incremental changes from baseline in QTcB or QTcF."

Table 2: Serious Adverse Events Occurring in Two or More Subjects in Any Treatment Group by System Organ Class and Preferred Term - Double-blind Adjunctive Therapy Phase 3 Studies in Subjects With Partial-onset Seizures (Safety Analysis Set)

		Perampanel[a]				
MedDRA System Organ Class Preferred Term	Placebo[a] (N=442) n (%)	2 mg/day (N=180) n (%)	4 mg/day (N=172) n (%)	8 mg/day (N=431) n (%)	12 mg/day (N=255) n (%)	Total (N=1038) n (%)
Subjects with any Treatment-Emergent SAE	22 (5.0)	6 (3.3)	6 (3.5)	24 (5.6)	21 (8.2)	57 (5.5)
Infections And Infestations	3 (0.7)	0	0	5 (1.2)	0	5 (0.5)
Wound Infection Staphylococcal	0	0	0	2 (0.5)	0	2 (0.2)
Injury, Poisoning And Procedural Complications	3 (0.7)	1 (0.6)	0	5 (1.2)	7 (2.7)	13 (1.3)
Head Injury	0	0	0	1 (0.2)	2 (0.8)	3 (0.3)
Nervous System Disorders	11 (2.5)	0	4 (2.3)	8 (1.9)	7 (2.7)	19 (1.8)
Convulsion	3 (0.7)	0	1 (0.6)	3 (0.7)	2 (0.8)	6 (0.6)
Grand Mal Convulsion	2 (0.5)	0	0	1 (0.2)	1 (0.4)	2 (0.2)
Status Epilepticus	1 (0.2)	0	0	0	2 (0.8)	2 (0.2)
Epilepsy	2 (0.5)	0	1 (0.6)	0	0	1 (0.1)
Psychiatric Disorders	4 (0.9)	3 (1.7)	0	2 (0.5)	7 (2.7)	12 (1.2)
Aggression	0	1 (0.6)	0	0	2 (0.8)	3 (0.3)
Depression	2 (0.5)	0	0	0	0	0

A treatment-emergent SAE is defined as a serious adverse event that begins on or after the first dose date and up to 30 days after the last dose date of study drug.

Subject with two or more treatment-emergent SAEs in the same system organ class (or with the same preferred term) is counted only once for that system organ class (or preferred term).

MedDRA = Medical Dictionary for Regulatory Activities, SAE = serious adverse event

a: Subjects treated during the double-blind study.

Source: 5.3.5.3.1, Table 20.7-1

Source: ISS, Table 35

Table 3: Listing of Adverse Events Leading to Death by Study – Other Populations

Study, Reference	Treatment Group	Subject Number	AE Leading to Death (Preferred Term)	Study Day of Death	Relationship to Study Drug
Studies in Subjects With Parkinson's Disease					
301, Section 12.3.1.1	Placebo	0102-0003	Acute myocardial infarction	189	Possibly related
	Perampanel 2 mg	0175-0007	Left ventricular failure	53	Not related
		0201-0004	Sick sinus syndrome	40	Not related
	Perampanel 4 mg	0129-0012	Bronchopneumonia	176	Not related
		0132-0008	Cardiac failure	195	Not related
		0165-0006	Circulatory collapse	129	Not related
302, Table 8	Placebo	0408-0002	Prostate cancer[a]	191	Not related
		0447-0013	Cardiorespiratory arrest	137	Possibly related
		0466-0001	Pneumonia[a]	124	Not related
		0476-0004	Myocardial infarction	56	Not related
		0584-0021	Bile duct cancer	40	Not related
	Perampanel 4 mg	0571-0002	Sepsis[b]	137	Not related
309, Table 8	Placebo	0203-0002	Coronary artery disease	29	Not related
	Perampanel 4 mg	0128-0003	Sepsis[b]	111	Not related
		0752-0004	Hip fracture	59	Not related
	Entacapone 200 mg	0210-0002	Cardiopulmonary failure	120	Possibly related
204, Section 12.3.1.1	Perampanel 0.5 mg	112-002	Cardiac failure	34	Possibly related
205, Section 14.3.3	Perampanel	0122-0004	General physical health deterioration	828	Not related
		0407-0015	Hypotension	260	Possibly related
			Back pain		Possibly related
		0604-0009	Sudden death	892	Not related
318, Section 14.3.3	Perampanel	0132-0005	Cardiopulmonary failure[b]	71	Not related
303, Section 2	Perampanel	0176-0001	Sepsis	157	Not related
		0178-0005	Cardiopulmonary failure	355	Not related
		0178-0013	Metastatic bronchial carcinoma	321	Not related
		0215-0002	Lung neoplasm malignant	189	Not related
		0239-0008	Cardiac failure	74	Not related
Studies in Subjects With Neuropathic Pain					
227, Table 34	Placebo	1007-1002	Lung neoplasm malignant	123	Not related
		1318-1018	Death of unknown cause	78	Possibly related
	Perampanel 8 mg	1301-1002	Pancreatitis acute	159	Not related
		1324-1004	Multi-organ failure	28	Not related
228, Section 12.3.1.1	Perampanel	1321-1010	Adenocarcinoma	357	Not related
		1407-1002	Fatal arrhythmia	105	Not related

AE = adverse event
a: Death occurred after the subject withdrew from the study, although the event that led to death started while the subject was in the study.
b: Event was not treatment-emergent; the start date was > 30 days after the last dose of study drug.
Source: 5.3.5.3.1, Table 20.22

Source: ISS, Table 34

Reviewer's comments: there were no ventricular arrhythmias or other clinical relevant ECG findings reported in thee studies. There were two sudden death reported in phase 3 that were not linked to study drug.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of perampanel's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 68368. The sponsor submitted the study report Perampanel-A001-013 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Randomized, Double-Blind, Active- And Placebo-Controlled, Combined Fixed-Sequence, Parallel Group Study To Investigate The Effect Of Perampanel On The QT Interval Duration In Healthy Volunteers

4.2.2 Protocol Number

Perampanel-A001-013

4.2.3 Study Dates

First subject enrolled: 04 September 2007
Last subject completed: 31 March 2008

4.2.4 Objectives

Primary objective

- To quantify the effect of perampanel on the QT interval duration in healthy subjects.

Secondary objectives

- To explore the relationship between perampanel plasma concentrations and QT interval duration in healthy subjects.
- To explore the safety and tolerability of perampanel in healthy subjects.

4.2.5 Study Description

4.2.5.1 Design

This was a phase 1, double-blind, active- and placebo-controlled, combined fixed sequence, three-arm parallel group study in healthy male and female subjects.

4.2.5.2 Controls

The sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

Perampanel and moxifloxacin treatments were double-blind through the use of placebo. Moxifloxacin tablets were over-encapsulated and matched with placebo capsules.

4.2.5.4 Treatment Arms

Treatments consisted of:

- Perampanel: 'Therapeutic' doses of perampanel, 6 mg, once daily, for 7 days (Days 1 to 7), followed by dose escalation, a single 8-mg dose of perampanel (Day 8), a single 10-mg dose of perampanel (Day 9), and then 'Supratherapeutic' doses of perampanel, 12 mg, once daily, for 7 days (Days 10 to 16).
- Placebo: Placebo tablets were given in the same manner and number to match perampanel.

- Moxifloxacin: Placebo tablets were given in the same manner and number to match perampanel. A single dose of moxifloxacin 400 mg (overencapsulated) was also administered on Day 16.

4.2.5.5 Sponsor's Justification for Doses

"It was judged that studying the effects of a perampanel 12 mg once daily dose in healthy subjects would be sufficient to cover the maximum concentrations that might occur from use of 4 mg once daily in patients. The available data indicate that perampanel is primarily cleared by hepatic metabolism and that the CYP3A4 pathway is the primary route of cytochrome P450-mediated metabolism. Hence, there is the potential for hepatic dysfunction or concomitant use of CYP3A4 inhibitors to increase perampanel exposure. While the effect of hepatic impairment on perampanel plasma concentrations has not yet been quantified, drug-drug interaction data indicate that even use of potent CYP3A4 inhibitors such as ketoconazole will only cause an approximately 20% increase in perampanel exposure (AUC0-inf), with no effect on Cmax. Consequently, it is predicted that concentrations achieved from a 12 mg once daily dose in healthy subjects will, on average, exceed those from use of 4 mg once daily in almost all individuals under most circumstances."

(Source: Clinical Study Report No. E2007-A001-013, Section 9.4.4, Pg 30)

Reviewer's Comments: Based on the gathered clinical experience of perampanel, the supratherapeutic dose selected for the TQT study is reasonable. The exposure obtained by the supratherapeutic dose selected (12 mg) is higher than what has been observed in the repeated administration of the therapeutic dose of 6 mg once daily (~2-fold for both C_{max} and AUC). The doses chosen for perampanel and moxifloxacin to conduct the TQT study are appropriate.

Since the half-life is doubled in mild or moderate hepatic impairment, the dosing of 12 mg once daily at steady state for healthy individuals would not cover the predicted exposures for subjects with mild or moderate hepatic impairment receiving ≥6 mg/day. There are no dosing adjustments proposed for patients with hepatic impairment.

4.2.5.6 Instructions with Regard to Meals

"During on-treatment QT assessment days, study drug administration was given in the morning after fasting. Water was allowed ad libitum (except 1 hour before and 1 hour after study drug administration). Subjects were not allowed to eat until 4 hours after dosing. Identical meals were served on Days -1, 7, and 16 to minimize potential sources of variability between assessment days. On days on which QT assessments were not being performed, study drug was administered in the evening. Study drug administration was not to be done on an empty stomach and either the main meal of the day was to be eaten in the 2 hours before dosing or an additional snack was to be given at the same time as dosing. There were no other food or water restrictions on these days."

(Source Clinical Study Report No. E2007-A001-013, Section 9.4.5, Pg 31)

Reviewer's Comment: According to clinical pharmacology experience, food does not affect the exposure of perampanel, but slows the rate of absorption (C_{max} reduced by 40% and delayed by 2 hours compared to fasting state). For the QT study, perampanel was administered under fasting conditions on the days of QT assessment, which would yield a higher C_{max} compared to the fed condition. This is appropriate for the purposes of the study.

According to the proposed label, (b) (4)

4.2.5.7 ECG and PK Assessments

Study Day	-1	7 (therapeutic, 6 mg) 16 (supra-therapeutic, 12 mg)
Intervention	No treatment (Baseline)	Therapeutic: Three (3) 2-mg perampanel tablets Supra-therapeutic: Six (6) 2-mg perampanel tablets
12-Lead ECGs	0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 14 h relative to the start (clock time) of subsequent day's administration of study medication on Day 1	0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 h relative to the dosing of study medication.
PK Samples for drug	None collected	Pre-dose (prior to dosing), and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 h, relative dosing of study medication.

Reviewer's Comment: The PK and ECG assessments are adequate to capture QT at peak concentrations of perampanel. The median T_{max} obtained in the study was ~ 1.5 h and is within the expected range of 0.5 to 2 h upon oral dosing of perampanel.

4.2.5.8 Baseline

The sponsor used QTc pre-dose values as QTc baseline value.

4.2.6 ECG Collection

"All ECGs provided by study sites were recorded using digital 12-lead electrocardiogram (ELI 250, Mortara Instruments, Milwaukee, WI or study specific) and were transmitted to the (b) (4). These digital ECGs were analyzed with a three level quality control check by skilled readers at the (b) (4).

"Recordings were acquired with a sampling frequency of 1000 Hz and with a 20-bit amplitude (specific to the machine used) resolution. The 12-lead ECG recorded at the site was transmitted via in-built modem to the (b) (4). An auto printout of the transmitted ECG was generated once the ECG was received at (b) (4). After the confirmation of demographics and morphology, it was passed through FDA compliant XML format from the E-scribe server through the E-agent. Once the XML format is created, the interval measurement of the ECG is done by on-screen analysis using digital on-screen calipers to measure all the ECG intervals, by the semiautomated method, in accordance with the ICH E14 guidelines.

"All ECGs analyzed by a cardiology associate were reviewed by a cardiologist and further reviewed by a senior cardiologist. After analysis, the medical quality control department reviewed all the ECGs for measurements as well as ECG diagnosis."

Source: Expert ECG report

4.2.7 Sponsor's Results

4.2.7.1 Study Subjects

There were 264 subjects planned for enrollment with a total of 261 subjects randomized. In addition to those subjects noted in the table as discontinuing the study, 1 subject was discontinued due to a positive pregnancy test.

Table 4 summarizes the demographic characteristics of subjects enrolled in the study.

Table 4: Demographic and Baseline Characteristics (Safety Population)

Characteristic	Statistic	Placebo N=75	Perampanel N=107	Moxifloxacin N=75
Age (years)	n	75	107	75
	Mean (SD)	28.4(10.06)	29.0 (10.68)	29.0 (10.06)
	Min, max	18, 55	18, 55	18, 54
Sex n (%)	Male	38 (50.7)	53 (49.5)	38 (50.7)
	Female	37 (49.3)	54 (50.5)	37 (49.3)
Race n (%)	Caucasian	64 (85.3)	95 (88.8)	60 (80.0)
	Black	2 (2.7)	5 (4.7)	6 (8.0)
	Asian	2 (2.7)	1 (0.9)	2 (2.7)
	Other	7 (9.3)	6 (5.6)	7 (9.3)
Body weight (kg)	n	75	107	75
	Mean (SD)	72.5 (13.19)	76.8 (12.68)	74.6 (12.55)
	Min, max	49.5, 105.3	51.8, 110.8	49.5, 100.8
Height (cm)	n	75	107	75
	Mean (SD)	171.06 (8.58)	171.15 (9.83)	170.36 (9.00)
	Min, max	154.9, 185.4	144.8, 195.6	147.3, 190.5
BMI (kg/m^2)	n	75	107	75
	Mean (SD)	24.66 (3.49)	26.17 (3.26)	25.61 (3.18)
	Min, max	18.2, 31.6	18.0, 32.0	20.0, 32.2

SD = standard deviation; BMI = body mass index.
Source: Table 14.1.3

Source: CSR, Table 6

4.2.7.2 Statistical Analyses

4.2.7.2.1 Primary Analysis

The primary endpoint was the largest time-matched baseline-adjusted mean differences between perampanel (6 mg and 12 mg) and placebo in QTcF. The sponsor used mixed model including treatment, time, and treatment and time point interaction. The upper limits of the 2-sided 90% CI for both perampanel groups were below 10 ms.

Table 5: Sponsor's results for ΔΔQTcF for Perampanel 6 mg (Day 7)

Time point (hr)	LS Mean		Difference (ΔΔQTcF)	Upper 95% CL[a]
	Placebo N=59	Perampanel 6 mg N=79		
-0.5	-4.73	-3.25	1.48	3.78
0.5	-6.53	-4.65	1.88	5.07
1.0	-4.46	-3.12	1.34	4.49
1.5	**-3.60**	**-1.26**	**2.34**	**5.24**
2.0	-3.12	-2.42	0.70	3.80
3.0	-3.08	-3.10	-0.02	2.95
4.0	-0.55	1.67	2.23	4.98
6.0	-3.30	-2.47	0.83	3.40
8.0	-2.56	-0.76	1.80	4.26
12.0	-1.78	-0.68	1.09	3.59

CL=confidence limit; ΔΔQTcF = time-matched, baseline-adjusted, placebo-corrected QTcF; ANOVA = analysis of variance; LS Mean=least-squares mean.
[a]One-sided 95% CL from an ANOVA model.
Source: Sponsor's CSR Table 9 on page 53/1276

Table 6: Sponsor's results for ΔΔQTcF for Perampanel 12 mg (Day 16)

Time point (hr)	LS Mean		Difference (ΔΔQTcF)	Upper 95% CL[a]
	Placebo N=59	Perampanel 12 mg N=69		
-0.5	-2.16	0.28	2.44	5.58
0.5	**-5.70**	**-1.78**	**3.92**	**7.48**
1.0	-3.95	-1.75	2.20	5.43
1.5	-2.36	-0.71	1.66	4.79
2.0	-1.63	-1.71	-0.08	3.43
3.0	-0.90	-2.64	-1.74	1.20
4.0	-0.68	1.05	1.72	4.80
6.0	-3.10	-1.79	1.31	4.21
8.0	-2.18	-1.21	0.96	3.80
12.0	-2.39	-0.59	1.80	4.49

CL=confidence limit; ΔΔQTcF = time-matched, baseline-adjusted, placebo-corrected QTcF; ANOVA = analysis of variance; LS mean = least-squares mean.
[a]One-sided 95% confidence limit from an ANOVA model.
Source: Sponsor's CSR Table 10 on page 55/1276

4.2.7.2.2 Assay Sensitivity

The sponsor used the same mixed model to analyze ΔQTcF effect for moxifloxacin. The analysis results were presented in Table 7. The lower limit of the 2-sided 90% CI for each placebo-corrected, change-from-baseline LS mean QTcF value was above 5 ms threshold, which demonstrate assay sensitivity.

Table 7: Sponsor's results for ΔΔQTcF for Moxifloxacin 400 mg (Day 16)

Time point (hr)	LS Mean		Difference (ΔΔQTcF)	Two-sided 95% CI	p-value	Lower One-sided 95% CL
	Placebo N=59	Moxifloxacin N=58				
-0.5	-2.16	-1.10	1.06	(-2.96, 5.08)	0.6023	-2.31
0.5	-5.70	-0.75	4.95	(0.66, 9.24)	0.024	1.36
1.0	-3.95	7.10	11.04	(6.71, 15.38)	<0.0001	7.41
1.5	-2.36	9.28	11.64	(7.31, 15.97)	<0.0001	8.01
2.0	-1.63	10.13	11.75	(7.07, 16.44)	<0.0001	7.83
3.0	-0.90	10.68	11.58	(7.60, 15.57)	<0.0001	8.25
4.0	-0.68	11.47	12.15	(8.22, 16.07)	<0.0001	8.86
6.0	-3.10	6.85	9.95	(6.23, 13.67)	<0.0001	6.84
8.0	-2.18	6.20	8.37	(4.67, 12.08)	<0.0001	5.27
12.0	-2.39	6.24	8.63	(4.83, 12.42)	<0.0001	5.45

CI=confidence interval; CL=confidence limit; LS Mean=least-squares mean.

Source: Sponsor's CSR Table 11 on page 57/1276

Reviewer's Comments: We will provide our independent analysis result in Section 5.2.

4.2.7.2.3 Categorical Analysis

Categorical analysis was used to summarize in the categories of QTc>450 ms, >480 ms, and >500 ms, and changes from baseline QTc >30 ms and >60 ms. No subject's absolute QTc >480 ms and ΔQTc >60 ms.

4.2.7.3 Safety Analysis

One subject (perampanel) had clinically significant abnormalities on ECG at Day 7 and Day 16 (see Expert ECG Report in Appendix 16.2.6.2.1).

Subject 0658, a 30-year-old Caucasian male, had occurrences of treatment-emergent abnormalities of atrial premature complexes: unifocal, atrial premature complexes: multifocal, and atrial trigeminy on Day 7 (perampanel 6 mg) and Day 16 (perampanel 12 mg). There was no AEs reported and no action taken with study drug.

A total of 15 (14.0%) subjects who received perampanel discontinued the study prematurely due to TEAEs; 7 (6.5%) subjects while receiving 6 mg, 2 (2.0%) subjects while receiving 10 mg, and 6 (6.3%) subjects while receiving 12 mg. Two (1.3%) subjects discontinued the study prematurely while receiving placebo due to TEAEs. No subjects discontinued the study prematurely while receiving moxifloxacin. The most commonly reported TEAEs were dizziness, headache, dysarthria, somnolence, ataxia, and positive rhombergism. There were no deaths reported. One subject (perampanel 12 mg) experienced an SAE of concussion with associated fall and head injury, which required hospitalization.

Table 8: Summary of Treatment-related Treatment-emergent Adverse Events by Decreasing Frequency, by MedDRA System Organ Class, and Preferred Term, Reported for ≥ 10% of the Subjects Receiving Any Treatment (Safety Population)

System Organ Class Preferred Term	Placebo N=150 n (%)	Perampanel 6 mg N=107 n (%)	Perampanel 8 mg N=99 n (%)	Perampanel 10 mg N=98 n (%)	Perampanel 12 mg N=96 n (%)	Perampanel Total N=107 n (%)	Moxifloxacin N=70 n (%)
Any Term	76 (50.7)	51 (47.7)	29 (29.3)	24 (24.5)	75 (78.1)	90 (84.1)	13 (18.6)
Nervous System Disorders							
Dizziness	13 (8.7)	25 (23.4)	10 (10.1)	9 (9.2)	40 (41.7)	62 (57.9)	4 (5.7)
Headache	30 (20.0)	8 (7.5)	5 (5.1)	1 (1.0)	15 (15.6)	25 (23.4)	4 (5.7)
Dysarthria	1 (0.7)	2 (1.9)	1 (1.0)	1 (1.0)	21 (21.9)	24 (22.4)	0
Somnolence	1 (0.7)	5 (4.7)	1 (1.0)	0	7 (7.3)	13 (12.1)	0
Ataxia	3 (2.0)	0	0	2 (2.0)	10 (10.4)	12 (11.2)	1 (1.4)
General Disorders & Administration Site Conditions							
Feeling drunk	1 (0.7)	5 (4.7)	0	2 (2.0)	9 (9.4)	16 (15.0)	0
Gait disturbance	1 (0.7)	1 (0.9)	4 (4.0)	0	14 (14.6)	16 (15.0)	2 (2.9)
Fatigue	3 (2.0)	5 (4.7)	1 (1.0)	2 (2.0)	7 (7.3)	13 (12.1)	1 (1.4)
Investigations							
Positive rombergism	16 (10.7)	3 (2.8)	3 (3.0)	6 (6.1)	34 (35.4)	41 (38.3)	0
Gastrointestinal Disorders							
Nausea	6 (4.0)	5 (4.7)	1 (1.0)	1 (1.0)	15 (15.6)	21 (19.6)	5 (7.1)
Injury, poisoning, and procedural complications	0	2 (1.9)	1 (1.0)	0	8 (8.3)	11 (10.3)	0
Fall							

Note: Perampanel-treated subjects were to receive an escalating dosage regimen of perampanel for 16 days (perampanel 6 mg for 7 days; then perampanel 8 mg for 1 day; then perampanel 10 mg for 1 day; then perampanel 12 mg for 7 days). Subjects randomized to moxifloxacin appear under placebo for AEs on Days 1 to 15 and under moxifloxacin for Day 16 onwards; n = total number of subjects with adverse events for each system organ class and preferred term; % = percentage of subjects with adverse eventsfor each system organ class and preferred term.
Source: Table 14.3.1.3

Source: CSR, Table 30

There were no deaths during the course of this study.

4.2.7.4 Clinical Pharmacology

4.2.7.4.1 Pharmacokinetic Analysis

The PK results are presented in Table 9 (perampanel). Both C_{max} and AUC values in the thorough QT study were doubled following administration of 12 mg compared with 6 mg, the intended clinical dose. Moxifloxacin pharmacokinetics was not characterized in this study.

Table 9: Sponsor's Summary of Perampanel Pharmacokinetic Parameters

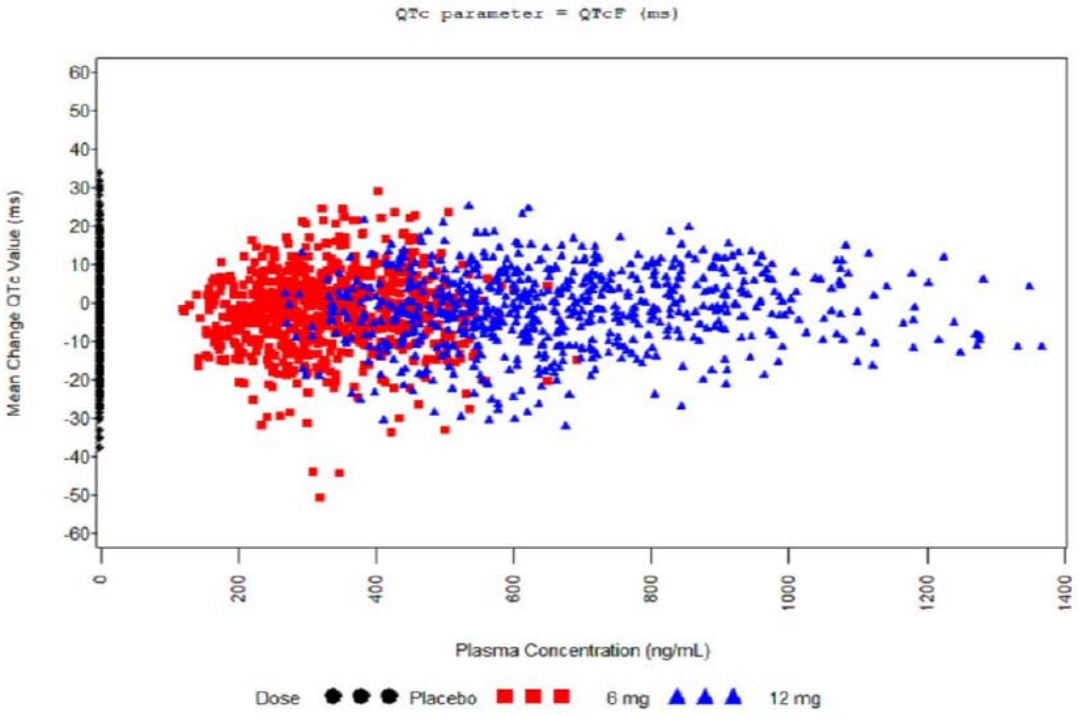
Parameters	Perampanel Day 7 (6 mg) n=79	Perampanel Day 16 (12 mg) n=69
C_{max} (ng/mL)	412.31 (97.251)	799.31 (221.756)
t_{max} (hr)[b]	1.5 (0.5-6.0)	2.0 (0.5-6.0)
AUC_{0-12} (ng*hr/mL)	3828.40 (1016.650)[c]	7899.14 (2313.023)

SD=standard deviation.
Notes:
[a] Included only subjects who had PK data.
[b] Median (min-max) reported for t_{max}.
[c] For AUC_{0-12}, n=77.

(Source Clinical Study Report No. E2007-A001-013, Section 11.4.2, Pg 51)

4.2.7.4.2 Exposure-Response Analysis

Figure 1: Mean baseline-adjusted QTcF v Perampanel Concentrations (Sponsor)



(Source: Clinical Study Report No. E2007-A001-013, Sec. 11.5.9, Pg 75)

Reviewer's Comments: A plot of ΔQTc vs. perampanel concentration is presented in Figure 1 with no evident exposure-response relationship. The sponsor did not provide a plot of ΔΔQTc vs. perampanel concentration.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

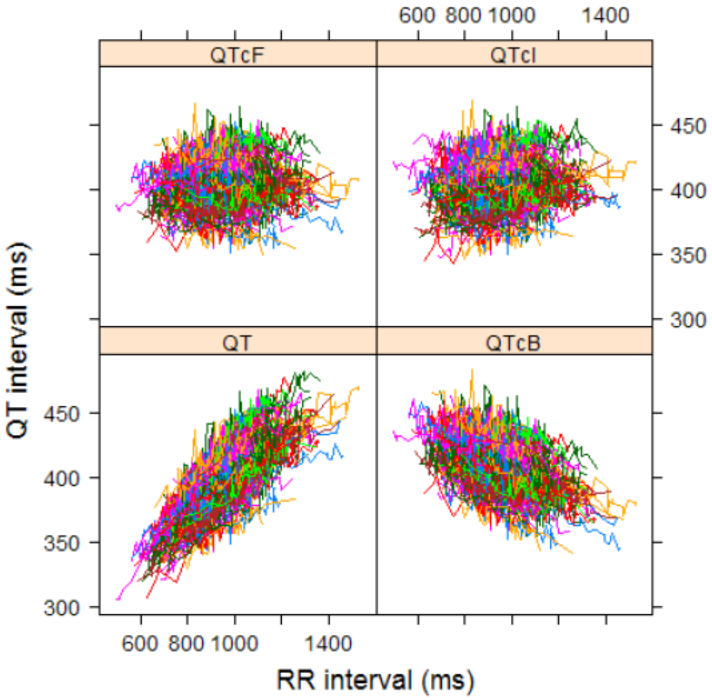
We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 10, it appears that both QTcI and QTcF are equally better than QTcB. Therefore, this statistical reviewer used QTcF for the primary statistical analysis. This is consistent with the sponsor's choice of QTcF for their primary analysis.

Table 10: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

Treatment Group	Correction Method					
	QTcB		QTcF		QTcI	
	N	MSSS	N	MSSS	N	MSSS
Perampanel 12 mg	69	0.0051	69	0.0017	69	0.0017
Perampanel 6 mg	79	0.0058	79	0.0010	79	0.0012
Moxifloxacin 400 mg	58	0.0049	58	0.0014	58	0.0009
All	196	0.0047	196	0.0012	196	0.0009

The QT-RR interval relationship is presented in Figure 2 together with the Bazett's (QTcB), Fridericia (QTcF), and individual correction (QTcI).

Figure 2: QT, QTcB, QTcF, and QTcF vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for the Study Drug

The statistical reviewer used mixed model to analyze the ΔQTcF effect. The model includes treatment as fixed effects and baseline values as a covariate. The analysis results are listed in Table 11 and

Table **12**. The largest upper bounds of the 2-sided 90% CI for the mean differences between perampanel 6 mg and placebo, and between perampanel 12 mg and placebo are 5.3 ms and 6.9 ms, respectively.

Table 11: Analysis Results of ΔQTcF and ΔΔQTcF for Perampanel 6 mg (Day 7)

		Perampanel 6 mg			
	Placebo ΔQTcF	ΔQTcF		ΔΔQTcF	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI
0.5	-6.4	79	-4.6	1.8	(-0.8, 4.4)
1	-4.5	79	-2.9	1.6	(-1.2, 4.5)
1.5	-3.7	79	-1.2	2.5	(-0.3, 5.3)
2	-3.3	79	-2.3	1.0	(-2.0, 4.0)
3	-3.4	79	-2.8	0.6	(-2.0, 3.3)
4	-0.6	79	1.7	2.2	(-0.4, 4.9)
6	-3.4	79	-2.4	1.1	(-1.4, 3.5)
8	-2.7	79	-0.7	2.0	(-0.3, 4.4)
12	-1.8	77	-0.4	1.4	(-0.9, 3.7)

Table 12: Analysis Results of ΔQTcF and ΔΔQTcF for Perampanel 12 mg and Moxifloxacin 400 mg (Day 16)

		Moxifloxacin 400 mg					Perampanel 12 mg			
	Placebo ΔQTcF	ΔQTcF		ΔΔQTcF			ΔQTcF		ΔΔQTcF	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	Adj. 90 % CI	N	LS Mean	LS Mean	90% CI
0.5	-5.6	56	-1.0	4.6	(1.2, 7.9)	(0.0, 9.1)	69	-1.9	3.7	(0.6, 6.9)
1	-4.0	56	6.7	10.7	(7.2, 14.2)	(6.0, 15.4)	69	-1.7	2.3	(-1.0, 5.6)
1.5	-2.4	56	9.2	11.6	(8.4, 14.8)	(7.2, 16.0)	69	-0.7	1.7	(-1.4, 4.8)
2	-1.8	56	10.0	11.8	(8.2, 15.3)	(6.9, 16.6)	69	-1.6	0.2	(-3.2, 3.6)
3	-1.2	56	10.4	11.5	(8.5, 14.5)	(7.4, 15.6)	69	-2.4	-1.3	(-4.1, 1.6)
4	-0.7	56	11.2	11.9	(8.8, 14.9)	(7.7, 16.1)	69	1.0	1.6	(-1.3, 4.6)
6	-3.3	56	6.5	9.8	(6.9, 12.6)	(5.9, 13.7)	69	-1.7	1.6	(-1.1, 4.3)
8	-2.2	56	6.0	8.3	(5.4, 11.2)	(4.3, 12.3)	69	-1.2	1.0	(-1.7, 3.8)
12	-2.5	56	6.0	8.4	(5.6, 11.2)	(4.6, 12.2)	69	-0.5	2.0	(-0.6, 4.6)

* Bonferroni method was applied for multiple endpoint adjustment for 4 time points.

5.2.1.2 Assay Sensitivity Analysis

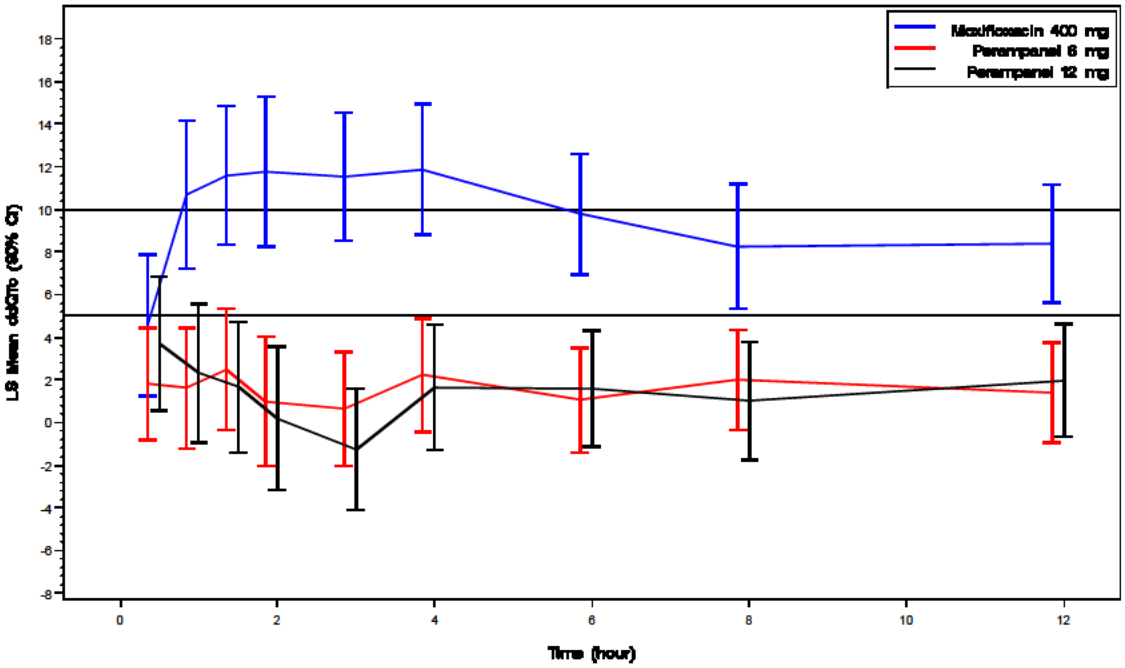
The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in

Table **12**. The largest unadjusted 90% lower confidence interval is 8.8 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 7.7 ms, which indicates that an at least 5-ms QTcF effect due to moxifloxacin can be detected from the study.

5.2.1.3 Graph of ΔΔQTcF Over Time

The following figure displays the time profile of ΔΔQTcF for different treatment groups.

Figure 3: Mean and 90% CI ΔΔQTcF Time Course for Perampanel and Moxifloxacin 400 mg



5.2.1.4 Categorical Analysis

Table 13 lists the number of subjects as well as the number of observations whose QTcF values are ≤450 ms and between 450 ms and 480. No subject's QTcF is above 480 ms.

Table 13: Categorical Analysis for QTcF

Treatment Group	Total N	Value<=450 ms	450 ms<Value<=480 ms
Perampanel 12 mg	69	68 (98.6%)	1 (1.4%)
Perampanel 6 mg	79	78 (98.7%)	1 (1.3%)
Moxifloxacin 400 mg	58	53 (91.4%)	5 (8.6%)

Table 14 lists the categorical analysis results for ΔQTcF. No subject's change from baseline was above 60 ms.

Table 14: Categorical Analysis of ΔQTcF

Treatment Group	Total N	Value<=30 ms	30 ms<Value<=60 ms
Perampanel 12 mg	69	69 (100%)	0 (0.0%)
Perampanel 6 mg	79	79 (100%)	0 (0.0%)
Moxifloxacin 400 mg	58	50 (86.2%)	8 (13.8%)

5.2.2 HR Analysis

The same statistical analysis was performed based on HR interval. The point estimates and the 90% CIs are presented in Table 15 and Table 16. The largest upper bounds of the 2-sided 90% CI for the mean differences between perampanel 6 mg and placebo, and between perampanel 12 mg and placebo are 2.2 bpm and 5.6 bpm, respectively.
Table 17 presents the categorical analysis of HR. Two subjects who experienced HR interval greater than 100 bpm in perampanel 12 mg.

Table 15: Analysis Results of ΔHR and ΔΔHR for Perampanel 6 mg (Day 7)

		Perampanel 6 mg			
	Placebo	ΔHR		ΔΔHR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI
0.5	1.4	79	0.5	-0.9	(-3.2, 1.5)
1	1.3	79	0.6	-0.7	(-3.0, 1.7)
1.5	0.2	79	-1.5	-1.7	(-4.1, 0.6)
2	-0.6	79	-0.7	-0.1	(-2.4, 2.2)
3	-0.0	79	-2.1	-2.1	(-4.3, 0.1)
4	2.1	79	-0.1	-2.2	(-5.0, 0.6)
6	2.6	79	0.4	-2.3	(-4.7, 0.2)
8	4.2	79	3.1	-1.1	(-4.0, 1.9)
12	3.7	77	2.5	-1.2	(-3.9, 1.6)

Table 16: Analysis Results of ΔHR and ΔΔHR for Perampanel 12 mg and Moxifloxacin 400 mg (Day 16)

		Perampanel 12 mg				Moxifloxacin 400 mg			
	Placebo	ΔHR		ΔΔHR		ΔHR		ΔΔHR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.5	3.7	69	2.0	-1.7	(-4.2, 0.9)	56	4.1	0.4	(-2.3, 3.1)
1	1.8	69	1.0	-0.8	(-3.7, 2.1)	56	5.9	4.2	(1.1, 7.2)
1.5	0.9	69	-0.5	-1.4	(-4.0, 1.2)	56	3.7	2.8	(0.0, 5.6)
2	0.5	69	-0.9	-1.4	(-3.9, 1.1)	56	3.3	2.8	(0.2, 5.4)
3	2.6	69	0.2	-2.4	(-5.0, 0.3)	56	4.1	1.6	(-1.2, 4.4)
4	1.7	69	-0.1	-1.8	(-4.4, 0.8)	56	4.3	2.5	(-0.2, 5.3)
6	3.9	69	0.6	-3.3	(-6.1, -0.5)	56	2.4	-1.5	(-4.5, 1.4)
8	5.2	69	3.9	-1.3	(-4.6, 2.0)	56	5.5	0.3	(-3.2, 3.8)
12	4.6	69	3.1	-1.5	(-4.3, 1.2)	56	5.6	1.1	(-1.8, 4.0)

Table 17: Categorical Analysis of HR

Treatment Group	Total N	HR < 100 bpm	HR >=100 bpm
Perampanel 12 mg	69	67 (97.1%)	2 (2.9%)
Perampanel 6 mg	79	79 (100%)	0 (0.0%)
Moxifloxacin 400 mg	58	56 (96.6%)	2 (3.4%)

5.2.3 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% CIs are presented in Table 18 and Table 19. The largest upper bounds of the 2-sided 90% CI for the mean differences between perampanel 6 mg and placebo, and between perampanel 12 mg and placebo are 6.0 ms and 4.8 ms, respectively. Table 20

presents the categorical analysis of PR. Eight subjects who experienced PR interval greater than 200 ms in both perampanel treatment groups.

Table 18: Analysis Results of ΔPR and ΔΔPR for Perampanel 6 mg

		Perampanel 6 mg			
	Placebo ΔPR	ΔPR		ΔΔPR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI
0.5	1.3	79	2.5	1.1	(-1.2, 3.5)
1	1.2	79	1.3	0.1	(-2.1, 2.4)
1.5	-1.0	79	2.6	3.6	(1.2, 6.0)
2	1.0	79	1.0	0.1	(-2.3, 2.4)
3	0.5	79	1.9	1.5	(-0.9, 3.8)
4	0.5	79	2.8	2.3	(-0.2, 4.8)
6	-1.1	79	0.1	1.2	(-0.8, 3.3)
8	-0.0	79	0.8	0.8	(-1.1, 2.7)
12	0.6	77	1.7	1.1	(-0.8, 3.1)

Table 19: Analysis Results of ΔPR and ΔΔPR for Perampanel 12 mg and Moxifloxacin 400 mg

		Moxifloxacin 400 mg				Perampanel 12 mg			
	Placebo ΔPR	ΔPR		ΔΔPR		ΔPR		ΔΔPR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.5	2.5	56	2.1	-0.5	(-3.1, 2.2)	69	4.1	1.6	(-0.9, 4.1)
1	2.2	56	-1.5	-3.7	(-6.7, -0.7)	69	1.7	-0.5	(-3.3, 2.3)
1.5	0.5	56	-1.2	-1.8	(-4.7, 1.1)	69	2.5	2.0	(-0.7, 4.8)
2	1.8	56	-1.3	-3.1	(-6.0, -0.2)	69	1.8	-0.0	(-2.7, 2.7)
3	1.8	56	-2.2	-4.0	(-6.7, -1.2)	69	0.9	-0.9	(-3.5, 1.7)
4	0.2	56	-2.3	-2.5	(-5.0, 0.0)	69	0.7	0.5	(-1.8, 2.9)
6	-0.7	56	-3.0	-2.3	(-4.6, -0.0)	69	-0.3	0.4	(-1.7, 2.6)
8	0.9	56	-1.5	-2.4	(-4.9, 0.0)	69	1.1	0.2	(-2.1, 2.5)
12	3.1	56	1.9	-1.2	(-3.8, 1.4)	69	3.6	0.5	(-1.9, 3.0)

Table 20: Categorical Analysis for PR

Treatment Group	Total N	PR < 200 ms	PR >=200 ms
Perampanel 12 mg	69	64 (92.8%)	5 (7.2%)
Perampanel 6 mg	79	76 (96.2%)	3 (3.8%)
Moxifloxacin 400 mg	58	52 (89.7%)	6 (10.3%)

5.2.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% CIs are presented in Table 21 and Table 22. The largest upper bounds of the 2-sided 90% CI for the mean differences between perampanel 6 mg and placebo, and between perampanel 12 mg and placebo are 1.8 ms and 1.7 ms, respectively.

Table 23 presents the categorical analysis of QRS. Six subjects who experienced QRS interval greater than 200 ms in perampanel treatment group.

Table 21: Analysis Results of ΔQRS and ΔΔQRS for Perampanel 6 mg (Day 7)

		Perampanel 6 mg			
	Placebo ΔQRS	ΔQRS		ΔΔQRS	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI
0.5	0.6	79	0.7	0.1	(-0.9, 1.1)
1	0.6	79	0.3	-0.3	(-1.3, 0.6)
1.5	0.4	79	0.5	0.1	(-0.9, 1.1)
2	0.2	79	0.5	0.3	(-0.7, 1.2)
3	0.3	79	-0.4	-0.7	(-1.7, 0.4)
4	-0.5	79	-0.4	0.1	(-0.9, 1.2)
6	-1.0	79	-0.2	0.7	(-0.3, 1.8)
8	-0.6	79	-0.3	0.4	(-0.7, 1.4)
12	-0.2	77	-0.7	-0.5	(-1.5, 0.5)

Table 22: Analysis Results of ΔQRS and ΔΔQRS for Perampanel 12 mg and Moxifloxacin 400 mg (Day 16)

		Perampanel 12 mg				Moxifloxacin 400 mg			
	Placebo ΔQRS	ΔQRS		ΔΔQRS		ΔQRS		ΔΔQRS	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.5	0.8	69	0.6	-0.2	(-1.3, 0.9)	56	0.5	-0.3	(-1.5, 0.9)
1	0.7	69	-0.0	-0.7	(-1.7, 0.3)	56	0.5	-0.2	(-1.3, 0.8)
1.5	0.7	69	0.6	-0.1	(-1.1, 1.0)	56	0.9	0.2	(-1.0, 1.3)
2	0.6	69	-0.0	-0.6	(-1.8, 0.5)	56	0.7	0.1	(-1.1, 1.3)
3	0.4	69	-0.7	-1.2	(-2.2, -0.1)	56	0.1	-0.4	(-1.4, 0.7)
4	0.4	69	-0.4	-0.8	(-1.8, 0.2)	56	0.4	-0.0	(-1.1, 1.0)
6	-0.8	69	-0.1	0.7	(-0.4, 1.9)	56	-0.4	0.4	(-0.8, 1.6)
8	-0.3	69	0.4	0.7	(-0.4, 1.7)	56	-0.1	0.2	(-0.9, 1.3)
12	-0.1	69	-0.4	-0.3	(-1.5, 0.9)	56	0.4	0.5	(-0.8, 1.7)

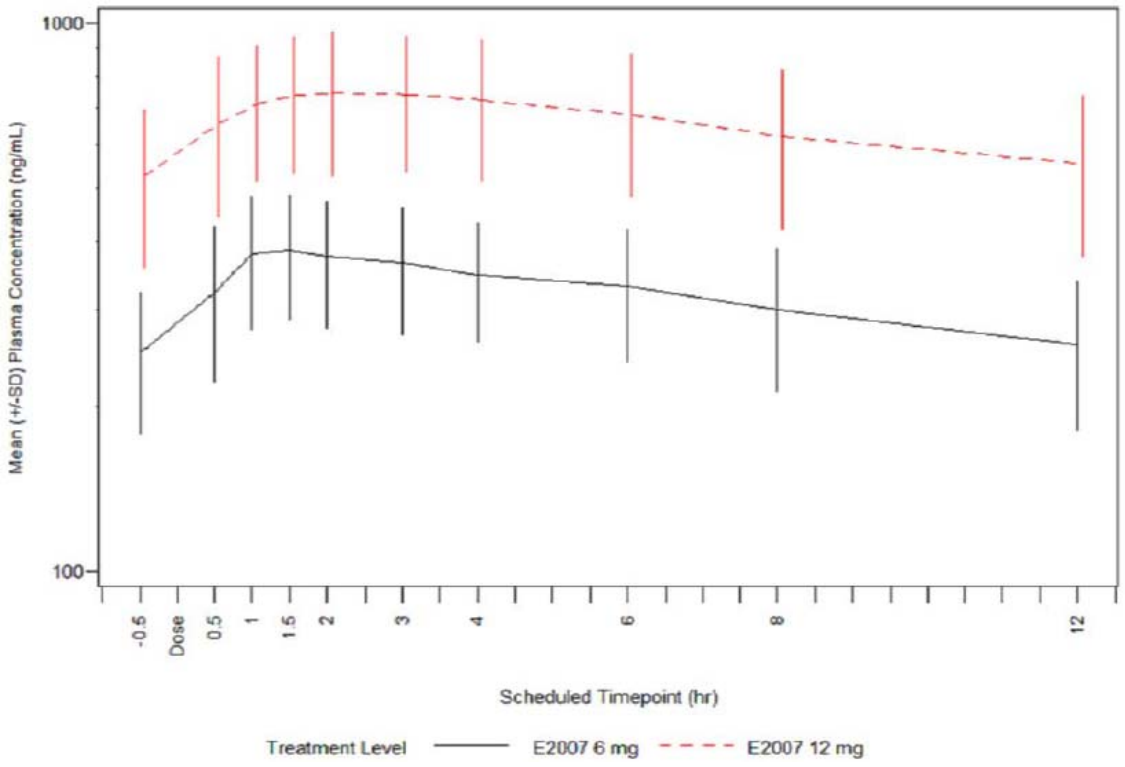
Table 23: Categorical Analysis for QRS

Treatment Group	Total N	QRS < 110 ms	QRS >= 110 ms
Perampanel 12 mg	69	66 (95.7%)	3 (4.3%)
Perampanel 6 mg	79	76 (96.2%)	3 (3.8%)
Moxifloxacin 400 mg	58	57 (98.3%)	1 (1.7%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

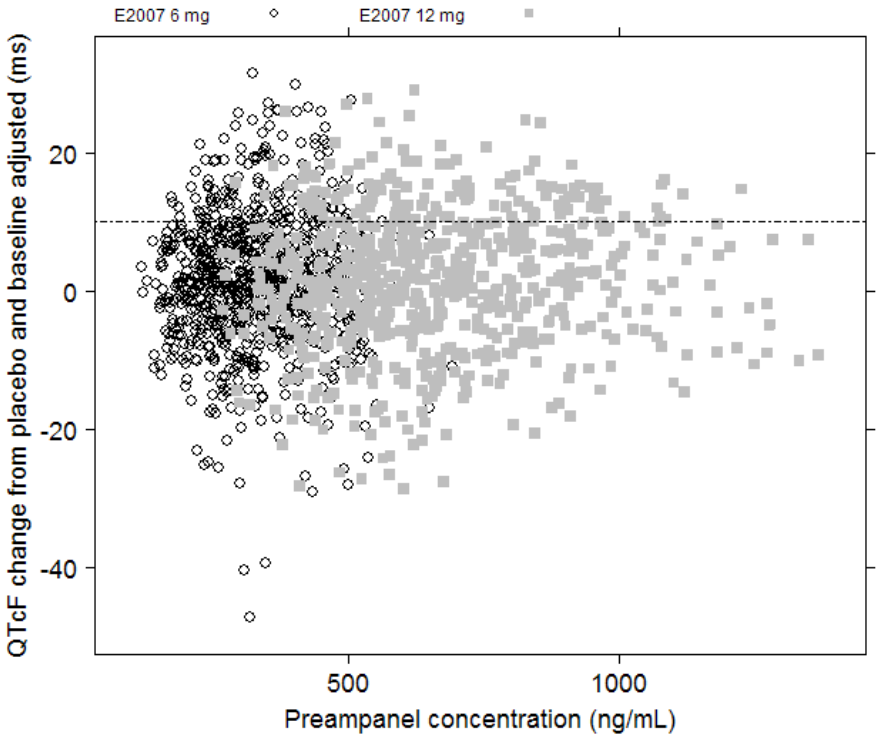
The mean perampanel concentration-time profile is illustrated in Figure 4.

Figure 4: Mean perampanel concentration-time profiles for 6 mg (black line) and 12 mg perampanel tablets (red dotted line)



The relationship between ΔΔQTcF and perampanel concentrations is visualized in Figure 5 with no evident exposure-response relationship.

Figure 5: ΔΔ QTcF vs. Perampanel Concentrations



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics ECGs were annotated in multiple leads (lead II, V2 and V5), with less than 0.05% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

Five subjects had a PR>200ms. Three were >200 ms at baseline and none had a postbaseline value >220 ms.

Three subjects had QRS>110 ms, two of them at baseline. Postbaseline increases were < 5% of baseline values. QRS duration was not >117 ms.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Highlights of Clinical Pharmacology

Therapeutic dose	4 mg/day to12 mg/day	
Maximum tolerated dose	12 mg/day titrated weekly from a dose of 2 mg/day	
Principal adverse events	dizziness, somnolence	
Maximum dose tested	Single Dose	12 mg in healthy volunteers 36 mg in healthy volunteers with a history of multi-drug use (Study 023, 024)
	Multiple Dose	12 mg once daily
Exposures Achieved at Maximum Tested Dose	Single Dose	C_{max}: Mean(SD) 709(181) ng/mL at 36 mg in Study 024 AUC_{0-72}: Mean(SD) 21017(3637) ng*h/mL at 36 mg in Study 023
	Multiple Dose	Study 013 On Day 16 after 6 mg QD (Days 1-7), 8 mg (Day 8), 10 mg (Day 9) and 12 mg QD (Days 10-16) C_{max}: Mean(SD) 799(222) ng/mL Ph 1 pooled population pharmacokinetic analysis model predicted AUC_{0-24} of 12 mg/day at steady state AUC_{0-24}: 18400 ng*h/mL
Range of linear PK	Over the range of 2 to 12 mg	
Accumulation at steady state	Study 002 Accumulation ratio (calculated as AUC_{0-24} on Day 14/AUC_{0-24}on Day 1) was 4.88 after 14 day once daily 4 mg dosing.	
Metabolites	Following administration of radiolabeled perampanel, only trace amounts of perampanel metabolites were observed in plasma. M1, M3, M4, M5, M6, M34, M35 (hydroxylate), M2 (carboxylate), M7 (dihydrodiol), M13, M14 (glucuronide conjugate), M15 (N-acetyl cysteine conjugate) were detected in samples obtained from clinical pharmacology studies, but no pharmacologically active metabolites were found.	
Absorption	Absolute/Relative Bioavailability	Study 017 Mean(SD) 116(9.42)%
	Tmax	Study 001 Median 0.54 - 1.00 h (range 0.25 – 2.00h)
Distribution	Vd/F	Study 001 Mean(SD) 51.22(19.55) L -

		95.67(17.91) L
	% bound	Human plasma protein binding ranged 95.3% - 95.8% at 20 – 2000 ng/mL.
Elimination	Route	Following administration of a radiolabeled perampanel dose to 8 healthy elderly subjects (Study 007), 30% of recovered radioactivity was found in the urine and 70% in the feces. Perampanel is extensively metabolized via primary oxidation (CYP3A4 and/or CYP3A5) and sequential glucuronidation.
	Terminal t½	Study 001 Mean(SD) 52.5(23.2) h - 122.8(72.4) h
	CL/F	Study 001 Mean(SD) 11.71(6.56) mL/min - 18.65(12.82) mL/min
.Intrinsic Factors	Age	In a population pharmacokinetic analysis of patients ranging in age from 12 to 74 years with partial-onset seizures, no significant effect of age on perampanel clearance was found.
	Sex	In a population pharmacokinetic analysis of patients with partial-onset seizures, perampanel clearance in females (0.605 L/h) was 17% lower than in males (0.730 L/h).
	Race	In a population pharmacokinetic analysis of patients with partial-onset seizures which included 576 Caucasians, 14 Blacks, 97 non-Chinese Asians, and 62 Chinese, no significant effect of race on perampanel clearance was found.
	Hepatic & Renal Impairment	Hepatic impairment The mean apparent clearance of unbound perampanel in mildly impaired subjects (Child-Pugh A) was 188 mL/min vs 338 mL/min in matched controls, and in moderately impaired subjects (Child-Pugh B) was 120 mL/min vs 392 mL/min in matched controls. Renal impairment The pharmacokinetics of perampanel have

		not been formally evaluated in patients with renal impairment. In a population pharmacokinetic analysis of patients with partial-onset seizures having creatinine clearances ranging from 39 to 160 mL/min, perampanel clearance was not influenced by creatinine clearance.
Extrinsic Factors	Drug interactions	**Effect of concomitant AEDs on perampanel** Carbamazepine After single 2 mg doses, C_{max} and AUC were 26% and 67% lower, respectively, when co-administered with steady state carbamazepine 300 mg b.i.d. than when administered alone. In a population pharmacokinetic analysis of subjects with partial-onset seizures, compared to subjects not on inducing AEDs, carbamazepine increased perampanel clearance 3-fold in both males (2.02 L/h vs 0.730 L/h) and females (1.89 L/h vs 0.605 L/h). Oxcarbazepine In a population pharmacokinetic analysis of patients with partial-onset seizures, compared to patients not on inducing AEDs, oxcarbazepine increased perampanel clearance 2-fold in both males (1.38 L/h vs 0.730 L/h) and females (1.25 L/h vs 0.605 L/h). Phenytoin In a population pharmacokinetic analysis of patients with partial-onset seizures, compared to patients not on inducing AEDs, phenytoin increased perampanel clearance 2-fold in both males (1.46 L/h vs 0.730 L/h) and females (1.33 L/h vs 0.605 L/h). **Effect of perampanel on concomitant AEDs** In a population pharmacokinetic analysis of patients with partial-onset seizures, perampanel did not significantly affect the clearance of

		clonazepam, levetiracetam, phenobarbital, phenytoin, topiramate, or zonisamide. Perampanel had a statistically significantly effect on the clearance of carbamazepine, clobazam, lamotrigine, and valproic acid, but the magnitude of these effects were each less than 10% at the highest perampanel dose evaluated (12 mg/day). Perampanel co-administration resulted in a 26% decrease in oxcarbazepine clearance. **Effect of other drugs on perampanel** Ketoconazole Multiple doses of ketoconazole increased perampanel $t_{1/2}$ by 15% (67.8 h vs 58.4 h) and $AUC_{(0\text{-inf})}$ by 20%, following single 1 mg doses of perampanel. Oral contraceptives C_{max} and $AUC_{(0\text{-}72h)}$ values of perampanel were each bioequivalent when dosed alone compared to dosing following 21 days of dosing of an oral contraceptive containing ethinylestradiol 30 µg and levonorgestrel 150 µg. **Effect of perampanel on other drugs** Midazolam Multiple daily does of perampanel 6 mg had no effect on midazolam $AUC_{(0\text{-inf})}$; C_{max} of midazolam was decreased by 15%. Oral contraceptives Multiple dosing (21 days) of perampanel 4 mg/day and 8 mg/day did not alter C_{max} or $AUC_{(0\text{-}24h)}$ of either ethinylestradiol 30 µg or levonorgestrel 150 µg. Following multiple dosing of perampanel 12 mg/day for 21 days, no effect was found on $AUC_{(0\text{-}24h)}$ of ethinylestradiol but C_{max} decreased by 18%. For levonorgestrel, C_{max} and $AUC_{(0\text{-}24h)}$ each decreased by approximately 40%. Levodopa Multiple dosing of perampanel 4 mg/day for 19 days had no

		effect on C_{max} or $AUC_{(0\text{-inf})}$ of levodopa.
	Food Effects	Food (high-fat meal) does not affect the extent of absorption, but slows the rate of absorption. When administered with food, C_{max} are reduced and delayed by 2 hours compared with dosing in a fasted state.
Expected High Clinical Exposure Scenario	Based on the accumulation factor observed after multiple dosing (up to 4.88-fold), and on the data that perampanel is not substantially impacted by CYP3A4 inhibition, highest expected clinical exposure is considered to occur after multiple daily doses of 12/mg day without co-administration of a CYP3A4 inducer of perampanel metabolism (carbamazepine, oxcarbazepine, phenytoin). High clinical exposures are expected to cause known adverse reactions such as dizziness, somnolence, headache, balance disorder (ataxia, gait disturbance, fall).	

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/s/

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M E M O R A N D U M

Date: July 14th, 2011

From: Virginia Elgin, M.D.

Through: Lisa Mathis, M.D.
Associate Director, OND
Pediatric and Maternal Health Staff

To: Russell Katz, M.D.
Director Division of Neurology Products

Re: New NME NDA

Drug: FYCOMPA (perampanel)

Indication: Adjunctive therapy in refractory partial onset seizures

Dosage form and route of administration:

- 2, 4, 6, 8, 10, 12 mg tablets
- (b) (4)

Materials Reviewed:

- Proposed Pediatric Study Request (PPSR)
- Study Synopses (Phase 3 Studies):
  - E2007-G000-304
  - E2007-G000-305
  - E2007-G000-306
- Literature
- Pediatric Waiver
- Pediatric Deferral

PMHS Consult Request: The request was made for PMHS to look at a new NDA application since as an NME it was eligible for the pilot program. PMHS was referred to an electronic link referencing the Waiver and Deferral Request. PMHS was asked to attend the filing meeting.

Background:

Perampanel is a selective non-competitive (allosteric) AMPA-type glutamate receptor antagonist. Perampanel has high affinity to the AMPA receptor and relatively low affinity for two other ionotropic glutamate receptors: kainate and NMDA. Perampanel inhibits AMPA-induced increases in intracellular calcium in rat cortical neurons. Animal models have demonstrated broad spectrum anti-seizure effects.[1]

In the current NDA submission, the Sponsor has submitted synopses of three Phase 3 trials performed in patients 12 years of age or older with uncontrolled partial onset seizures, taking 1 to 3 anti-epileptic drugs (AEDs).

Study ID	Type of Study	Patient Population	Results
E2007-G000-304 30 Apr 2008 to 11 Nov 2010	Phase 3 DB, PC dose-escalation, parallel group; safety and efficacy evaluation adjunctive therapy evaluation of placebo versus 8 and 12 mg doses of perampanel in patients with refractory partial onset seizures. 6 week titration followed by 13 week maintenance phase. Primary efficacy endpoint 50% responder rate.	320 Patients with refractory partial onset seizures aged 12 years or older	**Efficacy**: median change in frequency per 28 days during DB phase (-26.34%; 8 mg; p = 0.026) and (-34.49%;12 mg; p=0.0158) **Safety:** >10% headache, somnolence placebo, dizziness, somnolence, and headache in placebo, and dizziness, somnolence, headache, irritability, fall and ataxia in the 12 mg group.
E2007-G000-305 20 May 2008 to 14 Jan 2011	Phase 3 DB, PC, dose-escalation, parallel group study to evaluate safety and efficacy as adjunctive therapy in patients with refractory partial onset seizures.	321 patients aged 12 years of age and older with refractory partial onset seizures	**Efficacy**: 50% responder rate (primary EU efficacy endpoint) during maintenance was 33.3% for 8 mg; p=0.0008 and 33.9% for 12 mg; p=0.0006, where p values are

[1] Stephen, L., and Brodie, M. J. Pharmacotherapy of Epilepsy: Newly Approved and Developmental Agents. CNS Drugs 2011; 25(2): 89-107.

Study ID	Type of Study	Patient Population	Results
	Patients assigned to placebo, 8, or 12 mg dose. 6 week titration period followed by 13 week maintenance period.		compared to placebo. Safety: TEAE > 10%: headache in placebo, dizziness, fatigue and somnolence in 8 mg group, and dizziness, somnolence, fatigue, and headache in the 12 mg group.
E2007-G000-306 04 Aug 2008 to 19 May 2010	A DB, PC, dose-escalation, parallel group study to evaluate safety and efficacy of perampanel given as adjunctive therapy to patients with refractory partial onset seizures. Patients were randomized to placebo, 2, 4, or 8 mg. 6 week titration followed by 13 week maintenance period. Primary endpoint (EU only) was % of patients with 50% or > reduction in seizure frequency.	623 patients aged 12 years of age or older (in some countries > 18 years). 116 centers in Asia, Australia, Europe and Russia	**Efficacy**: compared to placebo 4mg and 8 mg showed statistical significance (p=0.0028 and ==0.0001 respectively) **Safety**: dizziness, somnolence, fatigue, and vertigo occurred more frequently (≥ 3% higher) with perampanel than placebo.

Regulatory Background:

Electronic link is: \\CDSESUB1\EVSPROD\NDA202834\202834.ENX

The Sponsor has submitted an application for a new NDA, NME, for the treatment of refractory partial onset seizures with or without secondary generalization. Perampanel, or FYCOMPA, has been studied under IND #68,368. An End of Phase 2 meeting was held December 5th, 2007. The following studies were included in the current NDA submission:

- 27 Phase 1 studies evaluating 0.2 to 36 mg of perampanel to healthy and female volunteers, patients with hepatic impairment, and poly-drug users. Note: renal impairment was not studied and it is believed this is because of limited renal metabolism.
- Four completed Phase 2 studies in adults ages 18-65 to assess safety, tolerability and pharmacokinetics (PK) in doses up to 12 mg.

- Three completed double-blind, placebo-controlled, randomized Phase 3 studies in patients ages 12 and older with doses up to 12 mg a day (304, 305, 306 study with an ongoing open-label extension (OLE) Study 307).
- Three ongoing OLE studies in adults (206,207,208, and 231(Japan))
- Additional studies were conducted for the following indications: Parkinson's disease, neuropathic pain, migraine, and multiple sclerosis.

Proposed Pediatric Waiver:

The Sponsor is requesting a waiver from ages 0 to 1 month on the grounds that studies are impossible or highly impractical. They also mention in the PPSR there are too few patients to study.

Reviewer's Comments:

This waiver is justified in that neonatal seizures tend to be multifocal or migratory due to brain maturity and therefore there would be too few patients to study with pure partial onset seizures.

Proposed Pediatric Deferral:

The Sponsor proposes to defer studies in the 1 month to 11 year age range on the grounds that adult studies are compete and ready for approval. The Sponsor believes adequate labeling exists for the pediatric population in the 12-17 year old age range.

Proposed Pediatric Development Plan
See the Proposed Pediatric Study Report (PPSR) for more details. The following table summarizes the current proposed pediatric development plan:

Study ID	Type of Study	Study Population	Formulation	Dates for Start and Completion
E2007-G000-232	52 week open-label, PK, safety and tolerability study; efficacy exploratory endpoint.	(b) (4) patients ages 1 month to 11 years; 24 ≥ 1 month and ≤ 23 months; 24 ≥ 2 years and ≤ 6 years; 24 > 6 to ≤ 11 years.	Suspension (b) (4)	Start: Oct 2011 Complete: August 2013
(b) (4)				

(b) (4)

Reviewer's Comments:

(b) (4)

The Sponsor has submitted a PPSR. This can serve as the pediatric development plan, however, they must provide the day, month, and year of when a study will be started, completed, and when a final report will be submitted to the Agency for review.

A question was raised at the filing meeting July 14th, 2011, as to whether or not the submission was a complete response to a Written Request (WR). Since no WR has been issued the answer is no.

Current Status of Application:
This application is currently a Refuse to File (RTF) due to but not limited to the following:
Pharmacology toxicology:

- Missing rat data.
- Problems with lamb fetal data
- Problems with need for juvenile tox studies if studying under age of 12 years. Note: this was discussed at the Decembe 5th, 2007 EOP2 meeting.
- Problems with inadequate mouse carcinogenicity study

Clinical:

- Issues with analyzability with raw data sets; especially with 306 larger study done in many sites.
- Lack of analyzable data in ISS; missing vitals, etc.
- Note: Sponsor was previously denied an NDA meeting due to lack of safety data.
- Studies for other indications like Parkinsons did check vitals; orthostasis and vitals not checked in epilepsy patients.
- End of Phase 2 meeting requested higher dose for QT study (>12 mg) and the Sponsor did not do that. Debate at meeting about the need for this given tolerability issues. May be a labeling issue. THIS MIGHT BE AN APPROVAL ISSUE

Recommendations to the Sponsor:
Currently the NDA submission will receive an RTF. At the time the Sponsor corrects the deficiencies listed above then the following must occur:

- Proposed pediatric studies (232 (b) (4)) must include a controlled study of patients aged 1 month to ≤ 2 years, including adequate safety, efficacy, and tolerability information. (b) (4)

- The Sponsor should consider additional cardiac ECG monitoring in pediatric trials since the recommendation by the QT-IRT team at the EOP2 meeting was to study the effects of dosing above 12 mg to look for evidence of QT prolongation and this was not done. This raises a safety concern especially in light of the prolonged half-life of perampanel (52-129 hours).[2]
- All proposed pediatric studies require these dates including the month, day, and year for:
    - Initiation of the study
    - Completion of the study
    - Submission of the study report.

[2] Stephen, L., and Brodie, M. J. Pharmacotherapy of Epilepsy: Newly Approved and Developmental Agents. CNS Drugs 2011; 25(2): 89-107.

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/s/

VIRGINIA E ELGIN
07/19/2011

LISA L MATHIS
08/01/2011

Executive CAC
Date of Meeting: December 16, 2003

Committee: David Jacobson-Kram, Ph.D., HFD-024, Chair
Abby Jacobs, Ph.D., HFD-540, Member
Joseph Contrera, Ph.D., HFD-901, Member
Robert Osterberg, Ph.D., HFD-520, Alternate Member
Lois Freed, Ph.D., HFD-120, Supervisory Pharmacologist
Ikram Elayan, Ph.D., HFD-120, Presenting Reviewer

Author of Minutes: Ikram Elayan, Ph.D., Presenting Reviewer

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

The committee did not address the sponsor's proposed statistical evaluation for the 2-yr carcinogen bioassays, as this does not affect the sponsor's ability to initiate the bioassays. The sponsor may seek guidance on the statistical evaluation of bioassay results from agency staff separately. Data files should be submitted electronically following section E of the 'Guidance for Industry, Providing Regulatory Submission in Electronic Format, New Drug Application.'

IND #: 68368
Drug Name: E2007
Sponsor: Eisai Medical Research Inc.

Background: E2007 is an AMPA type glutamate receptor antagonist that is being developed as an adjunctive therapy for the treatment of partial seizures in adults. The sponsor sought Agency concurrence for the dose selection for 2-year gavage carcinogenicity studies in CD-1mice and Sprague-Dawley rats. According to the sponsor, data from 4-week and 13-week gavage studies in CD-1 mice and 4-week, 13-week, and 26-week gavage studies in Sprague-Dawley rats were used as the basis for dose selection. The compound was negative in a battery of genotoxicity tests (i.e., Ames test, in vivo micronucleus assay, and in vitro mouse lymphoma assay).

Mouse Carcinogenicity Study Protocol and Dose Selection:
The sponsor proposed doses (b) (4) for both male and female mice in the 2-year carcinogenicity study. The sponsor based dose-selection on mortality, severe clinical signs, and decreases in body weight gain observed in the 13-week and 4-week studies at doses ≥ 60 mg/kg.

Rat Carcinogenicity Study Protocol and Dose Selection:
The sponsor proposed dose (b) (4) for males and 0, 3, 10, and 30 mg/kg for females. Dose-selection for males was based on mortality (one moribund sacrifice) and clinical signs at 100 mg/kg in males in the 4-week study. Dose selection for

females was based on the body weight effect (11% decrease in body weight compared to controls) in females at 30 mg/kg in the 26-week study.

Executive CAC Recommendations and Conclusions:

Mouse:
The Committee did not concur with the doses proposed for both male and female mice. This decision was based on the observation that deaths occurred in males and females at all doses used in the 13-week study. The 4-week study was considered inadequate to support dose-selection because of the short duration of the study. The Committee recommended that the sponsor conduct a 13-week study (to include histopathology and toxicokinetic evaluation) using lower doses in order to identify an MTD for the 2-year study.

Rat:
The Committee concurred with the doses selected by the sponsor for female rats based on the body weight effect (~10% decrease in body weight compared to control) observed at the end of the 26-week study. The Committee did not concur on the doses selected for male rats due to the lack of dose-limiting toxicities in the 4-week, 13-week, and 26-week studies in males. (The Committee did not consider the moribund sacrifice in one male at 100 mg/kg in the 4-week study to be drug-related). The Committee recommended that the sponsor conduct a 13-week study (to include histopathology and toxicokinetic evaluation) in male rats using higher doses in order to identify an MTD for the 2-year study.

If the sponsor plans histological evaluation of tissues from only control and high-dose treatment groups, they will also need to conduct histopathologic examination of other dose groups in addition to the control and high dose group under any of the following circumstances:

(a) for any macroscopic findings in the low and mid dose groups for a given tissue, they will need to look at that tissue for all of the dose groups
(b) for an increase in the incidence of tumors (rare or common) in the high dose group for a tissue, even if not statistically significant, they will also need to look at the next lower dose group
(c) for an increase in tumors in an organ for a tumor type that should be analyzed across tissue sites as well as by tissue site (e.g., hemangiosarcoma, lymphoma etc.; see McConnell et al, JNCI 76:283, 1986) they should look at all relevant tissues for that dose level and the next lower dose level,
(d) for an excessive decrease in body weight or survival in the examined dose group, they should examine lower dose groups.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\

/Division File, HFD-120
/Lois Freed, Supervisory Pharmacologist, HFD-120
/Ikram Elayan, Reviewer, HFD-120
/Melina Griffis, CSO/PM, HFD-120
/Adele Seifried, HFD

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/s/

David Jacobson-Kram

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