

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**022416Orig1s000**

**OTHER REVIEW(S)**

**PMR/PMC Development Template for Eslicarbazepine Acetate  
PMR # 2099-1**

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

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PMR/PMC Description: “A study conducted in juvenile dogs to assess the potential immunotoxicity of eslicarbazepine acetate.”

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PMR/PMC Schedule Milestones: Final protocol Submission Date: 03/2014  
Study Completion Date: 06/2015  
Final Report Submission Date: 12/2015

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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
- X Other

The sponsor is not seeking a pediatric indication in the current NDA submission. However, the nonclinical study would be required to support clinical trials in pediatric patients conducted under PREA.

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.”

A juvenile dog toxicology study under PREA to identify and characterize the unexpected serious risk of adverse effects of eslicarbazepine on the immune system of the developing organism. The study should utilize animals of an age range and stage(s) of development that are comparable to the intended 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 juvenile dog toxicology study under PREA to identify and characterize the unexpected serious risk of adverse effects of eslicarbazepine acetate on the immune system of the developing organism. The study should utilize animals of an age range and stage(s) of development that are comparable to the intended pediatric population.

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?

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**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 Aptiom (Eslicarbazepine Acetate)  
PMR # 2099-2**

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

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PMR/PMC Description: Pediatric Pharmacokinetic and Tolerability Study in Patients 1 month to < 24 months of age

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PMR/PMC Schedule Milestones:	Final protocol Submission Date:	12/2016
	Study/Clinical trial Completion Date:	8/2020
	Final Report Submission Date:	03/2021
	Other:	MM/DD/YYYY

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. The drug is ready to be approved in adults.

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 eslicarbazepine acetate following multiple administrations in patients with partial-onset seizures aged 1 month to < 24 months old, and also provide information about safety and tolerability 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 and tolerability study in pediatric patients ages 1 month to < 24 months with partial-onset seizures. At least two maintenance dose levels of eslicarbazepine acetate must be evaluated to characterize pharmacokinetic parameters following at least one week of administration for each dose level of oral eslicarbazepine acetate following titration. Pharmacokinetic data must be obtained and analyzed using intensive sampling, sparse sampling, or both approaches. If a sparse sampling approach is used, approximately 3-4 blood samples per patient should be collected to enable adequate characterization of the concentration-time profile. At least 20% of patients must come from the 1-month to 6-month age group, and at least 25% of patients must come from the 6- to 12-month and the 12- to 24-month age groups. Effort must be made to balance the gender distribution within each age cohort, with no less than 35% of patients in each gender.

This human study is not to be initiated until juvenile toxicity study (requested under PREA PMR 2099-1) is completed and can be reviewed to inform the design of this study.

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)
-

NDA 022416  
eslicarbazepine  
 Other

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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 Aptiom (Eslicarbazepine Acetate)  
PMR # 2099-3**

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

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PMR/PMC Description: A prospective, randomized, controlled, double-blind, efficacy and safety study of eslicarbazepine acetate in children ages 12 years to <18 years for the adjunctive the treatment of partial onset seizures. The primary efficacy endpoint must examine seizure frequency based upon diary data. Safety must be evaluated. Subgroup analyses of the effect of the concomitant use of enzyme-inducing anticonvulsants (i.e., carbamazepine, phenytoin, phenobarbital or primidone) on the safety and efficacy of eslicarbazepine acetate must be performed.

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PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>06/2014</u>
	Study/Clinical trial Completion Date:	<u>03/2018</u>
	Final Report Submission Date:	<u>12/2018</u>
	Other:	<u>MM/DD/YYYY</u>

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 deferral has been granted for those ages 1 month to < 18 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.

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 eslicarbazepine acetate for the adjunctive the treatment of partial onset seizures in children ages 12 to <18 years for the adjunctive the treatment of partial onset seizures with a long term safety extension. Efficacy and short term safety will be studied in the controlled phase and long term safety will be studied in an open-label long term extension PMR 2099-4).

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 eslicarbazepine acetate in children ages 12 years to <18 years for the adjunctive the treatment of partial onset seizures. The primary efficacy endpoint must examine seizure frequency based upon diary data. Safety must be evaluated. Subgroup analyses of the effect of the concomitant use of enzyme-inducing anticonvulsants (i.e., carbamazepine, phenytoin, phenobarbital or primidone) on the safety and efficacy of eslicarbazepine acetate must be performed.

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?

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**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 Aptiom (Eslicarbazepine Acetate)  
PMR # 2099-4**

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

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PMR/PMC Description: Open-label long term extension study for PMR 2099-#3 (A prospective, randomized, controlled, double-blind, efficacy and safety study of eslicarbazepine acetate in children ages 12 years to <18 years for the adjunctive the treatment of partial onset seizures). Safety must be evaluated. Subgroup analyses of the effect of the concomitant use of enzyme-inducing anticonvulsants (i.e., carbamazepine, phenytoin, phenobarbital or primidone) on the safety of eslicarbazepine acetate must be performed.

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PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>06/2014</u>
	Study/Clinical trial Completion Date:	<u>10/2018</u>
	Final Report Submission Date:	<u>06/2019</u>
	Other:	<u>MM/DD/YYYY</u>

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 deferral has been granted for those ages 1 month to < 18 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.

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 eslicarbazepine acetate for the adjunctive the treatment of partial onset seizures in children ages 12 to <18 years for the adjunctive the treatment of partial onset seizures with a long term safety extension. Efficacy and short term safety will be studied in a controlled phase and long term safety will be studied in the open-label 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.

Open-label long term extension study for PMR 2099-#3 (A prospective, randomized, controlled, double-blind, efficacy and safety study of eslicarbazepine acetate in children ages 12 years to <18 years for the adjunctive the treatment of partial onset seizures). Safety must be evaluated. Subgroup analyses of the effect of the concomitant use of enzyme-inducing anticonvulsants (i.e., carbamazepine, phenytoin, phenobarbital or primidone) on the safety of eslicarbazepine acetate must be performed.

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?

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**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 Aptiom (Eslicarbazepine Acetate)  
PMR # 2099-5**

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

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PMR/PMC Description: A prospective, randomized, controlled, double-blind, efficacy and safety study of eslicarbazepine acetate in children ages 2 years to < 12 years for the adjunctive treatment of partial onset seizures. The primary efficacy endpoint during the controlled phase must examine seizure frequency based upon diary data. Safety must be evaluated during the controlled phase. Subgroup analyses of the effect of the concomitant use of enzyme-inducing anticonvulsants (i.e., carbamazepine, phenytoin, phenobarbital or primidone) on the safety and efficacy of eslicarbazepine acetate must be performed.

This human study is not to be initiated until the juvenile toxicity study (requested under PREA PMR 2099-1) is completed and can be reviewed to inform the design of this study.

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PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>01/2017</u>
	Study/Clinical trial Completion Date:	<u>08/2022</u>
	Final Report Submission Date:	<u>02/2023</u>
	Other: _____	<u>MM/DD/YYYY</u>

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 deferral has been granted for those ages 1 month to < 18 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.

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 eslicarbazepine acetate for the adjunctive the treatment of partial onset seizures in children ages 2 to <12years for the adjunctive the treatment of partial onset seizures with a long term safety extension. Efficacy and short term safety will be studied in the controlled phase and long term safety will be studied in the open-label 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 eslicarbazepine acetate in children ages 2 years to < 12 years for the adjunctive treatment of partial onset seizures. The primary efficacy endpoint during the controlled phase must examine seizure frequency based upon diary data. Safety must be evaluated during the controlled phase. Subgroup analyses of the effect of the concomitant use of enzyme-inducing anticonvulsants (i.e., carbamazepine, phenytoin, phenobarbital or primidone) on the safety and efficacy of eslicarbazepine acetate must be performed.

This human study is not to be initiated until the juvenile toxicity study (requested under PREA PMR 2099-1) is completed and can be reviewed to inform the design of this study.

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?

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**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 Aptiom (Eslicarbazepine Acetate)**  
**PMR # 2099-6**

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

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PMR/PMC Description: Open-label long term extension study for PMR 2099-5 (A prospective, randomized, controlled, double-blind, efficacy and safety study of eslicarbazepine acetate in children ages 2 years to < 12 years for the adjunctive treatment of partial onset seizures). Safety must be evaluated. Subgroup analyses of the effect of the concomitant use of enzyme-inducing anticonvulsants (i.e., carbamazepine, phenytoin, phenobarbital or primidone) on the safety of eslicarbazepine acetate must be performed.

This human study is not to be initiated until the juvenile toxicity study (requested under PREA PMR 2099-1) is completed and can be reviewed to inform the design of this study.

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PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>01/2017</u>
	Study/Clinical trial Completion Date:	<u>03/2023</u>
	Final Report Submission Date:	<u>12/2023</u>
	Other:	<u>MM/DD/YYYY</u>

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 deferral has been granted for those ages 1 month to < 18 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.

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 eslicarbazepine acetate for the adjunctive the treatment of partial onset seizures in children ages 2 to <12years for the adjunctive the treatment of partial onset seizures with a long term safety extension. Efficacy and short term safety will be studied in the controlled phase and long term safety will be studied in the open-label 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.

Open-label long term extension study for PMR 2099-5 (A prospective, randomized, controlled, double-blind, efficacy and safety study of eslicarbazepine acetate in children ages 2 years to < 12 years for the adjunctive treatment of partial onset seizures). Safety must be evaluated. Subgroup analyses of the effect of the concomitant use of enzyme-inducing anticonvulsants (i.e., carbamazepine, phenytoin, phenobarbital or primidone) on the safety of eslicarbazepine acetate must be performed.

This human study is not to be initiated until the juvenile toxicity study (requested under PREA PMR 2099-1) is completed and can be reviewed to inform the design of this study.

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?

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**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 Aptiom (Eslicarbazepine Acetate)**  
**PMR # 2099-7**

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

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PMR/PMC Description: A prospective, randomized, controlled, double-blind, efficacy and safety study of eslicarbazepine acetate for the adjunctive treatment of partial onset seizures in children ages 1 month to < 4 years. The primary efficacy endpoint must examine seizure frequency based upon Video/EEG data. Safety must be evaluated. Subgroup analyses of the effect of the concomitant use of enzyme-inducing anticonvulsants (i.e., carbamazepine, phenytoin, phenobarbital or primidone) on the safety and efficacy of eslicarbazepine acetate must be performed. At least 75% of children in the study should be  $\leq 2$  years old.

This pediatric study is not to start until the protocol can be informed by the completion and review of the juvenile toxicity study (as requested under PREA PMR 2099-1) because of a potential safety signal in a previous juvenile toxicity study. In addition, this pediatric study should not initiate or enroll subjects in the age group of 1 to 2 years until the pharmacokinetic study requested under PREA PMR 2099-2 is completed.

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PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>03/2021</u>
	Study/Clinical trial Completion Date:	<u>01/2024</u>
	Final Report Submission Date:	<u>07/2024</u>
	Other:	<u>MM/DD/YYYY</u>

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 deferral has been granted for those subjects 1 month to < 18 years of age. It is appropriate for a PMR because the drug is about to be approved for 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 eslicarbazepine acetate 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 an open-label 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 eslicarbazepine acetate for the adjunctive treatment of partial onset seizures in children ages 1 month to < 4 years. The primary efficacy endpoint must examine seizure frequency based upon Video/EEG data. Safety must be evaluated. Subgroup analyses of the effect of the concomitant use of enzyme-inducing anticonvulsants (i.e., carbamazepine, phenytoin, phenobarbital or primidone) on the safety and efficacy of eslicarbazepine acetate must be performed. At least 75% of children in the study should be  $\leq 2$  years old.

This pediatric study is not to start until the protocol can be informed by the completion and review of the juvenile toxicity study (as requested under PREA PMR 2099-1) because of a potential safety signal in a previous juvenile toxicity study. In addition, this pediatric study should not initiate or enroll subjects in the age group of 1 to 2 years until the pharmacokinetic study requested under PREA PMR 2099-2 is completed.

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)
-

NDA 022416  
eslicarbazepine

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?

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**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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**PMR/PMC Development Template for Aptiom (Eslicarbazepine Acetate)**  
**PMR # 2099-8**

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

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PMR/PMC Description: Long term extension study for PMR 2099-7 (A prospective, randomized, controlled, double-blind, efficacy and safety study of eslicarbazepine acetate for the adjunctive treatment of partial onset seizures in children ages 1 month to < 4 years). Safety must be evaluated. Subgroup analyses of the effect of the concomitant use of enzyme-inducing anticonvulsants (i.e., carbamazepine, phenytoin, phenobarbital or primidone) on the safety of eslicarbazepine acetate must be performed. At least 75% of children in the study should be  $\leq$  2 years old.

This pediatric study is not to start until the protocol can be informed by the completion and review of juvenile toxicity study (as requested under PREA PMR 2099-1) because of a potential safety signal in a previous juvenile toxicity study. In addition, this pediatric study should not initiate or enroll subjects in the age group of 1 to 2 years until the pharmacokinetic study requested under PREA PMR 2099-2 is completed.

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PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>03/2021</u>
	Study/Clinical trial Completion Date:	<u>08/2024</u>
	Final Report Submission Date:	<u>05/2025</u>
	Other:	<u>MM/DD/YYYY</u>

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 deferral has been granted for those subjects 1 month to < 18 years of age. It is appropriate for a PMR because the drug is about to be approved for 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 eslicarbazepine acetate 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 an open-label 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.

Long term extension study for PMR 2099-7 (A prospective, randomized, controlled, double-blind, efficacy and safety study of eslicarbazepine acetate for the adjunctive treatment of partial onset seizures in children ages 1 month to < 4 years). Safety must be evaluated. Subgroup analyses of the effect of the concomitant use of enzyme-inducing anticonvulsants (i.e., carbamazepine, phenytoin, phenobarbital or primidone) on the safety of eslicarbazepine acetate must be performed. At least 75% of children in the study should be  $\leq 2$  years old.

This pediatric study is not to start until the protocol can be informed by the completion and review of juvenile toxicity study (as requested under PREA PMR 2099-1) because of a potential safety signal in a previous juvenile toxicity study. In addition, this pediatric study should not initiate or enroll subjects in the age group of 1 to 2 years until the pharmacokinetic study requested under PREA PMR 2099-2 is completed.

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)
-

NDA 022416  
eslicarbazepine

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?

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**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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**PMR/PMC Development Template for Aptiom  
PMR # 2099-9**

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

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PMR/PMC Description: “A study to investigate the etiology of the changes in thyroid function tests caused by eslicarbazepine acetate.”

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PMR/PMC Schedule Milestones: Final protocol Submission Date: 08/2014  
Study/Clinical trial Completion Date: 08/2015  
Final Report Submission Date: 03/2016  
Other: \_\_\_\_\_ MM//YYYY

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

Information regarding abnormal changes in thyroid function tests has been incorporated into the eslicarbazepine acetate labeling. There were no thyroid-related serious adverse events reported in the NDA. However, this PMR would be important to identify the etiology of these abnormal thyroid laboratory tests in order to prevent patients from receiving treatment (thyroxine) for abnormalities that are potentially laboratory artifacts.

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 the NDA resubmission, eslicarbazepine use was associated with dose-dependent decreases in free T4 and free T3. Some of these patients had concurrent increases in TSH and potential signs and symptoms of hypothyroidism. However, most of these patients did not have evidence of clinical hypothyroidism. The goal of the clinical trial would be to further investigate the etiology of these low serum free T4 and free T3 values with the measurement of these values a physical separation method.

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 ex vivo study to determine whether eslicarbazepine interferes with assays for free T3 and T4 as well as total T3, T4, and TSH. Collect blood samples from 30 subjects who have taken a daily dose of at least 1200 mg eslicarbazepine acetate for at least 6 weeks, as well as blood samples from 30 non-eslicarbazepine acetate-exposed age-matched subjects. Subjects must not be taking phenytoin, carbamazepine, or oxcarbazepine (or any other drugs known to displace T4 or T3 from binding proteins). Blood samples collected from eslicarbazepine acetate-exposed subjects will be assayed utilizing the clinical trial methods and the most suitable physical separation methodology (e.g., equilibrium dialysis, ultrafiltration, gel filtration) for comparison for serum free T4 and serum free T3 measurements. Blood samples from non-eslicarbazepine acetate-exposed subjects will be spiked with a range of eslicarbazepine and R-licarbazepine concentrations both above and below the known exposures of patients receiving at least eslicarbazepine acetate 1200 mg and assayed utilizing the clinical trial methods and the most suitable physical separation methodology to determine the effect on serum free T3 and T4, as well as effects on serum total T3, T4, and TSH. Results will be evaluated to determine if there is an artifact in the method.

Technical experts familiar with the artifactual effects of certain drugs (e.g., carbamazepine, phenytoin) on decreasing serum free T4 and free T3 with non-physical separation methodologies (e.g., analog immunoassays) will be consulted to determine the most suitable physical separation method (e.g., equilibrium dialysis, ultrafiltration, gel filtration) and a justification of the physical separation methodology will be submitted with the protocol.

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

NDA 022416  
eslicarbazepine

- 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 Aptiom  
PMR # 2099-10**

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

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PMR/PMC Description: A study based on routine postmarketing safety surveillance, pharmacovigilance and clinical trial reports will characterize clinical and genomic risk factors associated with the development of serious dermatologic reactions in eslicarbazepine acetate -treated patients, including Stevens-Johnson Syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and drug rash with eosinophilia and systemic symptoms (DRESS). The study must include a control group of eslicarbazepine-tolerant patients and use high-throughput genotyping approaches to determine whether specific genotypes are associated with the development of these serious skin reactions.

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PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>06/2014</u>
	Interim Report Submission:	<u>06/2015</u>
	Interim Report Submission:	<u>06/2016</u>
	Interim Report Submission:	<u>06/2017</u>
	Interim Report Submission:	<u>06/2018</u>
	Interim Report Submission:	<u>06/2020</u>
	Interim Report Submission:	<u>06/2021</u>
	Interim Report Submission:	<u>06/2022</u>
	Interim Report Submission:	<u>06/2023</u>
	Interim Report Submission:	<u>06/2024</u>
	Study Completion Date:	<u>12/2024</u>
	Final Report Submission Date:	<u>06/2025</u>
	Other:	<u>MM//YYYY</u>

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

Serious skin reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare. One possible case of SJS was identified in the NDA database. Serious skin reactions will be discussed in the label. It is not feasible to determine genomic risk factors based on one case; this will require evaluation of multiple cases over a period of years.

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.”

Genetic risk factors for SJS have been identified for several antiepileptic drugs. It is important to characterize risk factors predicting serious skin reactions for specific antiepileptic drugs across this class so that healthcare providers and patients can make informed decisions about use of a specific antiepileptic drug, and so that patients will be able to avoid those drugs for which they may be a greater risk than the general population. The goal of this study is to characterize the genetic risk factors for serious skin reactions including SJS, TEN, and acute generalized exanthematous pustulosis (AGEP) after administration of eslicarbazepine acetate.

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 study based on routine postmarketing safety surveillance, pharmacovigilance and clinical trial reports will characterize clinical and genomic risk factors associated with the development of serious dermatologic reactions in eslicarbazepine acetate -treated patients, including Stevens-Johnson Syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and drug rash with eosinophilia and systemic symptoms (DRESS). The study must include a control group of eslicarbazepine-tolerant patients and use high-throughput genotyping approaches to determine whether specific genotypes are associated with the development of these serious skin reactions.

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

NDA 22416  
eslicarbazepine

- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

Other

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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?

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**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 Aptiom (Eslicarbazepine Acetate)**  
**PMR # 2099-11**

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

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PMR/PMC Description: Abuse potential assessment – dependence trial in healthy volunteers

PMR/PMC Schedule Milestones: Final protocol Submission Date: 08/2014  
Study/Clinical trial Completion Date: 05/2015  
Final Report Submission Date: 12/2015  
Other: \_\_\_\_\_ MM/DD/YYYY

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

Eslicarbazepine is a new molecular entity (NME). The dependence liability data for a drug is often submitted as part of a Sponsor's abuse potential section and safety assessment in the NDA. The NDA database suggests that the drug has substantial experience that indicates safety. However, physical dependence is possible and it has not been fully addressed. Section 9.3 of the label will note that the potential for eslicarbazepine to produce withdrawal symptoms has not been adequately evaluated. Therefore, although a physical dependence study is required, it can be conducted postmarketing.

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 potential risk for withdrawal after abrupt discontinuation of eslicarbazepine. In the submitted NDA, withdrawal symptoms were not evaluated in a reliable fashion. The withdrawal data consists only of collection of adverse events after the discontinuation of eslicarbazepine, however this data has major drawbacks:

1. The human withdrawal/dependency data is incomplete and misleading
2. Abrupt withdrawal is confused with tapered withdrawal
3. The withdrawal data provided in the ISS is misleading as it became clear that the sponsor just reassembled all AEs which started within 30 days following discontinuation of eslicarbazepine and called it “withdrawal data” regardless of whether the patient was taking the drug eslicarbazepine (in open label treatment) or not.
4. Dependence study performed in mice is invalid

CSS concludes that the withdrawal/dependency data does not provide reliable information about dependency and withdrawal in patients treated with eslicarbazepine. Therefore, a human dependency study in healthy volunteers is required.

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 healthy volunteers in which subjects are titrated to 800 mg of eslicarbazepine acetate and maintained at this dose for four weeks. At the end of the treatment, the drug should be abruptly withdrawn. Withdrawal should be conducted in an inpatient setting with immediate access to physicians capable of managing medical emergencies (e.g., status epilepticus, cardiopulmonary arrest). Withdrawal questionnaires should be administered at the pre-treatment visit, within the last two days of treatment, on the first day post-treatment, on the fourth to fifth day post-treatment, on the tenth to eleventh day post-treatment, and on the twentieth to twenty- first day post-treatment. All adverse events occurring during the withdrawal period are to be collected. Plasma levels of eslicarbazepine should be measured and accompany every administration of withdrawal questionnaires through the fifth day post-treatment.

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 trial 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

NDA 22416  
eslicarbazepine

Nonclinical study, not safety-related (specify)

Other

---

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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?

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**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)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SALLY U YASUDA  
11/12/2013

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

Product Title <sup>1</sup>	APTIOM <sup>®</sup> (eslicarbazepine acetate) tablets, for oral use
Applicant	Sunovion Pharmaceuticals Inc.
Application/Supplement Number	NDA 22416
Type of Application	Original
Indication(s)	adjunctive treatment of partial-onset seizures
Established Pharmacologic Class <sup>1</sup>	
Office/Division	ODE I/DNP
Division Project Manager	Sulin Sun
Date FDA Received Application	February 11, 2013
Goal Date	November 11, 2013
Date PI Received by SEALD	November 4, 2013
SEALD Review Date	November 5, 2013
SEALD Labeling Reviewer	Elizabeth Donohoe
Acting SEALD Division Director	Sandra Kweder

<sup>1</sup> The product title or established pharmacologic class that appears in draft agreed-upon prescribing information (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.

# Selected Requirements of Prescribing Information

## 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 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:** HL will be 1/2 page when header is removed.

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

**Comment:**

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

**Comment:**

- YES** 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:**

- 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

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

**N/A**

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

**Comment:**

**N/A**

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

- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” in *italics* and centered immediately beneath the heading.

**Comment:**

- N/A** 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:**

- N/A** 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

- N/A** 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.

## Selected Requirements of Prescribing Information

### 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

- NO** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment: *The revision date is missing and should read: 11/2013; the clean version of the agreed-upon PI should include the revision date. [see the Draft Labeling Review MAPP; a link is on the SEALD internal website]*

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## 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:

- N/A** 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:

## Selected Requirements of Prescribing Information

- 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:
- YES** 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.

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

## Selected Requirements of Prescribing Information

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

### 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

N/A

42. All text is **bolded**.

### Comment:

N/A

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:

N/A

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

N/A

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:

## Selected Requirements of Prescribing Information

*“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 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/  
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ELIZABETH A DONOHOE  
11/05/2013

ERIC R BRODSKY  
11/05/2013

I agree. Eric Brodsky, SEALD labeling team leader, signing for Sandra Kweder, acting SEALD Director.

**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**

**Final Label and Labeling Memorandum**

Date: October 31, 2013

Reviewer: Julie Neshiewat, 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 Strengths: Eslicarbazepine Acetate Tablets  
200 mg, 400 mg, 600 mg, 800 mg

Application Type/Number: NDA 022416

Applicant: Sunovion Pharmaceuticals

OSE RCM #: 2013-2333

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

## **1 INTRODUCTION**

This memorandum evaluates the revised labels and labeling for Eslicarbazepine Acetate, NDA 022416, submitted on October 29, 2013 (Appendices A through D). DMEPA previously reviewed the proposed labels and labeling under OSE Review # 2013-554 dated September 12, 2013.

## **2 MATERIAL REVIEWED**

DMEPA reviewed the labels and labeling submitted on October 29, 2013. We compared the revised labels and labeling against the recommendations contained in OSE Review # 2013-554 dated September 12, 2013.

## **3 CONCLUSIONS AND RECOMMENDATIONS**

The revised labels adequately address our concerns from a medication error perspective. We have no additional comments at this time.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Ermias Zerislassie, at 301-796-0097.

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IRENE Z CHAN on behalf of JULIE V NESHIEWAT  
10/31/2013

IRENE Z CHAN  
10/31/2013

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

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

**Memorandum**

**Date:** October 24, 2013

**To:** Su-Lin Sun, RPh  
Senior Regulatory Project Manager  
Division of Neurology Products (DNP)  
Office of Drug Evaluation (ODE)-I

**From:** Melinda McLawhorn, PharmD, BCPS  
Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**CC:** Mathilda Fienkeng, PharmD  
Team Leader, OPDP

Julie Villanueva Neshiewat, PharmD  
Safety Evaluator  
Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Surveillance and Epidemiology (OSE)

**Subject:** **NDA 22416**  
Eslicarbazepine tablets

**Background**

On March 19, 2013, DNP consulted OPDP to review the draft package insert (PI), patient package insert (PPI), medication guide (MG), and carton and container labeling for the original NDA submission for eslicarbazepine tablets. On May 17, 2013, DMEPA requested that OPDP provide comments on the draft carton and container labeling submitted to the electronic document room on March 28, 2013. OPDP submitted a review of the carton and container labeling on May 30, 2013.

OPDP reviewed the draft substantially complete versions of the PI, PPI, and MG provided by DNP on October 9, 2013 and the carton and container labeling provided by DNP on October 2, 2013. The Division of Medical Policy Programs (DMPP) and OPDP provided comments on the MG and PPI under separate cover on October 18, 2013. Our comments on the PI and carton and container labeling are provided below.

Thank you for your consult. If you have any questions, please contact Melinda McLawhorn at 6-7559 or at Melinda.McLawhorn@fda.hhs.gov.

**General Comments**

Since the proprietary name, "Aptiom," has not been approved, we will not comment on the presentation of the proprietary name at this time.

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MELINDA W MCLAWHORN  
10/24/2013

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

**PATIENT LABELING REVIEW**

Date: October 17, 2013

To: Eric Bastings, MD  
Acting Director  
**Division of Neurology Products (DNP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**  
  
Melissa Hulett, MSBA, BSN, RN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**  
  
Mathilda Fienkeng, PharmD  
Team Leader  
**Office of Prescription Drug Promotion (OPDP)**

From: Sharon W. Williams, MSN, BSN, RN  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**  
  
Melinda McLawhorn, PharmD, BCPS  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): APTIOM (eslicarbazepine acetate)

Dosage Form and Route: Tablets

Application Type/Number: NDA 22-416

Applicant: Sunovion Pharmaceuticals Inc.

## 1 INTRODUCTION

On March 29, 2009, Sunovion Pharmaceuticals Inc. submitted for the Agency's review a New Drug Application for APTIOM (eslicarbazepine acetate) tablets indicated for adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy 18 years and older. On April 30, 2010 the Agency issued a Complete Response letter. The Applicant resubmitted the application on February 8, 2013.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology Products (DNP) on February 11, 2013, and February 10, 2013, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for APTIOM (eslicarbazepine acetate) tablets.

## 2 MATERIAL REVIEWED

- Draft APTIOM (eslicarbazepine acetate) MG received on February 8, 2013, and received by DMPP on February 11, 2013.
- Draft APTIOM (eslicarbazepine acetate) MG received on February 8, 2013, revised by the Review Division throughout the review cycle, and received by OPDP on October 9, 2013
- Draft APTIOM (eslicarbazepine acetate) Prescribing Information (PI) received on February 8, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on October 9, 2013.
- Draft APTIOM (eslicarbazepine acetate) Prescribing Information (PI) received on February 8, 2013 revised by the Review Division throughout the review cycle, and received by OPDP on October 9, 2013.
- Approved OXTELLAR XR (oxcarbazepine) extended-release tablets comparator labeling dated October 19, 2012.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> 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 collaborative 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 is free of promotional language or suggested revisions to ensure that it is free of promotional language
- 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 and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP 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/  
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SHARON W WILLIAMS  
10/17/2013

MATHILDA K FIENKENG on behalf of MELINDA W MCLAWHORN  
10/17/2013

MELISSA I HULETT  
10/17/2013

LASHAWN M GRIFFITHS  
10/18/2013

**MEMORANDUM**

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

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**CLINICAL INSPECTION SUMMARY**

DATE: October 10, 2013

TO: Sulin Sun, Regulatory Project Manager  
Teresa Podruchny, M.D., Clinical Reviewer  
Norman Hershkowitz, M.D., Clinical Team Leader  
Division of Neurology Products

FROM: John Lee M.D., Medical Officer  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H., Team Leader  
Kassa Ayalew, M.D., M.P.H., Acting Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

APPLICATION: NDA 022-416

APPLICANT: Sunovion Pharmaceuticals, Inc.

DRUG: Stedesa<sup>®</sup> (eslicarbazepine acetate) Tablets

NME: Yes

INDICATION: Adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy 18 years and older

THERAPEUTIC CLASSIFICATION: Priority

CONSULTATION REQUEST DATE: March 15, 2013

INSPECTION SUMMARY GOAL DATE: October 10, 2013

REVIEW DIVISION ACTION GOAL DATE: November 8, 2013

PDUFA DUE DATE: November 8, 2013

## I. BACKGROUND

This NDA 22-416 was submitted (resubmitted) by Sunovion Pharmaceuticals, Inc. (**Sunovion**, formerly Sepracor, Inc.) in support of eslicarbazepine acetate (**ESL**), a new molecular entity (**NME**) to treat partial-onset seizures in adult patients (age 18 years or older) with epilepsy. The NDA had been originally submitted by Sepracor, Inc. (**Sepracor**) in March 2009, and a complete response letter (**CRL**) was issued by the Agency in April 2010 for deficiencies in nearly all review disciplines, including major violative findings at good clinical practice (**GCP**) inspections of the two pivotal studies supporting the original submission.

### Regulatory and GCP Inspection History

ESL is currently approved and marketed in Europe and Albania (16 countries) as an adjunctive anti-epileptic drug (**AED**) in adult patients with partial-onset seizures with or without secondary generalization. Bial-Portela, Inc. (**BIAL**) had originally developed ESL under the Investigational New Drug Application (**IND**) 67466 as an adjunctive AED to treat partial onset seizures in adults with epilepsy. The sponsorship was transferred from BIAL to Sepracor (currently, Sunovion) in April 2008, several years after the completion of two pivotal studies, BIA-2093-301 (**Study 301**, completed in 2005) and BIA-2093-302 (**Study 302**, completed in 2006).

Three pivotal studies had supported the original NDA submission, Study 301, Study 302, and BIA-2093-303 (**Study 303**). All three studies had been conducted outside the United States (**US**). Based on Sepracor's violative GCP audit findings (internal to Sepracor), Study 303 was not considered in support of this NDA, for either efficacy (as proposed by sponsor) or safety (as determined by FDA).

The NDA was initially submitted in June 2009. For Studies 301 and 302, five sites were inspected (GCP) between September and October 2009: the sponsor site (abbreviated inspection) and four clinical study sites (two per study) selected based on subject enrollment and the sponsor's audit findings. No significant deficiencies were noted at the abbreviated sponsor inspection. However, serious GCP deficiencies were observed at two clinical study sites, one site in Croatia for Study 301 and a second site in Spain for Study 302. Major deficiency areas included protocol adherence, subject records, adverse event (**AE**) reporting, and drug accountability. The study data from both sites were deemed unreliable. Further, the inspectional outcome at these two sites raised concerns about GCP compliance at other sites not inspected by FDA.

#### *Study 301 (Croatia, Site 112, Danilo Hodoba, 18 subjects):*

- The assignment of study medication kits to subjects was not adequately documented (also no lot numbers on drug accountability log). On occasion, incorrect study medication was dispensed to an unintended subject. The amount of the study medication dispensed, returned, or destroyed was not adequately documented. For many subjects, the recorded number of tablets destroyed was greater than the number returned. All study medication (and labeling) was destroyed prior to inspection.
- Data reported in the NDA (data listings) did not match those recorded in corresponding source documents and/or case report forms (**CRFs**). For example: (1) one seizure count in the efficacy data listing did not match the count in the corresponding subject diary, and (2) a serious AE (**SAE**) of neutropenia (leading to subject discontinuation) documented on the CRF was not reported in the AE listing. Further, the translator was not identified on English translations of seizure diaries, and one could not verify the accuracy of the translation (and consequently, study data reliability).

#### *Study 302 (Spain, Site 395, Carmen Diaz-Obregon, 16 subjects):*

- At least four enrolled subjects did not meet the subject inclusion criterion for seizure disorder: (1) by history, the subjects did not have the required seizure frequency and pattern, and (2) by study conduct, seizure activity during the observational baseline period of the study was not documented, and one could not verify the seizure frequency and pattern specified as an inclusion criterion.

- The numbers of seizures recorded in the seizure diaries did not always match those on corresponding CRFs. In several subjects, source documents about seizure counts were missing. Further, in general, study records were disorganized, often not signed by study personnel, and typically contained many cryptic handwritten attached ("sticky") notes.

Based on these inspectional findings, FDA requested that the sponsor conduct at least one new clinical study, with or without additional information to support the acceptability of Studies 301 and 302. The sponsor received extensive FDA guidance since receiving the CRL.

The first NDA resubmission (September 4, 2012) was determined incomplete, and additional information was provided in a second resubmission (February 11, 2013) in response to FDA's letter to Acknowledge Incomplete Response (**AIR**). As requested by the FDA, the current (second) resubmission is supported by a new Study BIA-2093-304 Part 1 (**Study 304**) and new sponsor audits in support of the three pivotal Studies 301, 302, and 304.

### **Study BIA-2093-304 Part 1 (Study 304)**

#### *Efficacy and Safety of Eslicarbazepine Acetate (BIA 2-093) as Adjunctive Therapy for Refractory Partial Seizures in a Double-blind, Randomized, Placebo-controlled, Parallel-group, Multi-center Clinical Trial*

This study was the first of three sequential studies (Parts 1, 2 and 3) conducted in 653 subjects with refractory partial seizures (simple or complex, with or without secondary generalization) at 173 sites in 19 countries: Argentina, Australia, Brazil, Belgium, Canada, Cyprus, France, Germany, Greece, Hungary, India, Italy, Poland, Turkey, South Korea, Romania, South Africa, Ukraine, and US.

Part 1 of the study, the primary portion conducted over three years (December 2008 to January 2012), was a randomized, placebo-controlled, double-blind, parallel-group study consisting of three study periods over 22 weeks. Parts 2 and 3 were two open label extensions of Part 1, intended to permit eligible subjects to continue ESL therapy. Part 1 of the study consisted of the following study periods:

- *First Period:* During this eight-week observational baseline period, subjects were instructed on how to complete the seizure diary. Eligible subjects at the end of this period were randomized in equal ratio into three treatment groups: (1) ESL 800 mg, (2) ESL 1200 mg, and (3) placebo.
- *Second Period:* During this two-week dose initiation period (Weeks 1-2), subjects received 400 mg less than the final intended dose of the study medication, by mouth (**PO**) daily (**QD**): (1) ESL 400 mg for the 800 mg group, (2) ESL 800 mg for the 1200 mg group, or (3) placebo.
- *Third Period:* During this 12-week maintenance period (Weeks 3-14), subjects received the final intended maintenance dose of the study medication: (1) ESL 800 mg for the 800 mg group, (2) ESL 1200 mg for the 1200 mg group, or (3) placebo.

At completion of the third period, subjects who did not enter Part 2 were tapered off the study medication in 400 mg dose decrements: (1) ESL 800 mg decreased to 400 mg (two weeks), (2) ESL 1200 mg decreased to 800 mg (one week) then 400 mg (one week), or (3) placebo (two weeks).

Subjects completing Part 1 could enter Part 2, the first (one-year) open-label extension study during which the ESL dose was titrated as needed in 400 mg increments within the 400-1600 mg range. Subjects completing Part 2 could enter Part 3, the second (two-year) open-label extension study (identical in design to Part 2), or transfer to a local program that allowed continued ESL therapy.

#### **Major Study Features**

The primary study objective was to evaluate the efficacy of ESL at daily doses of 800 mg and 1200 mg as AED in subjects with refractory partial epilepsy. Secondary objectives were to evaluate: (1) safety and tolerability of ESL at daily doses of 800 and 1200 mg, (2) drug interactions between ESL and concomitant AEDs, and (3) health-related quality-of-life (**HR-QoL**) and depression during ESL therapy.

- Subject Selection: (1) subjects of age  $\geq 16$  years with epilepsy for  $\geq 12$  months currently being treated using a stable regimen of one or two AED for  $\geq$  one month (any except oxcarbazepine) and with  $\geq$  four partial-onset seizures in the last four weeks prior to screening, (2) on-going seizures, confirmed by  $>$  eight partial-onset seizures during eight weeks of observation with  $\geq$  three partial-onset seizures in each half (four weeks) and no seizure-free interval  $> 28$  consecutive days
- Primary Efficacy Endpoint and Analysis: Seizures and standardized seizure frequency (**SSF**) during dose maintenance (*Third Period*), calculated as mean number of seizures per four-week period
- Secondary Efficacy Endpoints and Analyses (assessments for *Third Period*): Clinical Global Impressions (**CGI**); Quality of Life In Epilepsy Questionnaire-31 (**QOLIE-31**), Seizure Severity Questionnaire (**SSQ**); Montgomery-Asberg Depression Rating Scale (**MADRS**), sensitivity analyses for the primary efficacy endpoint
- Safety Endpoints and Analyses: AEs, laboratory tests, physical and neurological examinations, electrocardiogram (**ECG**), ESL and concomitant AED levels, Columbia Suicide Severity Rating Scale (**C-SSRS**), Medical Outcomes Study Sleep Scale (**MOS-SS**)

### **Major Study Results**

- At the 1200 mg dose, the efficacy results for ESL were statistically significant (in comparison with placebo) in reducing SSF. ESL 800 mg also appeared to be effective (not statistically significant).
- There were two deaths (one placebo, one ESL 800 mg). SAEs were observed in less than 4% of the subjects with no apparent differences in SAE types: 3.1% placebo, 6.5% ESL 800 mg, and 1.4% ESL 1200 mg. ESL appeared to be well tolerated at either dose level.

### **Efficacy Results and GCP**

- Sponsor's analysis showed that the statistically significant efficacy margin of ESL 1200 mg over placebo was less pronounced for North America (**NA**) than for the rest of the world (**ROW**). Further, regarding the statistically non-significant efficacy results for ESL 800 mg: (1) for NA, the results were similar to those for placebo (apparently not effective), while (2) for ROW, the results were similar to those for ESL 1200 mg (apparently effective).
- It is unclear if these contrasting observations for NA and ROW reflect true differences between NA and ROW, including differences in subject responsiveness to ESL therapy and/or differences in the stringency of adherence to GCP requirements and standards in conducting clinical studies. A major goal of the GCP inspections for this resubmitted NDA is to rule out (or confirm) the possibility that Study 304 was conducted with greater attention to GCP in NA (US and Canada) than in ROW (South America, South Africa, Australia, South/East Asia, and Eastern/Western Europe).

### **Study BIA-2093-302 (Study 302)**

#### *Efficacy and Safety of BIA 2-093 as Adjunctive Therapy for Refractory Partial Seizures in a Double-blind, Randomized, Placebo-controlled, Parallel-group, Multicenter Clinical Trial*

This study (similar title and design as for Study 304) was conducted in two parts in 395 subjects at 46 sites in 13 countries: Argentina, Australia, Belgium, Brazil, Denmark, Germany, Netherlands, Portugal, Romania, South Africa, Spain, Sweden, and United Kingdom.

As in Study 304, Part 1 of this Study 302 was the primary portion of this two-part study. Part 1, conducted over 27 months (September 2004 to December 2006), was a randomized, placebo-controlled, double-blind, parallel-group study consisting of three periods over 22 weeks.

- *Baseline Observation Period:* Eligibility per seizure activity was confirmed during this period, after which subjects having  $\geq 4$  eligible seizures in each four-week half were randomized in equal ratio into four treatment groups: (1) ESL 400 mg, (2) ESL 800 mg, (3) ESL 1200 mg, and (4) placebo.

- **Dose Titration Period:** During this two-week dose titration period, subjects randomized to the ESL 1200 mg group received ESL 800 mg. In all other groups, initial dosing was the same as for the *Maintenance Period*. The study medication was given PO QD.
- **Dose Maintenance Period:** During this 12-week maintenance period, subjects received the final intended dose of the study medication as randomized.

Subjects who could not tolerate the study medication were withdrawn (dose decrease not allowed). Subjects completing *Dose Maintenance Period* entered Part 2, one-year of open-label treatment, at an initial ESL dose of 800 mg for one month, after which ESL dose was increased (to achieve further seizure reduction) or decreased (for severe AE) by 400 mg within the 400-1200 mg range. Subjects completing Part 2 could continue ESL treatment (until marketing authorization) with study visits per investigator discretion (at least every six months).

### **Major Study Features**

The primary study objective was to evaluate the efficacy of ESL at daily doses of 400, 800, and 1200 mg as adjunctive AED in subjects with refractory partial epilepsy. Secondary objectives were to evaluate: (1) safety and tolerability of ESL at daily doses of 400, 800, and 1200 mg, (2) drug interactions between ESL and concomitant AEDs, and (3) HR-QoL and depression during ESL therapy.

- Subject Inclusion
  - Age  $\geq 18$  years with epilepsy for  $\geq 12$  months
  - Current treatment for epilepsy using a stable regimen of one or two AED for  $\geq$  two months
  - Women of childbearing potential: negative pregnancy test and acceptable contraception
  - Four or more partial-onset seizures in each half (four weeks) of the eight-week baseline period
  - All seizure-free intervals during the baseline period not longer than 21 days
- Subject Exclusion
  - Only simple partial seizures with no motor symptomatology or primarily generalized epilepsy
  - Status epilepticus or cluster seizures ( $\geq$  three seizures within 30 minutes) within three months
  - Seizures of psychogenic origin within last two years
  - History of schizophrenia or suicide attempt
  - Known rapid progressive neurological disorder
  - Current exposure to felbamate or oxcarbazepine within one month of screening
  - More than occasional use of benzodiazepines (except chronic use as AED)
  - Known hypersensitivity to carbamazepine, oxcarbazepine or chemically related substances
  - History of abuse of alcohol, drugs or medications within last two years
  - Uncontrolled cardiac disorder; second or third-degree heart block not corrected with pacemaker
  - Uncontrolled renal disorder; estimated creatinine clearance  $< 50$  mL/min
  - Uncontrolled gastrointestinal, hepatic, or endocrine disorder
  - Alanine or aspartate transaminases  $>$  twice upper limit of normal
  - Uncontrolled metabolic or oncologic disorder; sodium  $< 130$  mmol/L
  - Uncontrolled hematologic disorder, including white blood cell count  $< 3000/\text{mm}^3$
  - Previous receipt of ESL or participation in an ESL study
  - Participation in other drug trials within last two months
  - Receipt of an investigational drug within five half-lives of the drug
  - Pregnancy or nursing; inability to comply with study requirements
- Primary Efficacy Endpoint and Analysis: Seizures and SSF during *Dose Maintenance Period*
- Secondary Efficacy Endpoints and Analyses (assessments for *Dose Maintenance Period*): CGI, QOLIE-31, MADRS, sensitivity analyses for the primary efficacy endpoint

- Safety Endpoints and Analyses: AEs, laboratory tests (including thyroid function tests), vital signs, body weight, ECG, ESL and AED levels, C-SSRS, MOS-SS

### **Major Study Results**

- At dose levels of 800 mg and 1200 mg, the efficacy results for ESL were statistically significant in reducing seizure frequency (33% reduction for ESL 800 or 1200 mg, 21% reduction for ESL 400 mg, and 5% reduction for placebo). One-third of patients on either 800 or 1200 mg ESL had > 50% reduction in seizure frequency.
- AEs were observed in 80% of subjects on ESL 800 mg or 1200 mg. The incidence and severity of common AEs (dizziness, headache, and nausea) appeared to be dose-dependent. SAEs in 12 subjects (3%, active groups only) resolved without intervention. No deaths were observed. ESL appeared to be well tolerated at all three ESL dose levels.

### **Study BIA-2093-301 (Study 301)**

#### *Efficacy and Safety of BIA 2-093 as Adjunctive Therapy for Refractory Partial Seizures in a Double-blind, Randomized, Placebo-controlled, Parallel-group, Multicenter Clinical Study*

This study (nearly identical title and design as for Study 302) was conducted in two parts in 402 subjects at 40 sites in 11 countries: Austria, Croatia, Czech Republic, Germany, Hungary, Lithuania, Poland, Romania, Russia, Switzerland, and Ukraine.

As in Studies 304 and 302, Part 1 of this Study 301 was the primary portion of this two-part study completed over 16 months (July 2004 to November 2005). Part 1 was the randomized, placebo-controlled, double-blind, parallel-group study consisting of four study periods over 26 weeks: *Baseline, Dose Titration, Dose Maintenance, and Dose Tapering*. The first and the third study periods (*Baseline, Dose Maintenance*) were identical in design as for Study 302.

- *Dose Titration*: During this two-week dose titration period, subjects randomized to the ESL 800 mg and 1200 mg groups received ESL 400 mg initially (first week), then 800 mg (second week). In the remaining groups, study medication dosing (PO QD) was the same as for the *Maintenance Period*.
- *Dose Tapering*: During this final four-week period, ESL dosing was decreased and discontinued in reverse parallel with dosing in *Dose Titration Period*. In the ESL 800 mg and 1200 mg groups, subjects sequentially received ESL 800 mg (first week), 400 mg (second week), and placebo (third and fourth weeks). In the ESL 400 mg group, subjects continued to receive 400 mg (first two weeks), then placebo (last two weeks).

As in Study 302, subjects who could not tolerate the study medication were withdrawn (dose decrease not allowed). Subjects completing *Dose Tapering Period* could enter Part 2 of the study for one year of open-label treatment. ESL was given at an initial dose of 800 mg for one month, after which the dose was increased (to achieve further seizure reduction) or decreased (for severe AE) by 400 mg within the 400-1200 mg range. The primary study objective and all major study features (including subject selection and major endpoints/analyses) were identical to those for Study 302.

### **Major Study Results**

At dose levels of 800 mg and 1200 mg, the efficacy results for ESL were statistically significant in reducing seizure frequency. Greater percent reduction in seizure frequency was achieved with greater ESL dose: 36% for ESL 800, 45% for ESL 1200 mg, 26% for ESL 400 mg, and 16% for placebo. Two-fifths (43%) of subjects on ESL 1200 mg and one-third (34%) of subjects on ESL 800 mg had > 50% reduction in seizure frequency (considered responders).

The incidence of AEs considered to be treatment-related increased with increasing ESL dose: 31% for placebo, 44% for ESL 400 mg, 50% for ESL 800 mg, and 61% for ESL 1200 mg. Most common AEs were dizziness, headache, somnolence, and nausea, and their severity appeared dose-dependent.

Treatment-related SAEs in 19 subjects (5%, no apparent correlation with treatment) resolved without intervention. One subject in the placebo group died (hypothermia). ESL appeared to be well tolerated at all three ESL dose levels.

### Sponsor Audit: Pivotal Studies 301, 302, and 304

The original Studies 301 and 302 were comparable in size (subjects and study sites). The new Study 304 was significantly larger than either original study; compared with the two combined, Study 304 enrolled nearly as many subjects (653 vs 797) at over twice as many study sites (173 vs 84). The number of subjects per site in Study 304 was less than half that for either original study (3.8 vs 9.5). Many sites participated in two of the three studies, either in Studies 301 and 304 or in Studies 302 and 304. No site participated in both Studies 301 and 302 (similar study dates/duration). In accordance with FDA's April 2010 CRL, new audits of all three pivotal studies (Studies 301, 302, and 304) were performed in 2010 by (b) (4) and other independent CROs:

- Study 304: 653 subjects were enrolled at 173 sites (3.8 subjects per site) in 19 countries: Argentina, Australia, Brazil, Belgium, Canada, Cyprus, France, Germany, Greece, Hungary, India, Italy, Poland, Turkey, South Korea, Romania, South Africa, Ukraine, and US. While on-going, the study had been monitored by (b) (4) for non-US sites and by (b) (4) for US sites. In the post-study audit, about one-half of all study sites were sampled (95 of 173, 55%).
- Study 302: 395 subjects were enrolled at 44 sites (9.0 subjects per site) in 13 countries: Argentina, Australia, Belgium, Brazil, Denmark, Germany, Netherlands, Portugal, Romania, South Africa, Spain, Sweden, and United Kingdom. The study had been monitored by (b) (4). Nearly all sites were sampled at post-study audit (39 of 44, 89%).
- Study 301: 402 subjects were enrolled at 40 sites (10.1 subjects per site) in 11 countries: Austria, Croatia, Czech Republic, Germany, Hungary, Lithuania, Poland, Romania, Russia, Switzerland, and Ukraine. The study had been monitored by (b) (4). Nearly all sites were sampled at post-study audit (37 of 40, 93%).

The sponsor's audit focused on five major GCP categories: (1) informed consent, (2) subject eligibility, (3) subject randomization, (4) AE reporting, and (5) drug accountability. For Studies 301 and 302, the audit included the review of nearly all subject records not reviewed during the original audit in 2008 (prior to NDA submission). For the new Study 304, about three-fourths of subject records (476 of 653, 73%) were reviewed at 88 clinical sites (39 NA and 49 ROW) and at two CRO sites (b) (4). The sites to be audited were selected based on high subject enrollment, SAEs, and geographic distribution.

For all three studies, the sponsor claims that the audit results support adequate and GCP-compliant study conduct. The sponsor notes: (1) audit findings for Studies 301 and 302 are consistent with those of the audit by European Medicines Agency (EMA), and (2) outcomes of Studies 301, 302, and 304 are consistent among each other. The major 2010 audit findings are:

- Deficiency types: findings similar to those in 2008 (original audit) for Studies 301 and 302
- AEs not reported: appreciably more found than in 2008 for Studies 301 and 302
- Eligibility violations: Study 302 > 301 > 304 (respectively 167, 91, and 28 subjects)
- Serious deficiencies, source records: two Poland sites in Study 301

For Studies 301 and 302, the greater number of deficiencies seen in 2010 (than in 2008) appears to reflect the greater rigor with which the audit was conducted in 2010. Studies 301 and 302, nearly identical in study design, were conducted in parallel (study dates and duration) under comparable study conditions (numbers of subjects and sites, both entirely foreign with many overlapping countries).

The number of deficiencies seen for Study 302 was significantly greater than that for Study 301 (approximately twice, reason unclear). Relatively few deficiencies were seen for the new Study 304,

possibly due to study conduct under heightened sponsor monitoring and/or fewer subjects per site. All three studies had been monitored by different monitoring CROs (b) (4)

The sponsor BIAL's original 2008 audit results (submitted as part of the initial NDA submission) had been deemed insufficient by the FDA. The follow up audit in 2010 was conducted in response to CRL, presumably according to an audit plan reviewed and approved by the FDA. The results of the 2010 audit were submitted as part of September 2012 and February 2013 NDA resubmissions.

## II. CLINICAL INSPECTIONS

Fourteen clinical (GCP) inspections were performed to support the review of this original NME NDA. The two tables below (for previous and current inspection cycles) show the FDA inspection outcomes and the sponsor's audit findings (numbers of deficiencies and rates of deficiencies per subject).

The sponsor's audit findings were a major consideration in selecting the clinical study sites to be inspected in support of the current review cycle (second inspection cycle). Other study site selection considerations included: (1) large subject enrollment, (2) multiple studies at same site, (3) world-wide distribution (Studies 301 and 302), and (4) US location (Study 304).

The major objectives of the sponsor inspection were to: (1) estimate the overall rate of GCP compliance across all clinical studies and sites, (2) identify clinical study sites at high risk for GCP non-compliance, and (3) validate and/or characterize the sponsor audit findings.

### Previous Inspection Cycle (Initial NDA Submission)

Inspected Entity					Sponsor Audit Findings (number of deficiencies)			FDA Inspection Outcome
Name	Study	Site	Country	Subjects	Subjects Audited	Total	Per Subject	
Obregon	302	395	Spain	16	6	7	1.2	OAI
Baldauf	302	338	Brazil	36	9	1	0.1	VAI
Hodoba	301	112	Croatia	18	7	10	1.4	OAI
Bitensky	301	213	Ukraine	28	12	1	0.1	VAI
Sunovion (abbreviated)	301, 302	sponsor	US					NAI

**NAI** = no action indicated (no significant GCP deviations); **VAI** = voluntary action indicated (significant GCP deviations); **OAI** = official action indicated (serious GCP deviations and/or data unreliable)

**Current Inspection Cycle (Second NDA Resubmission)**

Inspected Entity					Sponsor Audit Findings (number of deficiencies)			FDA Inspection Outcome
Name	Study	Site	Country	Subjects	Subjects Audited	Total	Per Subject	
Biton	304	005	US	20	20	0	0	VAI
Harvey	304	010	US	13	13	0	0	VAI
Kowacs	304	307	Brazil	13	2	0	0	VAI
	302	336		27	27	14	0.5	
Sakamoto	304	309	Brazil	4	3	0	0	VAI
	302	335		14	14	16	1.1	
Martinez	304	108	Argentina	8	6	0	0	NAI
	302	307		15	15	10	0.7	
Petranek	301	123	Czech Republic	13	13	29	1.5	VAI
Balogh	304	650	Hungary	1	0			NAI
	301	152		9	9	0	0	
Lee	304	352	South Korea	11	11	0	0	NAI
Meshram	304	951	India	15	15	1	0.1	NAI
Sunovion (complete)	301, 302, 304	sponsor	US					Preliminary VAI

**NAI** = no action indicated (no significant GCP deviations); **VAI** = voluntary action indicated (significant GCP deviations); **OAI** = official action indicated (serious GCP deviations and/or data unreliable)

**Preliminary:** The final inspection report has not been received from the field office and the classification is based on information on Form FDA 483 and preliminary communication with the field investigator. OSI's final classification remains pending as of this clinical inspection summary.

**1. Victor Biton, M.D. (Little Rock, AR)**

*Inspection dates (outcome): May 1 - 10, 2013 (VAI)*

a. What was inspected: Audit of Study 304

- General compliance review
  - Study protocols, standard operating procedures (**SOP**), and GCP regulations
  - Subject eligibility and informed consent
  - Subject randomization and blinding
  - Protocol violations, subject discontinuations, and concomitant medication use
  - Investigator financial disclosures
  - Test article disposition and accountability
  - Study monitoring by sponsor and local institutional review board (**IRB**)
  - Verification of sponsor's audit findings
- Verification of major endpoint data
  - Primary endpoint: seizures during the third study period (standardized seizure frequency)
  - Major secondary endpoints: CGI and QOLIE-31 during the third study period
  - Major safety endpoints: AEs, SAEs, and death
- Subject disposition and records review
  - In Study 304 at this study site: 28 subjects were screened, 20 were enrolled, and 11 withdrew or were discontinued from the study. Case records for all enrolled subjects were reviewed in detail.
  - As of the last day of inspection (May 10, 2013), nine subjects had completed Part 1 of the study and remained enrolled in the open-label extension Parts 2 and 3 of the study.

b. General observations and comments:

A Form FDA 483 was issued for the following minor deficiency observations:

- Informed consent document (**ICD**): For six subjects, signatures or initials (and their dates) were missing or not obtained in a timely manner. For example:
  - Subject 00504: One page of the ICD (version 3/11/2010, page 12 of 18 pages) was not signed and dated by the study personnel until 45 days after initially completing the ICD.
  - Subjects 00513 and 00519: One page of the ICD (version 8/26/2011, page 14 of 20 pages) was not signed and dated by the study personnel when re-consenting the subjects.
  - Subjects 00504 and 00517: The subjects did not initial one page of the ICD (version 10/28/2010, 19 pages), either page 17 (Subject 00504) or page 9 (Subject 00517).
- Drug accountability records
  - For six subjects, the number of tablets shown on *Investigational Product Return Form* and *Study Drug Inventory Log* were discrepant (differed by up to 11 tablets) between the two source records, or the numbers were corrected without adequate explanatory documentation.
  - For four subjects, the return of the unused study medication was not documented on *Investigational Product Return Form*.
  - The study records showed that the study medication from drug container 803198 may have been dispensed to Subject 00501 (as shown on *Investigational Product Return Form*) and/or Subject 00507 (as shown on *Study Drug Inventory Log*).

*Reviewer Comments:*

- *Subjects 01 and 07 had been randomized to different treatment groups. Subject 00507 (randomized to placebo) responded to the study treatment (decrease in SSF from 4.9 at baseline to 0 during the third study period) and Subject 00501 (randomized to ESL 800 mg) did not respond (insufficient decrease in SSF, from 6.1 to 3.3).*
- *These results and the inspectional finding suggest that the intended study medications for Subjects 00501 and 00507 may have been inadvertently switched, or the two subjects may have been given the same medication (possibly ESL 800 mg).*
- *Even if the medications had been administered incorrectly, the error is not expected to have a significant impact on the overall study outcome, since:*
  - *The error would favor an apparent overall study outcome of less ESL efficacy (than without the error).*
  - *The error appears to be an isolated finding (not suggestive of biased study conduct) limited to one subject pair (out of > 600 subjects in the study).*
  - *Study 304 is a superiority trial in which non-systematic (random) errors would decrease the ability to demonstrate superiority.*
- For six subjects at Visits 4 or 5, SSQ data were either not collected or superfluous data were inadvertently collected, as documented on both source documents and CRFs. For example, for Subject 00515 at Visit 5, SSQ Item 1B was not collected and superfluous Items 5-7 (not applicable to this subject) were inadvertently collected.

*Reviewer's Comments: This deficiency finding consists of a total of 10 pieces of SSQ data (7 missing, 3 superfluous) for a minor secondary efficacy endpoint.*

Four deficiency observations were verbally discussed (not cited, inspector discretion). These deficiencies were isolated (or sufficiently limited in scope) or were minor violations of relatively less important protocol criteria.

- For one subject, the first dose of the study medication was not given in the presence of clinical investigator as specified in the study protocol.
- For three subjects, pregnancy testing at subject screening was performed on a urine sample instead of on a serum sample.
- For two subjects, CGI (one of many secondary endpoints) was not always assessed according to the study protocol: one assessment (Visit 2) was missing for one subject, and one assessment (Visit 5) was performed late (at Visit 6) for a second subject.
- To be complete, the capture of seizure events (transcription from subject diary to CRF) required intervention (queries) by the study monitor, who missed one isolated dating error for one seizure event (date incorrect by one day).

The observed deficiencies (cited or verbal) are not expected to impact the study outcome. Other than as described above:

- Overall study monitoring by the sponsor and IRB appeared adequate.
  - All subjects signed the informed consent document.
  - Drug accountability was adequately documented.
  - Source records were complete and matched corresponding CRFs.
  - Endpoint data matched among source records, CRFs, and NDA listings.
- c. Assessment of data integrity: Data from this study site appear reliable.

**2. Jay Harvey, M.D. (Dallas, TX)**

*Inspection dates (outcome): April 17 - 23, 2013 (VAI)*

a. What was inspected: Audit of Study 304

- General compliance review
  - Study protocols, SOPs, and GCP regulations
  - Subject eligibility and informed consent
  - Subject randomization and blinding
  - Protocol violations, subject discontinuations, and concomitant medication use
  - Investigator financial disclosures
  - Test article disposition and accountability
  - Study monitoring by sponsor and IRB
  - Verification of sponsor's audit findings
- Verification of major endpoint data
  - Primary endpoint: seizures during the third study period (standardized seizure frequency)
  - Major secondary endpoints: CGI and QOLIE-31 during the third study period
  - Major safety endpoints: AEs, SAEs, and death
- Subject disposition and records review
  - In Study 304 at this study site: 17 subjects were screened, 13 were enrolled, and 9 completed the study.
  - Case records for all screened subjects were reviewed, including detailed review for all enrolled subjects.

b. General observations and comments:

A Form FDA 483 was issued for the following minor deficiency observations:

- Isolated cases of unreported non-serious AEs:
  - Subject 01004: A self-limited, mild, but prolonged (intermittent over three months) perceived decrease in motor coordination (considered possibly treatment-related) was not reported in the NDA as an AE. Subject records indicate that the AE was reported by the site to the sponsor. The sponsor may have failed to include the event in the NDA listing.
  - Subject 01014: A minor AE (bruised right forearm) was not reported to the sponsor. This deficiency appeared to be an isolated error (AE reporting oversight).
- Subjects 01001, 01003, 01008 and 01009: Study visits were held outside the time window specified in the protocol (by up to 11 days), presumably due to a system software error. These protocol violations apparently were not reported to the sponsor.
- Subject 01010: At Visit 5, physical and neurological exams were not performed, presumably because the subject refused to wait for the investigator.

Other than as described above:

- Overall study monitoring by the sponsor and IRB appeared adequate.
- All subjects signed the informed consent document.
- Drug accountability was adequately documented.
- Source records were complete and matched corresponding CRFs.
- Endpoint data matched among source records, CRFs, and NDA listings.

c. Assessment of data integrity: Data from this study site appear reliable.

### 3. Pedro Kowacs, M.D. (Curitiba, Brazil)

*Inspection dates (outcome): May 20 - 24, 2013 (VAI)*

a. What was inspected: Audit of Studies 304 and 302

- General compliance review
  - Study protocols, SOPs, and GCP regulations
  - Subject eligibility, informed consent, randomization, and blinding
  - Protocol violations, subject discontinuations, and test article accountability
  - Investigator financial disclosures, study monitoring (sponsor and IRB)
- Verification of major endpoint data
  - Primary endpoint: standardized seizure frequency during dose maintenance
  - Major secondary endpoints: CGI and MADRS
  - Major safety endpoints: AEs, SAEs, and death
- Subject disposition and records review
  - *Study 304:* 26 subjects were screened, 13 were enrolled, and 10 completed the study (Part 1). Case records for all screened subjects were reviewed, including detailed review and data verification (primary efficacy, major secondary efficacy, and adverse events) for nine enrolled subjects.
  - *Study 302:* 38 subjects were screened, 27 were enrolled, and 19 completed the study (Part 1). Case records for all screened subjects were reviewed, including detailed review for 14 enrolled subjects (nine complete and five abbreviated reviews) and data verification (primary efficacy, major secondary efficacy, and adverse events) for all enrolled subjects.

b. General observations and comments:

- A single-item Form FDA 483 was issued for Study 302: After completing the randomized phase, seven eligible subjects were permitted to continue receiving open-label ESL therapy under an Expanded Access Program. Two of the seven subjects did not sign an updated ICD, and the remaining five signed an updated ICD only after beginning open-label therapy.
- Four minor deficiency observations for Study 302 were verbally discussed (not cited, inspector discretion):
  - The ICD contained no contact information for the Ethics Committee (two subjects), or no documentation of caregiver consent (two subjects).
  - One subject did not meet subject inclusion criterion 8, at least four seizures in each half of the 8-week baseline period without a continuous seizure-free interval over 21 days. This criterion was waived by the sponsor, but not until after (one day) subject enrollment.

*Reviewer Comments:*

*The purpose of this criterion appears to be to enrich the subject population with those having frequent seizures, to increase the ability to detect ESL efficacy (increase study power). Waiving the criterion is not expected to detract from the validity of an eventual (positive) study outcome. Granting the waiver without a follow up protocol amendment (by the sponsor) or obtaining the waiver after subject enrollment (by the clinical investigator) appear to be regulatory deficiencies not related to data reliability.*

- Subject screening: For two subjects, the method of contraception was not documented. For one subject, the ability to keep an accurate study diary was not documented.
- Three AEs in three subjects (one per subject) were apparently not reported to the sponsor.

- Two minor isolated deficiency observations for Study 304 were verbally discussed (not cited, inspector discretion):
  - For four subjects, Ethics Committee contact information was not shown on the ICD.
  - Subject 70717: Seizure counts were discrepant between the subject diary (33 seizures) and the NDA listing (36 seizures).

These minor isolated deficiencies (cited or verbal) are not expected to impact the study outcome. Other than as described above:

- Overall study monitoring by the sponsor and IRB appeared adequate.
  - All subjects signed the informed consent document.
  - Drug accountability was adequately documented.
  - Source records were complete and matched corresponding CRFs.
  - Endpoint data matched among source records, CRFs, and NDA listings.
- c. Assessment of data integrity: Data from this study site appear reliable.

#### 4. Americo Sakamoto, M.D. (Ribeirão Preto, Brazil)

*Inspection dates (outcome): May 13 - 17, 2013 (VAI)*

- a. What was inspected: Audit of Studies 304 and 302
- General compliance review
    - Study protocols, SOPs, and GCP regulations
    - Subject eligibility, informed consent, randomization, and blinding
    - Protocol violations, subject discontinuations, and test article accountability
    - Investigator financial disclosures, study monitoring (sponsor and IRB)
  - Verification of major endpoint data
    - Primary endpoint: standardized seizure frequency during dose maintenance
    - Major secondary endpoints: CGI and MADRS
    - Major safety endpoints: AEs, SAEs, and death
  - Subject disposition and records review
    - *Study 304:* Eight subjects were screened (four screen failures), four were enrolled, and three completed the study (Part 1). Case records were reviewed in detail for all enrolled subjects, with data verification for the primary efficacy endpoint, major secondary efficacy endpoints (CGI and MADRS), and subject safety (AEs).
    - *Study 302:* 17 subjects were screened (three screen failures), 14 were enrolled, and seven completed the study (Part 1). Case records for seven enrolled subjects were reviewed in full, and abbreviated reviews were performed for the remaining seven enrolled subjects. Data were verified for the primary endpoint, major secondary endpoints (CGI, MADRS), and AEs for all enrolled subjects.
- b. General observations and comments:
- A Form FDA 483 was issued for Study 302:
    - After completing the randomized phase, six eligible subjects were permitted to continue receiving open-label ESL therapy under an Expanded Access Program. The subjects signed an updated ICD only after (nearly a year) beginning open-label therapy.

*Reviewer Comment: Typically, the sponsor granted a waiver to the study site to conduct additional study visits. The Ethics Committee, however, was not notified.*

- Three subjects did not meet subject inclusion criterion 8, at least four seizures in each half of the 8-week baseline period without a continuous seizure-free interval over 21 days.

*Reviewer Comment: Not meeting this subject inclusion criterion is not expected to detract from the validity of a positive study outcome.*

- The following minor deficiency observations were verbally discussed (not cited, inspector discretion):

*Study 304: Subject eligibility, AE reporting, and informed consent*

- Two (of four) randomized subjects did not meet the inclusion criterion for the frequency of seizures during the baseline period. In a newsletter, the sponsor provided special instructions related to this criterion (no follow up protocol amendment). One of the two subjects was included in the protocol deviations listing for violating this criterion.
- Five AEs (post-seizure trauma, headache, irregular menstruation, foot pain, and dizziness) in three subjects (80198, 80201, and 80213) were not reported, reported late, or reported with incorrect AE date.
- For one subject (30908), outdated (by one month) versions of the study protocol and the ICD were used. Risks of hypernatremia, rash, immunosuppression, pancreatitis, and suicidal ideation were not described to this subject (per updated ICD), and CSSR-S was not completed at Visit 1 (per updated protocol).

*Studies 302 and 304: Data discrepancies between source records and the NDA listing*

- Seizures: Visit 3 through Visit 5 (12 weeks maintenance therapy)

Subject	Treatment	Diary Count	NDA Count	Discrepancy	Responder
<b>Study 302</b>					
80199	ESL 400 mg	95	85	- 10	yes
80201	ESL 800 mg	34	30	- 4	no
80213	ESL 800 mg	65	64	- 1	no
<b>Study 304</b>					
30907	ESL 800 mg	61	59	- 2	no
30908	placebo	26	28	+ 2	no

*Reviewer Comments:*

*The discrepancies are small and do not appear significant. Correcting for the largest discrepancy (Subject 80199, substitute diary count 95 for NDA count 85) does not change the subject status as a treatment responder with over 50% reduction from baseline in SSF (62% in lieu of 66% reduction in seizures per four weeks).*

*More concerning than the magnitude of the discrepancies is the direction of the discrepancies in favor of increased ESL efficacy: for the two studies combined, seizure counts were underreported for ESL (four subjects) and overreported for placebo (one subject). However, the overall number of observed cases is small (three in Study 302 and two in Study 304), and the apparent inaccurate seizure count reporting appears to be minor isolated errors not suggestive of biased reporting.*

- o The following AEs were not included in the NDA listing:

Subject	Treatment	Unreported Adverse Event
Study 302		
80201	ESL 800 mg	body pain and trauma (fall)
80202	placebo	headache, irritability, bitter taste, and dizziness
80209	ESL 400 mg	dizziness
Study 304		
30908	placebo	headache

*Reviewer Comment: For the two studies conducted at this site, AE underreporting was observed equally for ESL or placebo (two cases for each). The cases appear isolated, were limited to common events, and do not suggest biased underreporting.*

The observed deficiencies (cited or verbal) appear minor and isolated, and are not expected to impact the study outcome. Other than as described above:

- Overall study monitoring by the sponsor and IRB appeared adequate.
- All subjects signed the informed consent document.
- Drug accountability was adequately documented.
- Source records were complete and matched corresponding CRFs.
- Endpoint data matched among source records, CRFs, and NDA listings.

- c. Assessment of data integrity: Data from this study site appear reliable.

#### 5. Oscar Martinez, M.D. (Buenos Aires, Argentina)

*Inspection dates (outcome): May 27 - 30, 2013 (NAI)*

- a. What was inspected: Audit of Studies 304 and 302

- General compliance review
  - o Study protocols, SOPs, and GCP regulations
  - o Subject eligibility, informed consent, randomization, and blinding
  - o Protocol violations, subject discontinuations, and test article accountability
  - o Investigator financial disclosures, study monitoring (sponsor and IRB)
- Verification of major endpoint data
  - o Primary endpoint: standardized seizure frequency during dose maintenance
  - o Major secondary endpoints: CGI and MADRS
  - o Major safety endpoints: AEs, SAEs, and death
- Subject disposition and records review
  - o *Study 304:* Eight subjects were screened and enrolled, and six completed study Part 1. Case records for all enrolled subjects were reviewed. Data were verified for the primary endpoint, major secondary endpoints (CGI, MADRS), and AEs.
  - o *Study 302:* 16 subjects were screened, 15 were enrolled, 14 received the study medication, and 12 completed study Part 1. Case records for all enrolled subjects were reviewed. Data were verified for the primary endpoint, major secondary endpoints (CGI, MADRS), and AEs for nine of 14 subjects that received the study medication.

## b. General observations and comments:

- A Form FDA483 was not issued.
- The following minor deficiencies for Study 302 were verbally discussed (not cited, inspector discretion):
  - One subject did not meet the inclusion criterion for frequency of seizures during the baseline period. The sponsor granted a waiver for this subject to remain in the study.  
*Reviewer Comment: Not meeting this subject inclusion criterion is not expected to detract from the validity of a positive study outcome.*
  - For one 20-year old subject, a legal representative's signature was not obtained on the ICD (required for subjects between 16 and 21 years of age). For one subject, the subject signed a caregiver agreement form instead of the ICD.
  - For two subjects, the study coordinator (not the subject) initialed and dated each page of the ICD. For one subject unable to complete the diary, the caregiver (brother) completed the diary without signing the ICD to document caregiver consent.
- The following minor deficiency for Study 304 were verbally discussed (not cited, inspector discretion): For two subjects (10804 and 10805), the ICD (version) approval date and the contact information for the clinical investigator were not documented on the ICD at time of obtaining subject consent.
- The following AEs in Study 302 were apparently reported to the sponsor but were not included in the NDA listing. This observation, an apparent deficiency for the sponsor (and not the clinical investigator), was neither cited nor verbally discussed. In Study 302, subjects were randomized in equal ratio to four groups (three ESL and placebo):

Subject	Group	Unreported AE in Study 302
80627	ESL 800 mg	exacerbation of seizure frequency
80642	ESL 800 mg	aboulia (inability to make decisions), headache, hypothyroidism
80699	ESL 400 mg	sinus tachycardia, impaired memory
80702	ESL 800 mg	post-seizure head trauma (serious AE)

The observed deficiencies (cited, verbal, or not discussed) appear minor and isolated, and are not expected to impact the study outcome. Other than as described above:

- Overall study monitoring by the sponsor and IRB appeared adequate.
  - All subjects signed the informed consent document.
  - Drug accountability was adequately documented.
  - Source records were complete and matched corresponding CRFs.
  - Endpoint data matched among source records, CRFs, and NDA listings.
- c. Assessment of data integrity: Data from this study site appear reliable.

## 6. Svojmil Petranek, M.D. (Praha, Czech Republic)

*Inspection dates (outcome): May 20 - 23, 2013 (VAI)*

### a. What was inspected: Audit of Study 301

- General compliance review
  - Study protocols, SOPs, and GCP regulations
  - Subject eligibility, informed consent, randomization, and blinding
  - Protocol violations, subject discontinuations, and test article accountability
  - Investigator financial disclosures, study monitoring (sponsor and IRB)
- Verification of major endpoint data
  - Primary endpoint: standardized seizure frequency during dose maintenance
  - Major secondary endpoints: CGI, MADRS, and QOLIE-31
  - Major safety endpoints: AEs, SAEs, and death
- Subject disposition and records review: 14 subjects were screened, 13 were enrolled, 13 completed study Part 1, and seven completed study Part 2. Case records for all screened subjects were reviewed in detail. Data were verified for the primary endpoint, major secondary endpoints (CGI, MADRS, and QOLIE), AEs, and concomitant medication use.

### b. General observations and comments:

- A Form FDA 483 was issued for: (1) not reporting AEs or concomitant medication use on CRF, and (2) inadequate drug accountability records. Specifically:
  - Not reported on CRF: febrile (viral) illness per Visit 4 diary (Subject 1232); use of intramuscular diazepam for grand mal seizure (Subject 1347); and use of anti-vertigo agents mesocain, guajacuran, sodium salicyl, and agapurian (Subject 1545)
  - Drug accountability records were incomplete and/or inconsistent for three subjects in randomized Part 1, and for nine subjects in the study overall (randomized Part 1 and subsequent open-label therapy):

Subject	Part 1	Documentation Deficiency
1231	yes	No documentation of returning IPBs 4, 14, or 15 IPBs 6, 7, and 8 returned twice (four and seven months after receipt)
1347	yes	IPB 8 returned twice (one and two months after receipt) Number of tablets remaining unused in IPBs 6, 7, and 8 not documented
1545	yes	No documentation of returning IPB 5
1211	no	No documentation of returning IPB 12, or the site dispensing IPBs 13 and 14
1230	no	IPB 13 returned twice, six and 13 months after receipt
1232	no	No documentation of returning IPBs 9 and 10
1345	no	No documentation of the subject returning IPB 10
1346	no	No documentation of returning IPBs 15, 16, and 17, or the site dispensing IPB 9
1348	no	No documentation of returning IPB 15

IPB = Investigational Product Box; IPBs  $\geq 9$  were for open-label therapy after Part 1

- The following minor deficiencies were verbally discussed (not cited, inspector discretion):
  - Missing or inaccurate information on ICD: clinical investigator's initials in lieu of full signatures, wrong (or no) site phone number
  - Information on CRFs filled out by subjects were often incomplete (e.g., missing QOLIE-31 source data) or not completely legible.

The observed deficiencies (cited or verbal) appear minor and isolated, and are not expected to impact the study outcome. Other than as described above:

- Overall study monitoring by the sponsor and IRB appeared adequate.
  - All subjects signed the informed consent document.
  - Source records were complete and matched corresponding CRFs.
  - Endpoint data matched among source records, CRFs, and NDA listings.
- c. Assessment of data integrity: Data from this study site appear reliable.

## 7. Attila Balogh, M.D. (Budapest, Hungary)

*Inspection dates (outcome): May 21 - 24, 2013 (NAI)*

- a. What was inspected: Audit of Studies 304 and 301
- General compliance review
    - Study protocols, SOPs, and GCP regulations
    - Subject eligibility, informed consent, randomization, and blinding
    - Protocol violations, subject discontinuations, and test article accountability
    - Investigator financial disclosures, study monitoring (sponsor and IRB)
  - Verification of major endpoint data
    - Primary endpoint: standardized seizure frequency during dose maintenance
    - Major secondary endpoints: CGI and MADRS
    - Major safety endpoints: AEs, SAEs, and death
  - Subject disposition and records review
    - *Study 301*: Nine subjects were screened and enrolled, and all nine completed study Part 1. Case records for all nine subjects were reviewed. Data were verified for the primary endpoint, major secondary endpoints (CGI, MADRS), and AEs.
    - *Study 304*: One subject was screened and enrolled. The subject completed study Parts 1 and 2, and continued into Part 3. The subject's case records were completely reviewed with verification of the study data for the primary endpoint, major secondary endpoints (CGI, MADRS), and AEs.
- b. General observations and comments:
- No significant deficiencies were observed and a Form FDA483 was not issued.
  - Overall study monitoring by the sponsor and IRB appeared adequate.
  - All subjects signed the informed consent document.
  - Drug accountability was adequately documented.
  - Source records were complete and matched corresponding CRFs.
  - Endpoint data matched among source records, CRFs, and NDA listings.
- c. Assessment of data integrity: Data from this study site appear reliable.

**8. Sang Ahm Lee, M.D. (Seoul, South Korea)**

*Inspection dates (outcome): July 8 - 12, 2013 (preliminary NAI)*

**a. What was inspected: Audit of Study 304**

- General compliance review
  - Study protocols, SOPs, and GCP regulations
  - Subject eligibility, informed consent, randomization, and blinding
  - Protocol violations, subject discontinuations, and test article accountability
  - Investigator financial disclosures, study monitoring (sponsor and IRB)
- Verification of major endpoint data
  - Primary endpoint: standardized seizure frequency during dose maintenance
  - Major secondary endpoints
  - Major safety endpoints: AEs, SAEs, and death
- Subject disposition and records review: 14 subjects were screened, 11 were enrolled, and six completed study Part 1. Case records were completely reviewed for all enrolled subjects with verification of the study data for the primary endpoint, major secondary endpoints, and AEs.

**b. General observations and comments:**

- No significant deficiencies were observed and a Form FDA 483 was not issued.
- Overall study monitoring by the sponsor and IRB appeared adequate.
- All subjects signed the informed consent document.
- Drug accountability was adequately documented.
- Source records were complete and matched corresponding CRFs.
- Endpoint data matched among source records, CRFs, and NDA listings.

**c. Assessment of data integrity: Data from this study site appear reliable.****9. Chandrashekhhar Meshram, M.D. (Nagpur, India)**

*Inspection dates (outcome): April 29 - May 6, 2013 (NAI)*

**a. What was inspected: Audit of Study 304**

- General compliance review
  - Study protocols, SOPs, and GCP regulations
  - Subject eligibility, informed consent, randomization, and blinding
  - Protocol violations, subject discontinuations, and test article accountability
  - Investigator financial disclosures, study monitoring (sponsor and IRB)
- Verification of major endpoint data
  - Primary endpoint: standardized seizure frequency during dose maintenance
  - Major secondary endpoints: MADRS and CGI
  - Major safety endpoints: AEs, SAEs, and death
- Subject disposition and records review:
  - 18 subjects were screened, 15 were enrolled, and all 15 completed study Part 1 and continued into Part 2. All but one subject completed Part 2 (one lost to follow-up). There was no Part 3 (optional two-year open-label extension) at any study site in India.
  - Case records were completely reviewed for all screened subjects. Data were verified for all enrolled subjects, for the primary efficacy endpoint, major secondary efficacy endpoints (MADRS and CGI), and AEs.

## b. General observations and comments:

- No significant deficiencies were observed and a Form FDA483 was not issued. The following minor deficiencies were verbally discussed (not cited, inspector discretion):
  - Two subjects (95111 and 95112) were registered for screening within the Interactive Voice Response System prior to obtaining informed consent. Screening procedures were performed after the subjects signed the ICD.
  - Subject 95103: This subject was enrolled despite having only three (not four or more) seizures within the four weeks prior to screening (violation of inclusion criterion). Although the Medical Monitor had granted a waiver to allow this subject to remain in the study, the enrollment of this subject may be considered a protocol violation, particularly since the sponsor's *Global Monitoring Plan* specifies that waivers are not permitted.

*Reviewer Comment: Not meeting this subject inclusion criterion is not expected to detract from the validity of a positive study outcome.*

The deficiency observations (not cited, discussed verbally) appear minor and isolated, and are not expected to impact the study outcome. Other than as described above:

- Overall study monitoring by the sponsor and IRB appeared adequate.
- All subjects signed the informed consent document.
- Drug accountability was adequately documented.
- Source records were complete and matched corresponding CRFs.
- Endpoint data matched among source records, CRFs, and NDA listings.

## c. Assessment of data integrity: Data from this study site appear reliable.

**10. Sunovion Pharmaceuticals, Inc. (Marlborough, MA)**

*Inspection dates (outcome): April 24 - May 24, 2013 (preliminary VAI)*

## a. What was inspected: Sponsor's oversight of Studies 301, 302, and 304

- Compliance with GCP regulations as applicable to sponsor, including financial disclosure for clinical investigators
- Adequacy of monitoring study sites and CROs, handling of protocol deviations, AE reporting, data management, and drug accountability
- Monitoring files were reviewed in detail for (all) nine clinical sites inspected during the current review cycle, to include the audit of (all) 13 site-specific studies conducted at the nine clinical study sites (four sites with two studies).

## b. General observations:

- A Form FDA 483 was issued for the following deficiency observations about study oversight:
  - *Studies 301 and 302:* Sponsor's oversight of site monitoring (by monitoring CROs, (b) (4) and (b) (4) was not documented (no records of sponsor's review of site monitoring reports). Monitoring visits were often late and infrequent: for (all) six sites audited for Study 302, the sites were visited initially much later (up to 108 days), and subsequently at intervals much longer (up to 22 weeks), than as specified in the protocol (initially 14 days after enrolling the first subject, then every eight weeks).

*Reviewer Comments:*

- *Monitoring oversight by the previous sponsor (BIAL's oversight of monitoring CROs, (b) (4) and (b) (4) appears to have been inadequate. The findings for the current*

*(complete) sponsor inspection (VAI) are inconsistent with those for the previous (abbreviated) sponsor inspection (NAI).*

- *If GCP non-compliant sites were highly prevalent in Studies 301 or 302 (as suggested by previous OAI outcomes) additional OAI outcomes may be expected for the current follow up clinical site inspections linked with this sponsor inspection.*
- *The non-OAI outcomes for all five follow up inspections (three VAI, two NAI) indicate that GCP non-compliance in Studies 301 or 302 was not as highly prevalent as might be expected from the initial findings. Given one OAI outcome (or more), the prevalence is difficult to evaluate with any degree of confidence, even if a large number of follow up inspections were to be performed.*
- *For this current inspection cycle, additional sites were inspected to rule out an obviously unacceptable level of GCP non-compliance. The results indicate that sites in Studies 301 and 302 were generally GCP-compliant (studies acceptable as secondary to Study 304) despite inadequate site monitoring and/or monitoring oversight.*
- *Study 304: The monitoring plan specifies the monitoring reports to be finalized within 15 working days and sent electronically to the sponsor. For all eight sites, nearly one-half of the monitoring reports audited (63 of 131) were finalized after an interval significantly longer than 15 working days. Further, the sponsor's oversight of site monitoring (review of monitoring reports) was often not timely: 55% of the reports (72 of 131 audited) were reviewed after one month, and 41% (54 of 131) after two months.*

*Reviewer Comments:*

- *The findings for Study 304 are not unusual. Overall, the findings of the sponsor inspection (and linked clinical site inspections) indicate that sites in Study 304 were generally GCP-compliant, with adequate site monitoring and monitoring oversight.*
- *Eight clinical sites were inspected for Study 304, significantly more than are typical for any single study (e.g., initially two each for Studies 301 and 302). All non-OAI outcomes for this relatively larger number of inspections indicate a significantly higher fraction of GCP-compliant sites, and with greater confidence.*
- *Sponsor's Audit:* At least for Study 304, the quality of both the (real-time) study monitoring and the (retrospective) sponsor audit appeared adequate. As might be expected (for an audit of prior monitoring), the audit appeared to be more thorough than prior monitoring; many deficiencies in study conduct were discovered during the sponsor's audit that were not previously noted by the study monitors.
- *Data Verification:* Major study data as reported in the NDA were verified against the original CRFs, including the data for efficacy (seizure counts, SSF, CGI, and QOLIE-31 during maintenance therapy), AEs, subject randomization, protocol violations, and subject discontinuations. Only a few minor discrepancies were discovered; the primary and major secondary endpoints matched with little to no discrepancies.
- *AE Reporting:* Previously unreported AEs (many for Studies 301 and 302, few for Study 304) were discovered at the 2010 sponsor audit. These additional AEs were reported to the sponsor on CRF addenda for inclusion in the NDA. The discrepant numbers of additional AEs (Studies 301 and 302 versus Study 304) appeared to reflect the change in the sponsor's thinking (per discussion with the review division) in the definition of a reportable AE; those AEs noted in the subject diary had been initially considered not reportable.
- *Protocol Conflict with Local Law:* Brazil requires its study sites to continue providing the study drug after the last study visit (compassionate use), and new (continued) study visits had

to be created in violation of the study protocol. The local law complicated site compliance with the requirements for informed consent as specified in the study protocol, including Ethics Committee approval of informed consent. (*See above, Kowacs and Sakamoto.*)

- c. Assessment of data integrity: The data for Studies 301, 302, and 304 appear reliable as reported in the current NDA resubmission.

Note: These observations are based on preliminary communications with the field investigator. The final inspection report has not been received from the field office and OSI's final review and classification of the inspection outcome remains pending.

### III. OVERALL ASSESSMENT AND RECOMMENDATIONS

Three pivotal studies were audited at fourteen GCP inspections over two inspection cycles to support the review of this original NME NDA.

- For the current (second) cycle, the sponsor's audit findings were a major consideration in selecting the clinical study sites to be inspected. Other considerations included: (1) large subject enrollment, (2) multiple studies at same site, and (3) world-wide site distribution.
- The sponsor was also inspected to confirm the findings at clinical study sites, estimate the overall rate of GCP compliance across all clinical studies and sites, and validate the sponsor's audit results.

The observed deficiencies (sponsor audit and FDA inspections) for the three pivotal studies are summarized below. The deficiencies were well-documented in the sponsor's audit. The FDA inspections focused more on the nature and seriousness of the deficiencies, and less on the number (frequency) of deficiencies.

#### Studies 301 and 302

Clinical Investigator	Subjects	Deficiencies (Sponsor Audit)	Major FDA Findings	Data Reliable?
Study 301				
Petranek	13	frequent	isolated instances of not reporting AEs or concomitant medication use, inadequate drug accountability; isolated instances of imperfect ICD follow up and/or recordkeeping	yes
Balogh	9	minimal	no significant deficiencies observed	yes
Bitensky	28	minimal	isolated instances of not observing subject eligibility criteria (laboratory assessment intended to protect subject safety)	yes
Hodoba	18	frequent	discrepant seizure and AE data (NDA listing vs CRF), inadequate drug accountability including incorrect or undocumented assignment of study kits to subjects	no
Study 302				
Kowacs	27	infrequent	non-critical subject selection criterion not observed, isolated instances of not reporting non-serious AEs; isolated instances of imperfect ICD and other recordkeeping	yes
Sakamoto	14	frequent	minimal seizure and AE data discrepancies (diary vs CRF)	yes
Martinez	15	infrequent	AE data discrepancies (subject diary vs CRF)	yes
Baldauf	36	minimal	Reporting of serious AEs were not timely	yes
Obregon	16	frequent	discrepant seizure data (NDA listing vs CRF), poor general recordkeeping practices	no

**Study 304**

Clinical Investigator	Subjects	Deficiencies (Sponsor Audit)	Major FDA Findings	Data Reliable?
Biton	20	minimal	one or two subjects may have been given incorrect study medication; initials or signatures on informed consent document missing or not timely, isolated deficiencies in drug accountability recordkeeping, isolated instances of imperfect secondary endpoint data collection	yes
Harvey	13	minimal	one instance of physical and neurological exams not performed; isolated cases of unreported non-serious AEs, study visits not timely (days)	yes
Kowacs	13	minimal	isolated instances of imperfect ICD recordkeeping, minor seizure data discrepancy (subject diary vs CRF)	yes
Sakamoto	4	minimal	non-critical subject selection criterion not observed, isolated instances of not or imperfectly reporting AEs, minimal seizure and AE data discrepancies; imperfect ICD follow up	yes
Martinez	8	minimal	isolated instances of imperfect ICD follow up and/or recordkeeping	yes
Balogh	1	no audit	no significant deficiencies observed	yes
Lee	11	minimal	no significant deficiencies observed	yes
Meshram	15	minimal	no significant deficiencies observed	yes

Studies 301 and 302 (sponsored by BIAL) were comparable in size and nearly identical in study design. The two studies were conducted in parallel (study dates and duration) under comparable study conditions (similar numbers of subjects and sites, both entirely foreign, many overlapping countries). The newer Study 304 (sponsored by Sunovion) was also similar in study design but was significantly larger (comparable in size to Studies 301 and 302 combined) and conducted also in the US. The monitoring CROs were different for all three studies. The inspectional findings support the following observations about Studies 301, 302, and 304:

- The sponsor's oversight appears to have been more real-time for Study 304 (closer monitoring while the study was on-going) and more retrospective for Studies 301 and 302 (90% of study sites audited). In either case, the sponsor claims adequate GCP compliance for all three studies, as (also) supported by their claims of consistent outcomes for Studies 301, 302, and 304.
- Study 304 was conducted in the US and worldwide (Canada, South America, South Africa, Australia, Asia, and Europe). Adherence to GCP appeared adequate for all sites inspected and not appreciably different between US and non-US sites.
- The FDA findings (limited to few sites) were consistent with the sponsor's (more extensive) audit findings. Deficiency frequency did not correlate with seriousness. The FDA findings served to validate the sponsor's findings. Sites with frequent deficiencies (per sponsor audit) were not consistently VAI (or OAI) per FDA inspection.
- Study sites in Studies 301 and 302 appear to be at higher risk for GCP non-compliance than those in Study 304. The overall rate of GCP compliance across all clinical studies and sites appears to be sufficient to support this NDA, with greater confidence for Study 304 than for Studies 301 and 302.

*Previous and Current Inspections*

FDA's inspectional findings for the current review cycle (resubmission) are consistent with the sponsor's audit findings and claims. FDA's previous findings (two OAI outcomes) are not necessarily inconsistent

with the current findings; they may reflect fortuitous initial site sampling and/or outcome overcall. The distinction between VAI and OAI is not always clear, and the frequent violation (with or without a sponsor waiver) of the inclusion criterion about baseline seizure frequency (intended to enhance study power) made the distinction difficult. No additional OAI outcomes were obtained despite five additional inspections for the two Studies 301 and 302.

Overall, OAI outcomes were limited to the two of four initial inspections. OAI outcomes were not observed at 14 additional inspections, eight for Study 304, three for Study 302, two for Study 301, and the sponsor inspection. At the clinical sites (indirectly) and at the sponsor site (directly), the study records indicated that the current sponsor (Sunovion) maintained adequate real-time oversight and control for Study 304 while the study was on-going. There was no evidence of unblinding or biased data collection. For the older Studies 301 and 302, the previous sponsor (BIAL) may not have had adequate real-time control. The quality assurance (QA) audit plan (for clinical site oversight) and the QA program (for CRO oversight) appear adequate, but with inadequate implementation (including corrective actions taken) when the studies were on-going. Evidence of unblinding or biased data collection was not observed.

All three Studies 301, 302, and 304 were placebo-controlled (superiority) studies in which non-biased (careless and random) deficiencies in study conduct may be expected to decrease the ability to demonstrate efficacy. The data from Study 304 appear reliable based on direct inspectional findings. Data reliability for Studies 301 and 302 are less clear (with or without data from OAI sites), but the totality of findings (sponsor's audit, FDA inspections, consistent study outcomes) nonetheless support the acceptability of these two older studies as well (acceptable overall data reliability), as secondary supplemental studies to the primary pivotal Study 304.

Note: For the sponsor inspection (Sunovion), the final inspection report has not been received from the field office and OSI's final inspection outcome classification remains pending. The inspectional observations noted above are based on preliminary communications with the field investigator. An addendum to this clinical inspection summary will be forwarded to the review division if the final classification changes or if additional observations of clinical or regulatory significance are discovered upon receipt and review of the final inspection report.

{See appended electronic signature page}

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JONG HOON LEE  
10/10/2013

JANICE K POHLMAN  
10/10/2013

KASSA AYALEW  
10/10/2013

## Consultation Response

FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY  
OFFICE OF PHARMACOVIGILANCE AND EPIDEMIOLOGY

DATE: 7 October 2013

FROM: John R. Senior, M.D., Associate Director for Science, Office of Pharmacovigilance and Epidemiology (OPE), Office of Surveillance and Epidemiology (OSE)

TO: Eric Bastings, M.D., Director, Division of Neurology Products (DNP), Office of Drug Evaluation I (ODE I), Office of New Drugs (OND)  
Mary Doi, M.D., Medical Reviewer for Safety, DNP  
Sally Yasuda, M.D., Clinical Safety Team Leader, DNP  
Norman Hershkowitz, M.D., Clinical Team Leader, DNP  
Teresa Podruchny, M.D., Medical Reviewer, DNP

VIA: Solomon Iyasu, M.D., Director, OPE

SUBJECT: Hepatic effects of eslicarbazepine: NDA 022416, originally submitted by Sepracor (Marlborough MA) 29 March 2009, complete response 10 April 2010, resubmissions 31 August 2012 and 10 February 2013

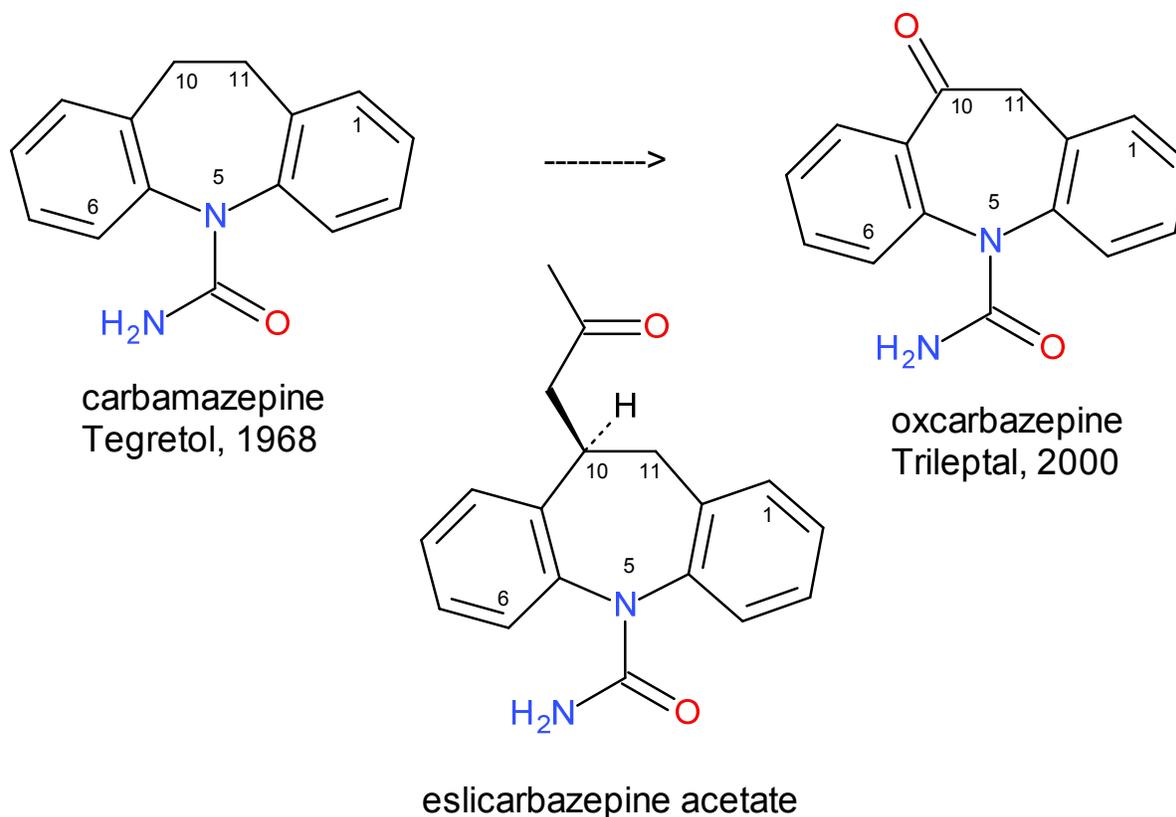
### Documents reviewed:

- 1) Informal consultation request via email message 5 November 2012 from Dr Podruchny, for review of two cases of possibly serious drug-induced injury from eslicarbazepine, expected resubmission of NDA 022416 for which complete response had been issued 30 April 2010
- 2) Resubmission of the NDA on 10 February 2013, followed by repeat request for consultation from Su-Lin Sun, Project Manager DNP, via Laurie Kelley, OSE Project Management staff, 11 February 2013, assigning OSE tracking number 2013-174
- 3) Request to sponsor, Sunovion, for data from key clinical trials, formatted for analyses using the eDISH program, with narratives for possibly serious cases of liver injury
- 4) Withdrawal of consultation request 13 May 2013 from Dr. Hershkowitz, DNP
- 5) Renewed request for official consultation request from Dr. Hershkowitz, dated 2 October 2013, via Su-Lin Sun and Ermias Zerislassie, OSE Project Management staff with new date for requested response 16 October 2013
- 6) Clinical safety reviews submitted by Dr. Doi, 6 September 2013 (228 pages) and Dr. Yasuda, 16 September 2013 (21 pages)
- 7) Reviews for Complete Response NDA 022416, by Dr. Podruchny, Norman Hershkowitz dated 30 April 2010, with concurring opinions by Dr. Russell Katz (former Director, DNP) 29 April 2013, and Dr. Ellis Unger, Director ODE I, 30 April 2010.
- 8) Follow-up safety commentaries by Dr. Podruchny to IND 067466 during 2010-2012
- 9) DNP response 2 November 2012 not accepting 31 August resubmission (as incomplete)
- 10) Analyses of selected phase II and phase III trial data submitted by the sponsor in parts over the period April-September 2013 for eDISH entry by Dr. Ted Guo, research statistician, Office of Biostatistics, Office of Translational Science, CDER.
- 11) Medical literature on eslicarbazepine, oxcarbazepine, carbamazepine, and related subjects

- 12) Updated Investigator Brochure 13 June 2013, version 5, submitted to IND 12 July 2013
  - 13) Sunovion submission of special inquiries concerning their cases 2093-203-337-058 and 2093-206-563-010, as identified by Dr. Podruchny in the 5 November 2012 request
  - 14) Sponsor's draft labeling, submitted 2 October 2013
- 

This drug was originally developed in Portugal by the Bial Portela company, and IND 067466 was submitted 17 November 2006 via a U.S. company PharmaNet (Princeton NJ). Sponsorship was changed in April 2008 to Sepracor, Inc. (Marlborough MA), who submitted the original NDA 022416 to DNP on 29 March 2009. It was not approved, and a complete response (CR) was sent 30 April 2010. This was followed by resubmission 31 August 2012 by Sunovion (former name Sepracor), but was incomplete, and a second resubmission was made 10 February 2013.

Search for a better, less toxic, drug for prevention of epileptic seizures and partial seizures (more common) has been underway since approval of carbamazepine (TEGRETOL<sup>®</sup>, Novartis) in 1968 which caused serious off-target adverse effects such as Stevens-Johnson syndrome and its even worse variant, toxic epidermal necrolysis, that was recently found to be especially to occur in Asian people with the HLA B\*1502 gene. Development of a 10-keto derivative, oxcarbazepine, also by Novartis (approved in 2000 as TRILEPTAL<sup>®</sup>), led to exploration of other derivatives by the Portuguese company Bial-Portela, to discovery and to development of a reduced compound, 10-hydroxy-carbamazepine and choice of the S-enantiomer acetate as a drug product, Bial 2-093, approved in Europe as Zebinix<sup>®</sup> and now under consideration in NDA 022416 as SEP 0002093.



The eslicarbazepine acetate product is a pro-drug, which may be hydrolyzed to the free drug (S)-licarbazepine that is active to block fast-acting voltage-gated sodium channels responsible for neuronal signal propagation, to protect against mouse and rat seizure induction by drugs such as metrazole, bicuculline, picrotoxin, and others, as summarized in the Investigator's Brochure, version 5.0, 7 June 2103, submitted by Sunovion to IND 067466 on 12 July 2013.

The question of possible hepatotoxicity was first reported to me by the clinical reviewer, Teresa Podruchny, in late October 2012, after her review of the resubmission of 31 August 2012. She sent an email message with three attachments, including two case reports describing patients in phase II studies identified by the sponsor (Sunovion, formerly Sepracor) in their Integrated Safety Summary (ISS), as two of six cases of special interest because they had showed elevated serum aminotransferase activities  $>3xULN$  and bilirubin concentration  $>2xULN$ . The sponsor attempted to use the causality assessment method developed at the Roussel-Uclaf company in 1993, known as the RUCAM (Benichou and Danan, 1993), but found it not appropriate for the three phase one subjects in Study 111 (subjects 003, 011, 017) and in a patient in phase II Study 207 (#011 at site 222) who had gastric cancer and died. The two other patients, from phase II Study 203 (#058 at site 337) and Study 206 (#010 at site 563) generated RUCAM scores of 1 to 3 suggesting that eslicarbazepine-associated injury was possible, though not probable (see pages 153-164 of 2465 in the ISS, Section 5.3.5.3 in NDA 022416 submission 31 August 2012). Dr. Podruchny sent me copies of the narratives of the two cases prepared by the sponsor (in ISS, Appendix 7.7 Narratives: pp. 1169-72/6507 for #058; pp. 1624-7/6507 for #010).

Dr. Podruchny and I discussed the cases the sponsor had identified as "Hy's Law" cases, and I stressed to her that a case cannot be so diagnosed unless the cause of the abnormal laboratory chemistry findings can be at least probably attributed to the drug administered, and not to some another agent or disease. That cannot be done simply by looking at serum chemistry values for ALT and bilirubin. At the very minimum, a time course of all abnormalities and events should be shown and a valid clinical narrative provided, indicating that the investigator or a responsible physician had made a reasonable effort to find out what had been happening to the patient, and the true medical cause of the problem. The most useful and valid document for establishing the probable cause would be a good clinical narrative. We discussed what that should include, and that was conveyed to the sponsor in the 2 November 2012 response letter explaining why the resubmission was not accepted, and was ruled incomplete. The resubmission document had included in its Integrated Safety Summary (Section 5.3.5.3) a very large file (6507 pages) in which were listed some 1589 "narratives" that were simply computerized summaries of the data recorded in the case report forms (almost 4 pages each, on average, but containing no additional information that could be used in trying to make a medical differential diagnosis of the most likely cause of the patient's abnormal test values.

In addition to description of other deficiencies in the resubmission, a section of the document listed some features and characteristics of what a good narrative should include:

- 3. The narratives should allow the reviewer to come to a conclusion regarding the cause of the death or adverse event, and the relatedness to study drug, independent of your interpretation. For this reason, the narratives must include all supportive data, even if negative. We note that the narratives from the original NDA and the resubmission do not provide the same supportive information.*

*For narratives, please use a common template that is easy to review. Narrative summaries should provide a common synthesis of all available clinical data and an informed discussion of the case. Narrative summaries should allow a better understanding of what the patient experienced. The following items should be included:*

- *Patient age and gender*
- *Signs and symptoms related to the adverse event being discussed*
- *An assessment of the relationship of exposure duration to the development of the adverse event*
- *Pertinent medical history*
- *Concomitant medications with start dates relative to the adverse event*
- *Pertinent physical exam findings*
- *Pertinent test results (e.g., lab data, ECG data, biopsy data, autopsy results)*
- *Discussion of the diagnosis as supported by the available clinical data*
- *For events without a definitive diagnosis, a list of differential diagnoses*
- *Treatment provided*
- *Re-challenge results (if performed)*
- *Outcomes and follow-up information*

*In the narratives, we noted that dates (including adverse event onset and stop dates) were included. Please include relative study day number for all of the narratives for serious adverse events and deaths.*

What Dr. Podruchny asked me in her email message of 5 November was:



On inspection of what the sponsor had sent, the so-called narratives were simply data summaries from case reports and did not contain sufficient clinical information to allow diagnosis of the most likely cause of the abnormal test findings, which is essential for determining whether or not the cases really meet criteria for “Hy’s Law.” I explained the need for narratives that are much more informative, that go beyond just what was in case reports, and supplemental information that might make differential diagnosis of the cause of the findings. I also suggested that I might need data to be submitted also for the phase III studies in format suitable for eDISH analyses. The August 2012 was judged incomplete and was not accepted, but a message was included in the response from DNP that described clearly what good narratives should provide, as was sent on 2 November 2012, along with notice to the sponsor that the resubmission was incomplete and would not set a date for regulatory action. The follow-up resubmission arrived 10 February 2013, and was accepted as completing the resubmission so review could proceed.

Just two weeks later, Ms. Laurie Kelley of OSE inquired 26 February 2013 about the status of my response to the email message of 5 November 2012 sent to me by Dr. Podruchny, which she had thought had been an official consultation request and had assigned an OSE tracking number 2012-174. I could not find any DNP entry into DARTTS requesting clinical consultation, and search for it revealed only the email message and the three attachments. After trying to resolve the confusion and considerable back-and-forth by emails over following weeks. I explained on 30 March 2013 that we really need the full clinical data, especially for the phase III studies to be submitted for eDISH analyses, that what we had received were not useful clinical narratives, as stated below:

(b) (5)



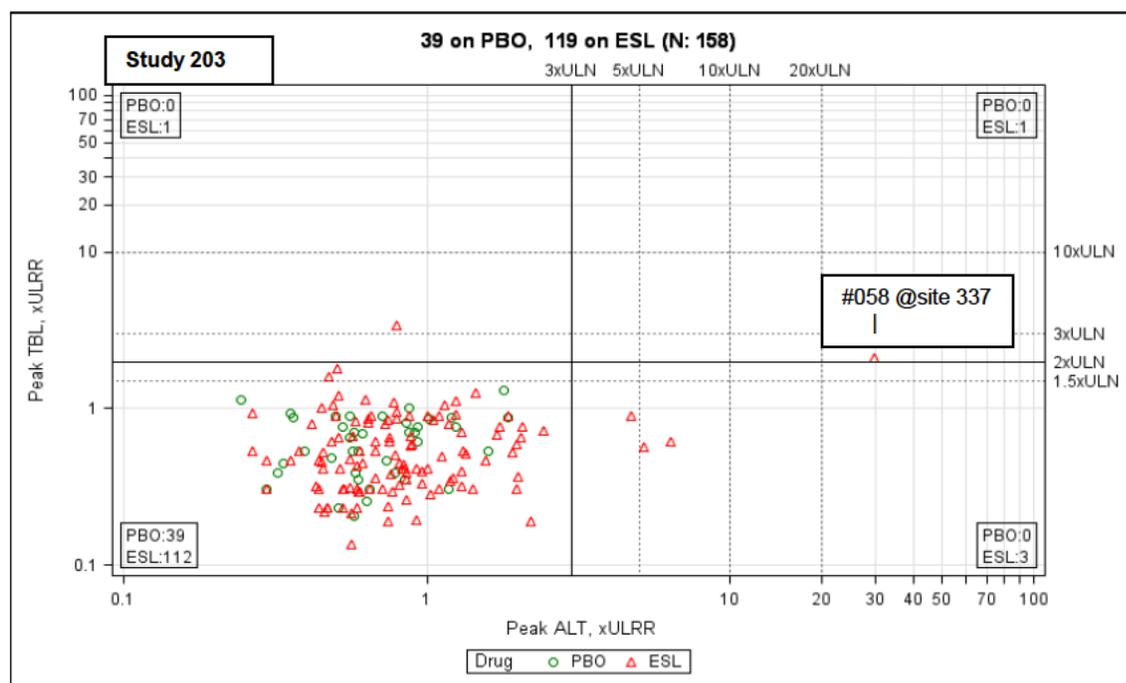
My error in transcribing the IND number was quickly corrected (to IND 67466), and efforts were made to get the data submitted by the sponsor to Dr. Ted Guo for entry into the eDISH program.

On 13 May, a message came from Dr. Hershkowitz that DNP was withdrawing the consultation request, saying that the NDA was under review by the DNP safety group, and notified Mr. Ermias Zerislassie, who had taken over from Laurie Kelley the tracking of OSE consultation request 2103-174. Consequently, we put the consultation on hold until the DNP safety review was done.

The eDISH data trickled in over the next months and was entered by Dr. Guo, including five phase II studies and three phase III studies: Both of the two cases identified by the sponsor and called to our attention by Dr. Podruchny were from phase II studies: SUBJECT 203-337-058 and SUBJECT 206-563-010, and a third case was found to have ALT >3xULN and TBL >2xULN. SUBJECT 207-.

There were no cases from the phase III studies of special interest, because none showed at any time peak levels of ALT >3xULN and TBL >2xULN, but graphic plots of all patients will be shown.

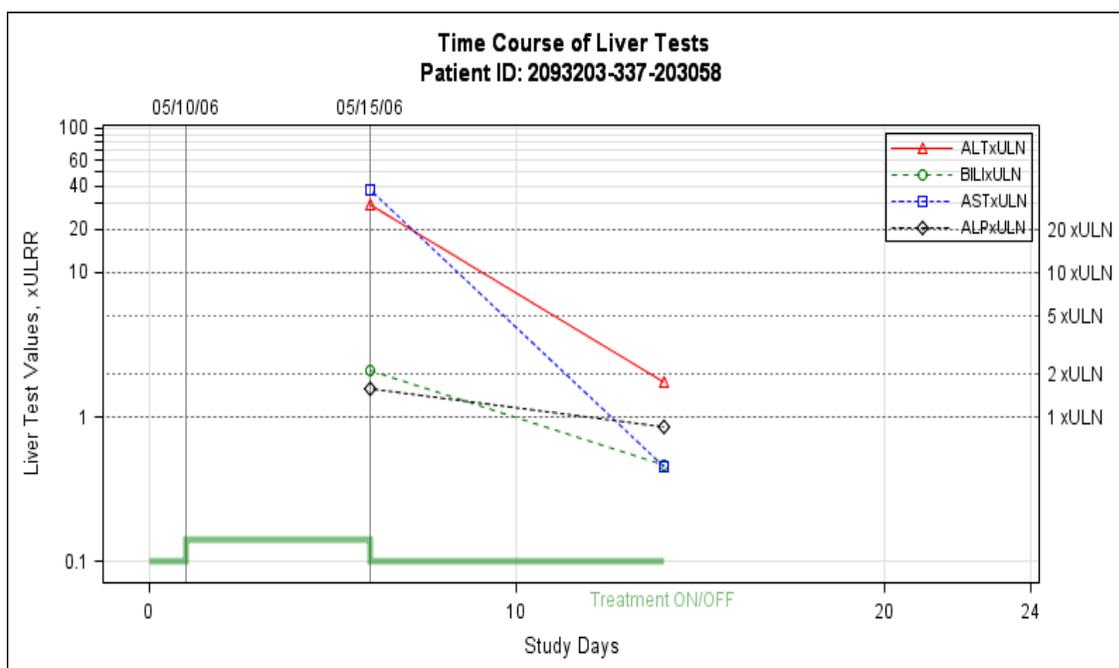
Starting with the cases of main interest to Dr. Podruchny, first SUBJECT 203-337-058:



It can be seen that only one subject in the Study 203 was found to have at any time during observation in the phase II study the combination of ALT >3xULN (actually 29.7 xULN) and TBL >2xULN (2.1xULN) to trigger a closer look at the circumstances of the case. The data submitted by the sponsor for eDISH analysis indicated that she was a Slovakian woman 57, with bipolar disorder who started taking eslicarbazepine 600 mg daily on 10 May 2006. She reported some vomiting and diarrhea, and stopped on 13 May, and was found to have on 15 May 2006 her ALT high at 1154 U/L (29.7 xULN), TBL 2.6 mg/dL (2.1 xULN), AST 1447 U/L (37.3 xULN) and ALP 252 (1.6 xULN). Repeat testing 8 days later on 23 May 2006 showed the AST, ALP, and bilirubin back in the normal range, and ALT only 68 U/L (1.7 xULN). She was reported to

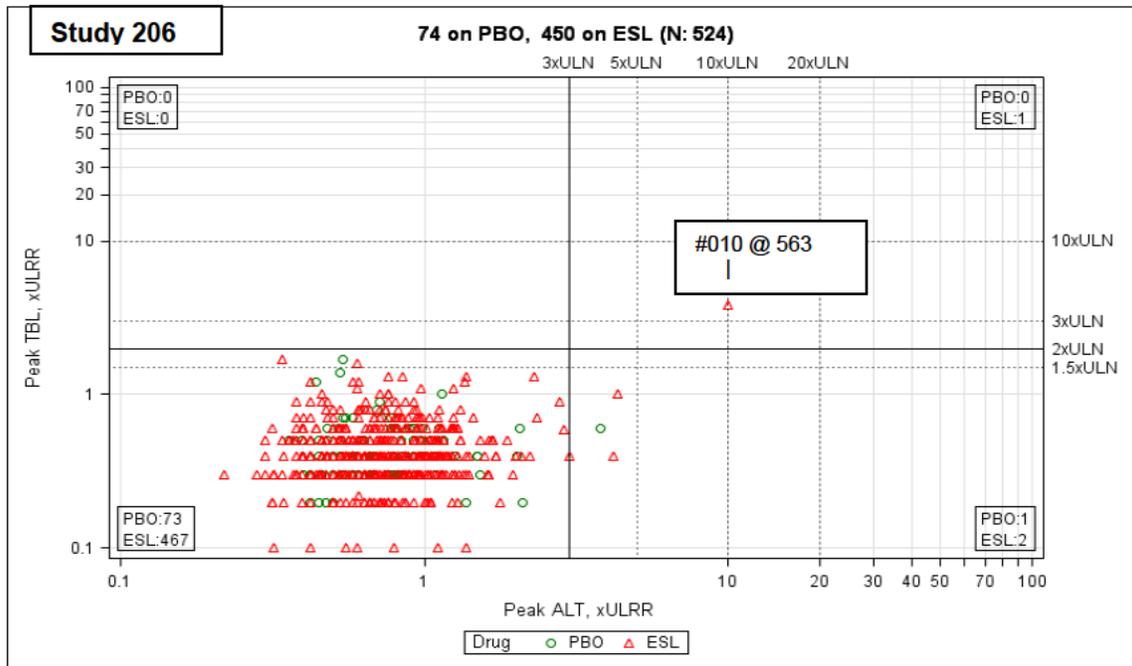
have also taken some valproic acid, and had a history of chronic pancreatitis. The sponsor tried to use the RUCAM process and obtained a score of 3, suggesting that the drug “possibly” caused the liver test abnormalities.

The data submitted for eDISH analysis of the time course for this patient were very sparse, and did not even include the test results done on 9 May 2006, the day before eslicarbazepine was started, and the late follow-up data on 16 June, a month after it was stopped. Both sets of liver test data were within the normal range for all four variables, and had been included in the 4-page narrative submitted for readmission of NDA 022416 in section 5.3.5.3. Narratives Appendix 7.7, page 1169-72 of 6507 on 31 August 2012, and sent forward by Dr. Podruchny.

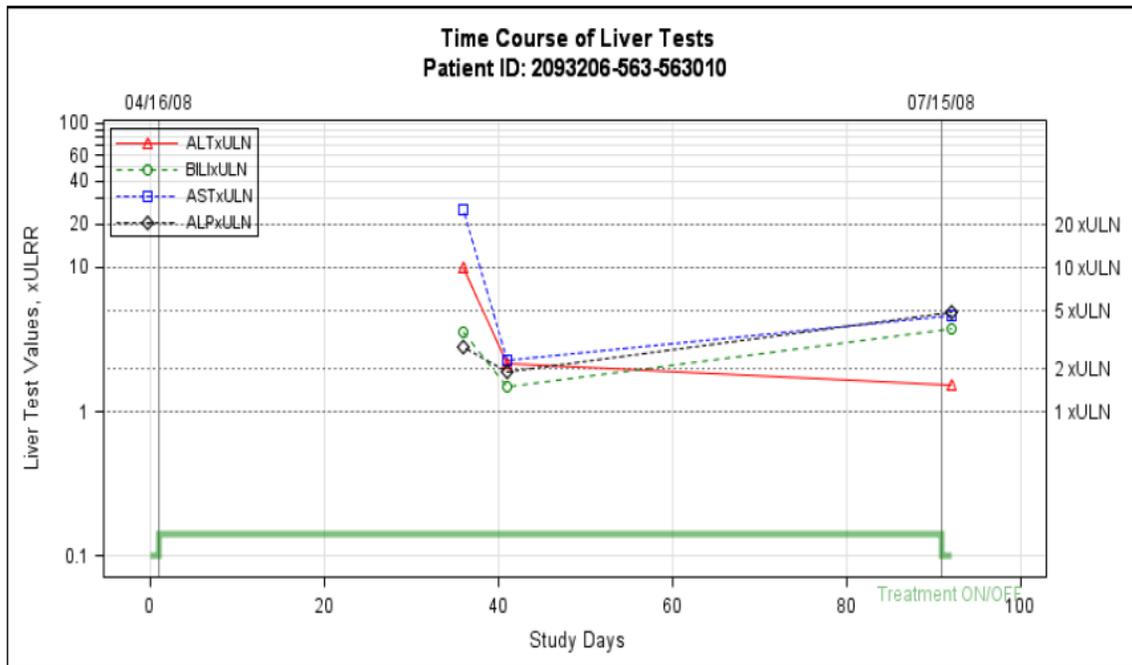


The sponsor also tried to obtain more information from the site where this patient had been studied, in response to a DNP inquiry of 6 June and through an international translation firm reached Dr. Ivan Doci, investigator at site 337. Despite passage of more than 7 years, he was able to provide copies of his records. He had consulted an internist, but no definite diagnosis of the cause was found, although no additional work-up was done at the time of the events. He reported that the patient had no further pancreatitis, but did have a cholecystectomy in 1992 and had a history of possible toxic hepatopathy in April 1992, obviously not from eslicarbazepine.

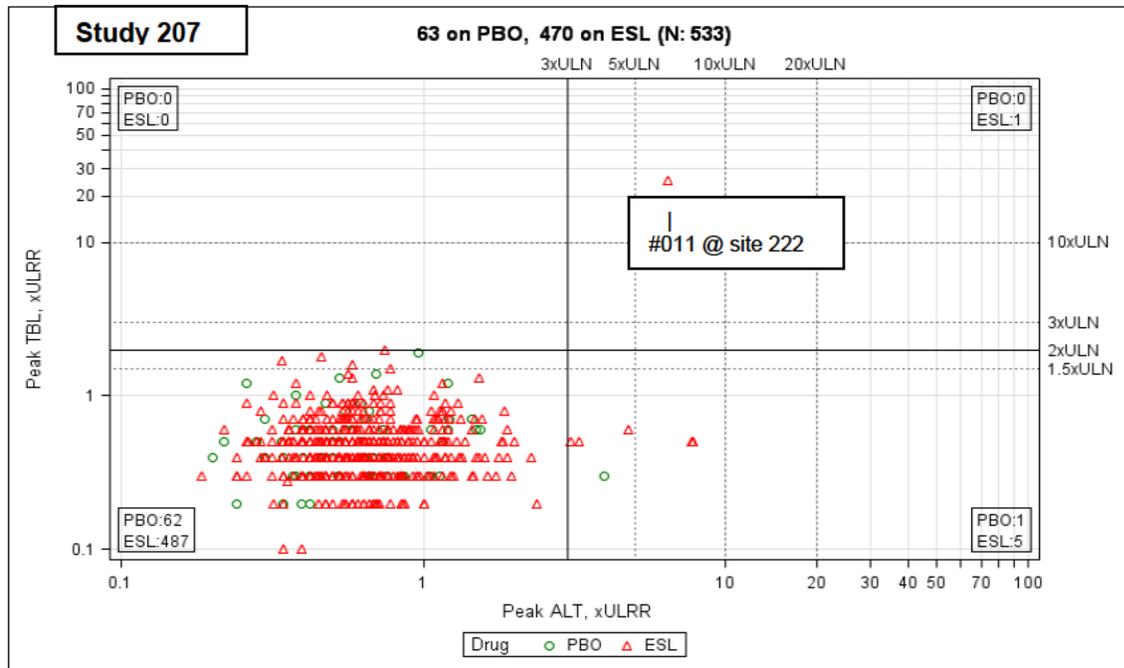
The other case of interest and concern, identified by the sponsor as worthy of special attention, was found in Study 206, in a Czech male 57 with painful diabetic neuropathy treated in 2008 with eslicarbazepine. He had a history of fatty liver, and was obese (BMI 32.8 kg/m<sup>2</sup>), according to the narrative submitted with the August 2012 resubmission (pp. 1624-7 of 6507 in Appendix 7.7 of the ISS). His alkaline phosphatase was modestly elevated at 1.8 xULN pre-study, but the other values were in the normal range, He also was diabetic, using insulin, and was taking metoprolol, perindopril, and spironolactone for control of hypertension.



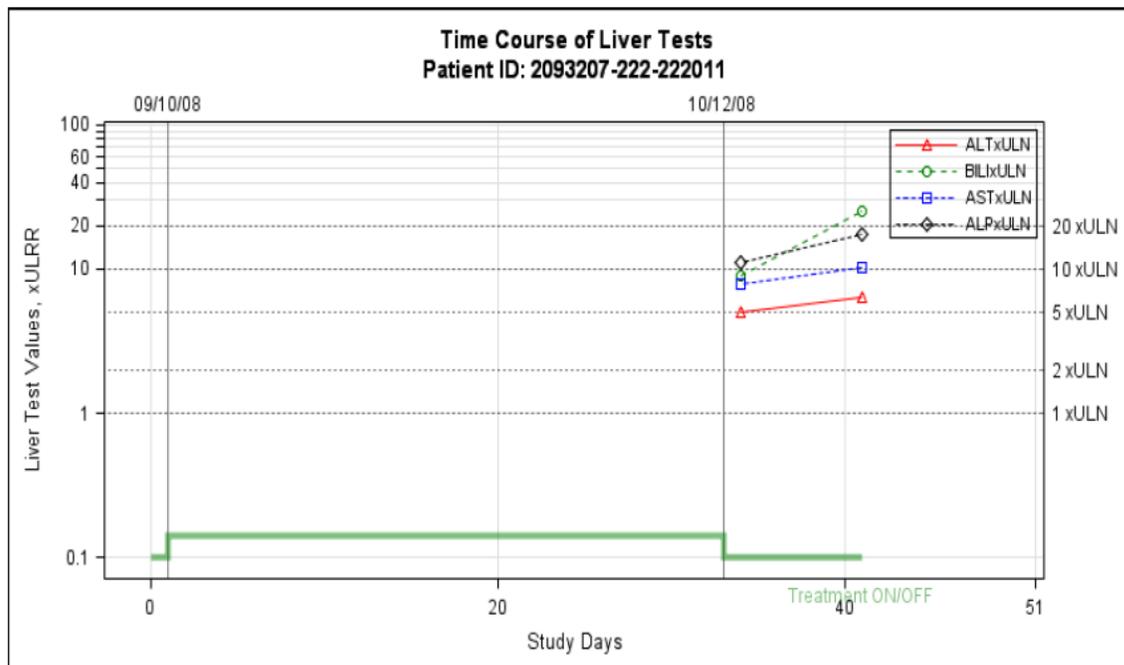
Again, the normal pre-treatment values for liver tests done on 7 April 2008 before starting 600 mg daily eslicarbazepine on 16 April were not provided with the eDISH data, but were included in the narrative from the August 2012 resubmission (pp.1668-72/6507, App.7.7, ISS).



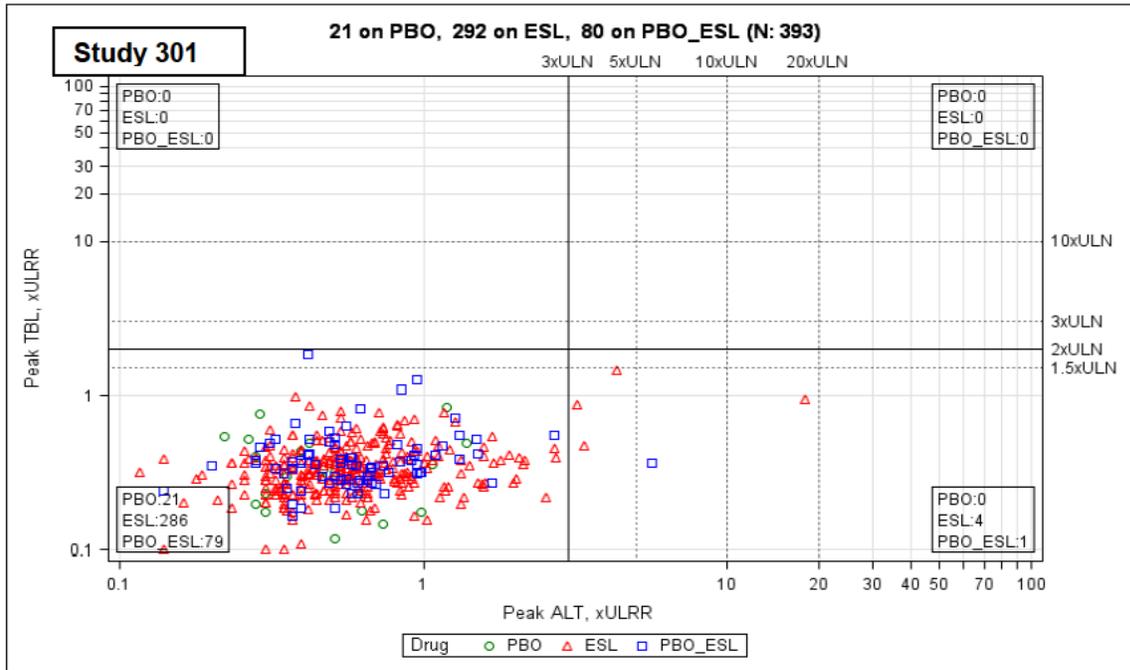
The follow-up inquiries to the site in Czech Republic via Bial to Dr. Eva Lengálová disclosed that he was a chronic alcoholic, probably with some cirrhosis (no biopsy reported), hospitalized with jaundice in (b) (6) before participation in Study 206. He admitted to drinking alcohol “occasionally, once a week” and also used paracetamol in unspecified doses.



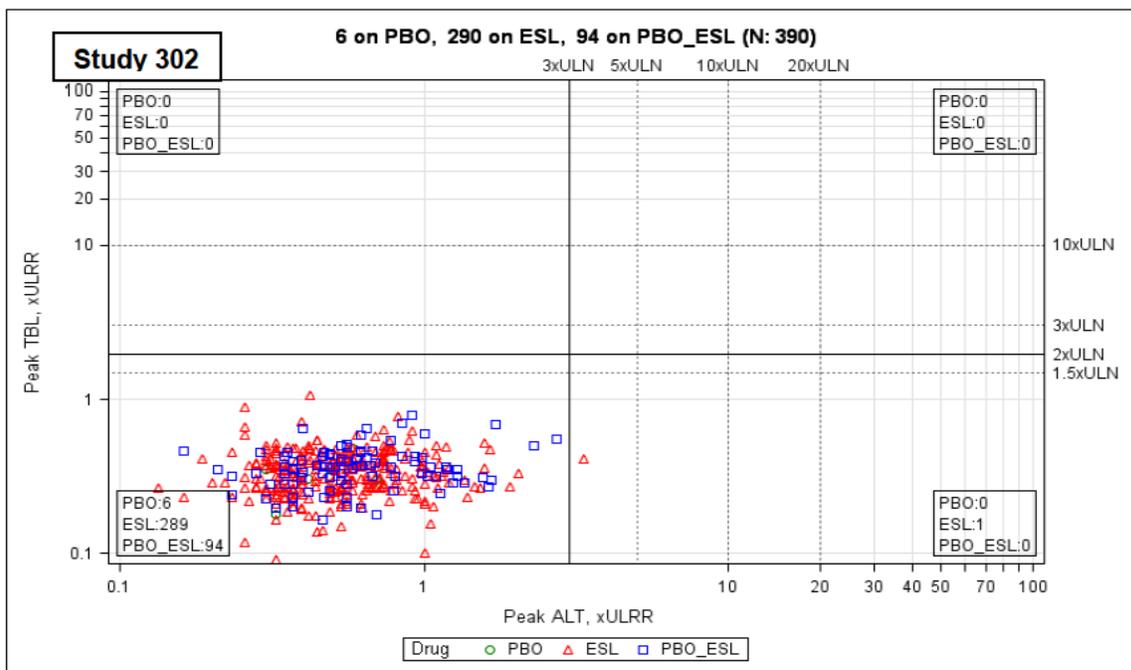
The third patient was a Hungarian man 76, started on eslicarbazepine 10 September 2008 (prestudy normal values of liver tests except for borderline elevation of AST (1.14 xULN), anemia (Hgb 9.8 g/dl), and low body weight (BMI 17.8 kg/m<sup>2</sup>) on 1 September). On 13 October he was found to be jaundiced (TBL 8.9 mg/dL), with ALP 1424 U/L (11.0 xULN), ALT U/L 253 (5.1 xULN), AST 283 U/L (7.9 xULN), and diagnosed as having gastric carcinoma, with involvement of the common duct and pancreatic head. He developed acute cholangitis, septic shock, and died on [REDACTED] (b) (6). His liver abnormalities were not drug-induced.



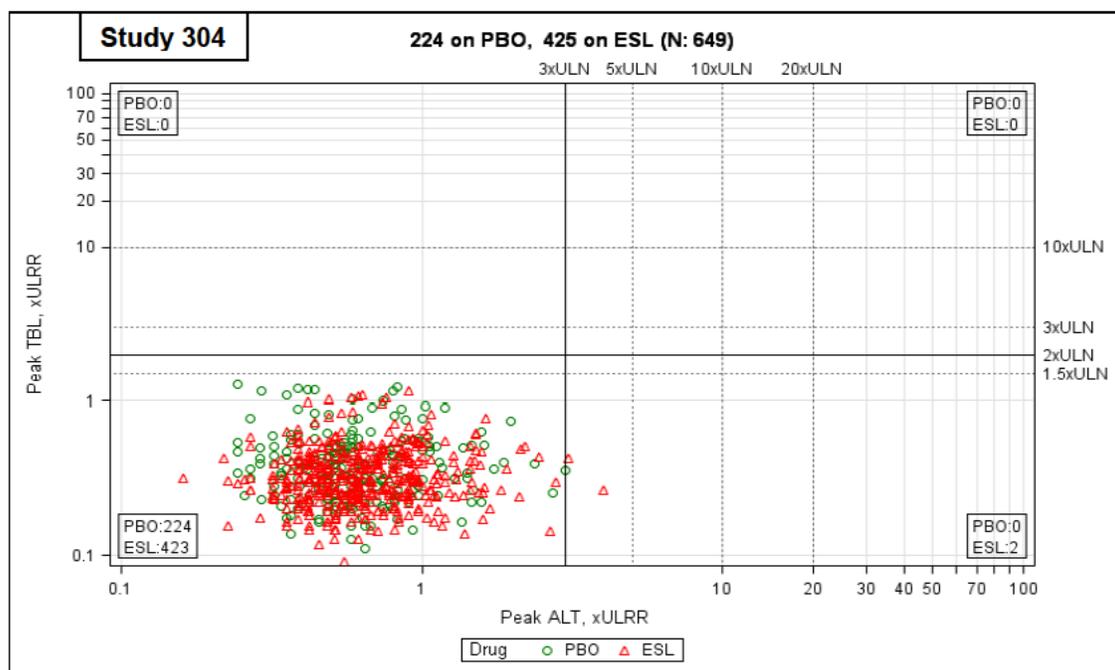
In the phase III studies 301, 302, and 304, there were no notable liver test abnormalities observed



among more than 1000 patients on eslicarbazepine, 254 on placebo, and 174 on both, as is evident at a glance from the eDISH x-x plots of peak ALT and TBL values for each patient studied.



Even the larger study, 304, which included 425 on eslicarbazepine and 224 on placebo, showed only one patient with a very minor, asymptomatic, and reversible ALT elevation despite staying on the drug.



In all the material reported, we have only some elevated serum aminotransferases, and three cases in which possible functional loss is evident, one with clear alternative explanation (the gastric carcinoma (Patient 207-222-011), one that may be mild acute drug-induced injury in a patient with underlying chronic alcoholic liver disease (Patient 207-337-010) and one borderline bilirubin elevation to 2.09 xULN (Patient 203-564-058). This is not an impressive record for a drug likely to be seriously hepatotoxic to patients.

The careful reviews by Drs. Doi and Yasuda are noted and appreciated. While we were waiting for the sponsor to submit the liver test data and narratives over the period from March-September so that Dr. Guo could enter the material into the eDISH program, Dr. Doi embarked on using the J Review program to access the data already submitted in the resubmissions of 31 August 2012 and 10 February 2013. It was exhaustive (and exhausting) work that led to her producing the excellent graphics contained in her review of 6 September 2013. She focused attention on safety aspects, leaving efficacy considerations to those previously analyzed by Dr. Podruchny in April 2010 when the Complete Response had been issued. Dr. Podruchny also made numerous entries into IND 067466 in 2011 and 2012 about reports of safety findings reported by the sponsor from approved and marketed use of eslicarbazepine in Europe, where it had been on the market since 2009. After a thorough review of all of the submitted and resubmitted data, Dr. Doi concluded that there were no safety issues that would preclude approval. She did state that eslicarbazepine acetate be prescribed only for adults (persons at least 18 years of age), that warnings should be listed for drug-induced liver injury; adverse skin reactions; allergic effects such as anaphylaxis and angioedema; hyponatremia and hypochloremia; neurologic effects including dizziness and

gait disturbance, fatigue and somnolence, cognitive dysfunction, visual changes and injuries from falls; thyroid function changes; PR prolongation; suicidal ideation and behavior, as required for all antiepileptic drugs; and withdrawal cautions, as outlined by Dr. Podruchny. She advised also that the labeling provide clinical pharmacology recommendations, dose adjustment in cases of moderate and severe renal impairment, and a Medication Guide warning about suicidality, and postmarketing surveillance for anemia, but no Risk Evaluation and Mitigation Strategy (REMS) document. For drug-induced liver injury, she recommended expedited reporting of any cases of severe DILI, in addition to the routine annual analyses and reports.

Dr. Yasuda commented (16 September 2013) on the safety review by Dr. Doi, concurring with the conclusions and recommendations, and emphasizing the many discrepancies, omissions of data, programming errors, and generally poor execution and reporting of the studies done, and the need for repeated corrections of errors from the original NDA submission of NDA 022416 on 29 March 2009 and resubmissions 31 August 2012 and 10 February 2013. She agreed with Dr. Doi's recommendations for postmarketing surveillance for anemia, evaluation of the risk of acid-base abnormalities, study of genetic risk factors for severe skin reactions, expedited reporting of any cases of severe DILI.

Also noted was the report on 29 September 2013 by Dr. Yasmin Choudhry, medical officer in the OSE Division of Risk Management (DRISK), concurring that no REMS was needed, and the labeling and a Medication Guide should suffice.

However, in contrast to the above recommendations, the draft labeling submitted by the sponsor on 2 October 2013 contains (b) (4)

 Presumably these points will need to be dealt with in the coming negotiations with the sponsor, as the action date of 8 November 2013 approaches.

What have we all learned from these extensive reviews about evaluation of submitted NDA data for predicting safety of the drug from causing serious liver injury and dysfunction after it is to be marketed to many more patients than could be studied in controlled clinical trials? The problems started with design of the studies and drafting of the protocols, followed by poor execution and even poorer analysis and reporting of results. The sponsor of the original studies was a relatively small Portuguese company that began corresponding with FDA in July 2003, sought help from a small Princeton contract organization to prepare and submit IND 067466 on 17 November 2006, and in April 2008 found a small company in Massachusetts (Sepracor) to sponsor the preparation and submission of NDA 022416 on 29 March 2009, only to have it change its name to Sunovion in October 2010 after the Complete Response of 10 April 2010. All the name changes did not much improve the performance, which has delayed and complicated review and approval. It may be understood that much has been learned about evaluation of DILI since eslicarbazepine was discovered and developed, but this new understanding was promulgated to the Industry in the FDA Guidance of July 2009 that certainly could and should have been applied at least for the NDA resubmissions of August 2012 and February 2013.

The importance of making clinical determination of the most likely cause of abnormal liver test findings has been amply emphasized, and the need for supplemental information to rule out the many possible alternative causes clearly stated. Yet the sponsor kept on relying upon the relative height of serum enzyme rises as measures of liver dysfunctional severity, and slavishly taking laboratory test peak values of {ALT >3xULN & TBL >2xULN} as ‘diagnostic’ of Hy’s Law. That misunderstanding has been very costly, both to the sponsor and to FDA reviewers, in terms of excessive time wasted. Even when the importance of good clinical narratives was spelled out and sent to the sponsor on 2 November 2012 after the resubmission of 31 August was judged to be incomplete, no improvement in the quality of medical diagnostic information was made in the submitted narratives in 2013, and those sent for the eDISH analyses were not even as complete as those prepared for the ISS in the August 2012 resubmission.

We have all concluded that eslicarbazepine is not likely to cause serious liver injury in patients, injury severe enough to damage performance of the whole organ so that its functioning is not able to clear bilirubin from plasma, synthesize the appropriate amount of prothrombin, or many of its other true functions (NOT including regulation of the aminotransferase activities found in serum). Both carbamazepine (TEGRETOL®) and oxcarbazepine (TRILEPTAL®) have been reported to cause rare but serious liver injury, including liver failure and death. No evidence has been provided that this cannot occur with the successor drug, eslicarbazepine. It will very likely to be very rare, and will probably be preceded by early symptoms of liver dysfunction such as mild jaundice of the sclera, dark urine, prolonged prothrombin time if tested, and elevated serum enzymes indicating cellular injury. Physicians who prescribe eslicarbazepine should be aware of this possibility, should *immediately* confirm, follow the adverse effect, interrupt administration of the drug while medical investigation is underway to determine the likely cause by ruling out the many alternative possibilities. This is just good medical practice and should be mentioned in the labeling.

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John R. Senior, M.D.

cc: OSE 2013-174  
E. Bastings, DNP  
N. Hershkowitz, DNP  
S. Yasuda, DNP  
M. Doi, DNP,  
T. Podruchny, DNP  
S- Iyasu, OPE/OSE

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/s/  
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SU-LIN SUN  
10/08/2013

JOHN R SENIOR  
10/08/2013



**MEMORANDUM**  
**Department of Health and Human Services**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**

**Date:** September 19, 2013

**To:** Eric Bastings, M.D., Acting 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 22-416 APTIOM** (Eslicarbazepine acetate)  
**Indication:** Adjunctive therapy for the treatment of partial-onset seizures in patients with epilepsy age 18 years and older.  
**Dosages:** 200, 400, 600, 800 mg tablets for oral administration  
**Sponsor:** Sunovion Pharmaceuticals Inc.

**Materials reviewed:** NDA 22416 Post-Incomplete-Response Resubmission is in EDR (Feb 11 2013)  
 STATS Consult by Dr. Ling Chen, May 15 2013  
 OSE Consult by Dr. Monica Munoz, April 12 2013  
 Clinical Safety Review by Dr. Mary Doi Sep 6 2013

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**I. Summary**

A. Background

The Division of Neurology Products consulted CSS to evaluate the abuse potential of eslicarbazepine acetate, NDA 22-416, resubmitted after receiving a Complete Response on Nov 2 2012. Eslicarbazepine acetate (ESL) is an antiepileptic drug (AED) developed by Sunovion as a third generation single-enantiomer of the dibenzazepine AEDs represented by carbamazepine

(first-generation) and oxcarbazepine (second-generation). In humans, ESL is rapidly metabolized to the S-enantiomer, eslicarbazepine (S-licarbazepine), the major active metabolite in plasma in humans. ESL is a novel voltage-gated sodium channel blocker, with additional calcium-channel blocking properties. During drug development, the Sponsor conducted 53 clinical trials in which 4,827 subjects participated, and eslicarbazepine was administered to 3,993 subjects. The marketing authorization for ESL under the trade names of Zebinix® and Exalief® was granted by the European Commission in April 2009. Eslicarbazepine acetate has not been marketed in the United States. As a central nervous system (CNS)-active new molecular entity (NME), its abuse potential needs to be fully characterized to determine the appropriateness of recommending scheduling of ESL under the Controlled Substances Act (CSA).

#### B. Conclusions:

Eslicarbazepine acetate exhibited a low abuse potential in clinical studies. Therefore, ESL is not recommended for scheduling at this time.

1. The portions of the submission that relate to adverse events (AE) reporting, including abuse-related adverse events, have major quality issues. The ISS was missing information or had insufficient details about the AEs, especially those related to abuse potential, overdose, medication errors and drug discontinuation. The latter point (drug discontinuation) relates to the CSS assessment of dependency. There is a discrepancy in the number of cases of suicidality due to ESL administration reported by the Sponsor but not accounted in ISS (see safety review by Dr. Mary Doi, Sep 6 2013). Therefore, the data is of questionable reliability (see Discussion, Section D. Quality and integrity of this NDA submission as it relates to AE reporting including AEs related to abuse potential).
2. The human and animal data concerning dependency and withdrawal were limited in providing information about whether chronic administration of the test drug, ESL, produces withdrawal behaviors indicative of physical dependence. Therefore, a post-marketing requirement (PMR) will be requested (see Discussion, Section F) for assessment of dependency.

#### C. Recommendations:

1. The following PMR is requested:
  - a. Perform a human dependency study in healthy volunteers.
2. CSS may be consulted to review and provide comments on the Sponsor's protocol prior to conducting the study.

## II. Discussion

#### D. Quality and integrity of this NDA submission as it relates to AE reporting including AEs related to abuse potential

I noted a number of serious integrity and quality issues in the dependency/withdrawal data and in the safety data, as described below.

#### **CSS comment regarding withdrawal/dependency data:**

1. The human withdrawal/dependency data is incomplete and misleading
2. Abrupt withdrawal is confused with tapered withdrawal
3. The ISS withdrawal data is misleading as it became clear that the Sponsor just reassembled all AEs which started within 30 days following discontinuation of eslicarbazepine and called those AEs “withdrawal data” regardless of whether the patient was taking the drug ESL (in open label treatment) or not.

**Below is a description of serious integrity and quality issues in data related to human dependency/withdrawal**

The majority of integrity and quality issues were noted after CSS received on June 7, 2013, a response to our information request. The issue is presented (in bold), followed by the Sponsor’s answer and then CSS comment (in italics).

**1. Withdrawal data is mislabeled and misleading.**

**CSS asked the sponsor to provide CRFs for all cases of seizures occurring during the drug withdrawal period after eslicarbazepine treatment.**

Sponsor: The Sponsor responded (email May 29 2013): Given that studies demonstrate ESL to be effective in reducing seizure frequency and that ESL is not known to have disease-modifying properties, subjects with refractory epilepsy are expected to have seizures during this period and a request to provide CRFs for all seizures during withdrawal periods would not provide meaningful information.

*CSS: Responded that the Sponsor respond meaningfully.*

*CRFs were provided. We found that 2 out of 5 patients who were supposed to undergo withdrawal period and discontinue ESL actually had seizures when on eslicarbazepine. As the sponsor later explained “We note that tables showing AEs up to 30 days post-discontinuation include all events beginning within 30 days of discontinuation, regardless of what drugs are started during that time period (including start of open-label ESL).”*

*So, the submitted ISS withdrawal data was misleading. The Sponsor reassembled all AEs which started within 30 days following discontinuation of eslicarbazepine and called it “withdrawal data” regardless of whether the patient was taking the drug (in open label treatment) or not.*

**2. Abrupt withdrawal is confused with tapered withdrawal**

**The Sponsor was asked to provide an explanation why epilepsy patients who were supposed to have tapered withdrawal were included in the table for abrupt withdrawal. Below is the Sponsor’s explanation.**

“Please note that subjects may have been evaluated for abrupt withdrawal from a dose different from their assigned maintenance dose, if they had stayed on a lower dose for >7 days (see ISS DARP Section 11.1, consideration 4b). For example, a subject randomized to 800 mg for maintenance therapy may have taken 400 mg for 14 days during the taper period, and thus

qualifies as having abruptly withdrawn from 400 mg. Therefore the “abrupt withdrawal” and “taper” tables describe different groupings of subjects. They are not mutually exclusive. Refer to Table 5.”

*This seems to be very confusing and it is impossible to distinguish abrupt withdrawal AEs from tapered withdrawal if they are considered “not mutually exclusive” ...In the medical language there is a fast withdrawal and slow withdrawal, though not noted by the Sponsor.*

### **3. No response to our request to provide the data.**

**CSS asked the Sponsor in request # 5 to provide withdrawal data for epilepsy study # 201 (below):**

The Sponsor responded that “ Only 2 subjects on ESL and 41 subjects on placebo met the subject-level criteria for inclusion in an analysis of physical dependence, and in this population, only 2 AEs occurred during the withdrawal period (2 in the Placebo group and none on ESL)” Of note, according to ISS, this study enrolled 147 patients, 109 completed the full the study (75 patients taking eslicarbazepine and 34 patients on placebo); the patients had 1 week taper. Also, CSS did not ask specifically for **abrupt** withdrawal data (“physical dependence population”), just for withdrawal data. The Sponsor again did not provide the requested data.

*We concluded that the Sponsor was reluctant to reveal the data, or does not want to admit that they did not collect this data.*

### **4. Another example of withdrawal AE reported during the time when the patient is taking ESL**

**CSS requested the Sponsor to provide CRFs for all incidents of drug toxicity (ISS: Table A.1.2.3.2) during the withdrawal period.**

The sponsor responded: There was one incident of an AE of drug toxicity occurring during the withdrawal period, in subject 2093301-171-90403. The event is “study drug intoxication” (refer to ISS Table A.1.13.1, page 26 of 38). The subject was randomized to ESL 400 mg in Part 1 of study 301. The subject entered the tapering period on 24 MAY 2005 and completed the ESL tapering on 06 JUN 2005. The subject was on PBO from 07 JUN 2005 to 14 JUN 2005 in accordance with the protocol specified tapering, and started Open-Label dosing on 15 JUN 2005. The AE began 26 JUN 2005 (11 days after the start of open-label ESL) and ended on 01 JUL 2005.

*CSS comment:*

- 1. The AE of drug toxicity occurred while on ESL, therefore it was not really a withdrawal AE.*
- 2. The patient had a 2 week taper, so should not have been reported in the dependency population which included only patients after abrupt withdrawal.*

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/s/  
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ALICJA LERNER  
09/19/2013

MICHAEL KLEIN  
09/19/2013

**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: September 12, 2013

Reviewer: Julie Neshiewat, 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 Holquist, RPh  
Division of Medication Error Prevention and Analysis

Drug Name and Strengths: Eslicarbazepine Acetate Tablets  
200 mg, 400 mg, 600 mg, 800 mg

Application Type/Number: NDA 022416

Applicant: Sunovion Pharmaceuticals

OSE RCM #: 2013-554

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

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## **1 INTRODUCTION**

This review evaluates the proposed labels and labeling for Eslicarbazepine Acetate, NDA 022416, for elements in their design that can lead to medication errors.

### **1.1 REGULATORY HISTORY**

The Division of Medication Error Prevention and Analysis (DMEPA) previously reviewed proposed container labels, blister labels, carton labeling, and insert labeling for Eslicarbazepine Acetate in OSE Review # 2009-996 dated February 25, 2010. The Applicant received a Complete Response Letter on April 30, 2010, which included DMEPA's recommendations for the proposed container labels, blister labels, and carton labeling. On February 22, 2013, the Applicant resubmitted the NDA application.

### **1.2 PRODUCT INFORMATION**

The following product information is provided in the May 1, 2013 insert labeling submission.

- Active Ingredient: Eslicarbazepine Acetate
- Indication of Use: Adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy 18 years and older
- Route of Administration: Oral
- Dosage Form: Tablets
- Strength: 200 mg, 400 mg, 600 mg, 800 mg
- Dose and Frequency: Initiate with 400 mg once daily for one week; increase at increments of 400 mg at weekly intervals to a maximum recommended dose of 1200 mg once daily; usual maintenance dose is 800 mg once daily
  - For some patients, therapy may be initiated at 800 mg once daily if the need for seizure control outweighs a potentially increased risk of adverse events during initiation
  - For patients with a creatinine clearance below 50 mL/min: Initiate with 200 mg once daily for two weeks followed by 400 mg once daily; maximum dose of 600 mg
- How Supplied:
  - 200 mg: 30-count retail bottles
  - 400 mg: 30-count retail bottles; 7-count professional sample blister wallet (carton contains 4 blister wallets)
  - 600 mg: 60-count and 90-count retail bottles; 7-count professional sample blister wallet (carton contains 4 blister wallets)
  - 800 mg 30-count and 90-count retail bottles; 7-count professional sample blister wallet (carton contains 4 blister wallets)

- 400 mg and 800 mg Sample Pack: 14-count professional sample blister wallet includes 7-count of each strength (carton contains 4 blister wallets)
- Storage: Store tablets at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)
- Container and Closure System: High-density polyethylene bottles and (b) (4) caps; (b) (4) blisters and aluminum foil lidding

## 2 METHODS AND MATERIALS REVIEWED

DMEPA evaluated the Eslicarbazepine Acetate labels and labeling submitted by the Applicant and looked at our previously completed label and labeling review.

### 2.1 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>1</sup> the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Retail (Preferred) Oblong Bottle Container Labels submitted March 28, 2013 (Appendix B)
- Retail (Alternate) Round Bottle Container Labels with Carton Labeling submitted March 28, 2013 (Appendix C)
- Professional Sample Blister Wallet Labeling with Carton Labeling submitted March 28, 2013 (Appendix D)
- Medication Guide submitted May 1, 2013 (No image)
- Insert Labeling submitted May 1, 2013 (No image)
- Physical Samples of Blister Wallets received May 3, 2013 (No image)
- OSE Label and Labeling Review # 2009-996

## 3 MEDICATION ERROR RISK ASSESSMENT

There were several changes made to the labels and labeling since our previous review. In the resubmission, the Applicant included an additional strength, 200 mg, and included an alternate packaging configuration, round bottle container labels with carton (b) (4)

Additionally, the blister labels and carton labeling for the professional samples were redesigned into a blister wallet.

The layout of the blister wallets appears similar to other currently marketed products packaged in blister wallets, and we do not have concerns with the packaging design itself. Overall, we have identified some areas of the proposed labels and labeling that can be

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

improved for clarity and readability to ensure the safe use of the product, and we provide recommendations in Section 4 below.

We note that the professional sample blister wallets contain statements, such as (b) (4) and (b) (4) which appear promotional. We notified the Office of Prescription Drug Promotion (OPDP), and they will be conducting a separate review to evaluate the container labels and carton labeling from a promotional perspective.



#### 4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling can be improved for clarity and to increase the readability and prominence of important information on the label to promote the safe use of the product.

If you have further questions or need clarifications, please contact Ermias Zerislassie, project manager, at 301-796-0097.

##### 4.1 COMMENTS TO THE DIVISION

DMEPA provides the following comments for consideration by DNP prior to the approval of this NDA.

###### A. Highlights of Prescribing Information: Dosage Forms and Strengths

1. We recommend adding the dosage form, tablets.

###### B. Full Prescribing Information: Dosage and Administration

1. (b) (4)
2. We note that Section 5.5 *Withdrawal of AEDs* states that “As with all antiepileptic drugs, Tradename should be withdrawn gradually (b) (4) (b) (4)” We recommend adding this information to Section 2 *Dosage and Administration* . Furthermore, if there is data to support a specific tapering schedule (i.e.

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<sup>2</sup> Guidance for Industry – Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation. March 2013.

Discontinue Tradename slowly over X days), we recommend adding this information to Section 2 *Dosage and Administration*.

C. Full Prescribing Information: Description

We recommend adding a unit of measure immediately following all numbers, as appropriate. For example, revise the “(b) (4)” statement to read “Each Tradename tablet contains 200 mg, 400 mg, 600 mg, or 800 mg eslicarbazepine acetate.”

D. Full Prescribing Information: How Supplied / Storage and Handling

See Comment C above.

## 4.2 COMMENTS TO THE APPLICANT

DMEPA advises the recommendations below be implemented prior to approval of this NDA.

A. General Comments for Labels and Labeling

1. Revise statements that appear in all upper case letters to title case to improve readability. For example, revise the presentation of the proposed proprietary name from all upper case letters “STEDESA” to title case “Stedesa.”
2. The established name lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2). In addition, the entire established name “(Eslicarbazepine Acetate) Tablets” should have the same font size, color, and style.
3. 60-count and 90-count bottles: Although the 60-count and 90-count bottles may be a unit-of-use container, it may also be used for more than one patient. Ensure a sufficient number of medication guides are provided.

B. Retail Preferred Oblong Bottle Container Labels: All Strengths

1. Remove or minimize and move the graphic appearing to the left of the proprietary name.
2. Relocate the statement “Keep out of reach of children” to the side panel.
3. As currently presented, the “Attention Dispenser: Each time... (b) (4)” statement appears more prominent than the established name. Debold and decrease the font size of the “Attention Dispenser: Each time... (b) (4)” statement and remove the (b) (4) surrounding the statement. In addition, relocate the website information and telephone number (b) (4),” and (b) (4) from the principal display panel to the side panel to minimize the cluttered appearance on the principal display panel.
4. Your proposed Medication Guide statement does not comply with 21 CFR 208.24(d). As currently presented, it does not state how the Medication

Guide is provided (i.e. it is unclear if the Medication Guide is “enclosed,” “accompanied,” “attached,” etc.) Revise the Medication Guide statement to include how the Medication Guide is provided per 21 CFR 208.24(d).

5. Increase the font size of the strength statement for increased prominence.
6. Revise the storage statement to read as follows ‘Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)’.
7. If space permits, we recommend separating out the “Usual Dosage” statement and the storage statements to improve readability.
8. For the 600 mg and 800 mg strength labels, decrease the font size of the “Bial” statement on the side panel since it is overly prominent.

C. Retail Alternate Round Bottle Container Labels: All Strengths

1. Please see Comments B1, B3, B4, B5, and B6 above
2. Decrease the font size of the “Bial” statement on the side panel since it is overly prominent.

D. Retail Alternate Round Bottle Carton Labeling: All Strengths

1. Please see Comments B1, B4, B5 and B6 above
2. As currently presented, the “Attention Dispenser: Each time.. (b) (4)” statement appears more prominent than the established name. Debold and decrease the font size of the “Attention Dispenser: Each time.. (b) (4)” statement and remove the (b) (4) surrounding the statement. In addition, remove (b) (4) from the principal display panel since this information is already present on the side panel.
3. Remove the (b) (4) colored area at the bottom of the carton labeling. The use of this color on all labeling adds similarity between the packaging for the different strengths. Alternatively, consider replacing the (b) (4) color with the same color used for the strength. For example, for the 200 mg strength, use the pink color in place of the (b) (4) colored area at the bottom of the carton labeling so it matches the colored font used for statement of strength.

E. Professional Sample Blister Wallet Labeling: 400 mg, 600 mg, 800 mg, and Sample Pack

1. Please see Comments B1 and B6 above.
2. Revise the larger strength presentation so that “mg” appears on the same line of text as the number. In addition, the font used for “mg” should match the font used for the number in the strength.
3. Revise the strength presentation to read “XX mg per tablet”

4. Add dosing information similar to “Take one tablet by mouth once daily” to the panels containing drug and to the “Usual Dosage” statement on the back panel.
5. Include instructions that state how the tablets should be removed from the blister wallet. For example, “Peel the backing from the tablet blister. Push down on the pill with your thumb so that the pill releases through the back of the blister.”
6. Remove the (b) (4) that appears on the back side of the panel containing drug product. This may confuse the patient regarding which side to push through the tablet from.
7. Remove the (b) (4) located near the colored box containing the strength statement, as these graphics are distracting.
8. Remove the (b) (4) since it is redundant to the “Attention Dispenser...” statement.
9. The “Bial” statement on the bottom of the back panel is overly prominent. Decrease the font size of this statement.
10. Decrease the font size of the “Rx Only” statement since it appears more prominent than the established name.

F. Professional Sample Blister Wallet Labeling: Sample Pack

1. The Agency does not consider starter packs to be drug samples; therefore, the use of the term “starter” on drug sample labeling is inappropriate and should not be used per 21 CFR 203.38 (c) and 64 FR 67720 at 67741. Revise the statement (b) (4) to read similar to “Sample Pack.”
2. There should be sufficient drug information on all panels of the blister wallet containing drug product in the case that the blister wallet panels are separated from each other. Add the proprietary name and established name to appear above the strength on the panels containing drug product.
3. Revise presentations of “400 & 800 mg” to read “ 400 mg and 800 mg”.

G. Professional Sample Blister Carton Labeling: 400 mg, 600 mg, 800 mg, and Sample Pack

1. Please see Comments F1 and F3 above
2. Relocate the Stedesa indication to below the proprietary name, established name, and strength.
3. Revise the net quantity statement to read “This package contains 28 tablets on 4 sample cards. Each sample card contains 7 tablets each.”

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

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/s/  
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JULIE V NESHIEWAT  
09/12/2013

IRENE Z CHAN  
09/12/2013

CAROL A HOLQUIST  
09/13/2013

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

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

**Memorandum**

**Date:** May 30, 2013

**To:** Su-Lin Sun, RPh  
Senior Regulatory Project Manager  
Division of Neurology Products (DNP)  
Office of Drug Evaluation (ODE)-I

**From:** Melinda McLawhorn, PharmD, BCPS  
Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**Through:** Mathilda Fienkeng, PharmD, Acting Group Leader, OPDP

**CC:** Julie Villanueva Neshiewat, PharmD  
Safety Evaluator  
Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Surveillance and Epidemiology (OSE)

**Subject:** **NDA 22416**  
Eslicarbazepine tablets

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**Background**

On February 10, 2013, DNP consulted OPDP to review the proposed package insert (PI), patient package insert (PPI), medication guide (MG), and carton and container labeling for the original NDA submission for eslicarbazepine tablets. On May 17, 2013, DMEPA requested that OPDP provide comments on the proposed carton and container labeling in advance of the mid-cycle meeting on June 11, 2013.

OPDP reviewed the carton and container labeling submitted to the electronic document room on March 28, 2013 and our comments are provided below. Images of the representative labels are provided in the attachment. OPDP will provide comments under a separate cover on the PI, PPI and MG once this labeling is substantially complete.

**General Comments**

Since the proprietary name, "Stedesa", has not been approved, we will not comment on the presentation of the proprietary name at this time.

Please apply the following comments to same or similar claims and presentations in other labeling for eslicarbazepine.

**Trade Round Bottle Label**

We note that the established name is presented in small, (b) (4) font which is less prominent than the other text on the proposed round bottle labeling. We recommend that the established name be presented in manner consistent with 21 CFR 201.10(g)(2) which requires that the established name be at least half the size of the letters comprising the proprietary name and have a prominence consistent with the proprietary name in terms of type, size, color, and font.

### Professional Sample Blister Wallet (sample wallet)

The proposed sample wallet includes the following claims (emphasis original):

- (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)

These claims are misleading (b) (4)

We note that the primary endpoint in clinical studies with eslicarbazepine was reduction in seizure frequency from baseline to the end of the maintenance period. We recommend deleting these claims.

The front and back panels of the proposed sample wallet present (b) (4)  
These claims are misleading (b) (4)

We acknowledge that some risk information is presented on other panels of the blister wallet and reference is made to the medication guide. However, this is not adequate. Therefore, we recommend deleting these claims or providing sufficient disclosure of the most serious and most common risks associated with the drug in depth and detail to balance these claims. Please note that reminder labeling should not include indications for use and should make no representation or suggestion relating to the drug product [21 CFR 201.100(f)].

The proposed sample wallet includes the following claims:

- (b) (4)
- (b) (4)

These claims are misleading (b) (4)

Furthermore, these claims are misleading (b) (4)

We recommend deleting these claims.

The proposed sample wallet claims, (b) (4)

This claim is misleading (b) (4)

We recommend deleting this claim.

The claim, (b) (4), " is misleading (b) (4)

We recommend deleting this claim or presenting adequate risk information in conjunction with this claim.

Thank you for your consult. If you have any questions, please contact Melinda McLawhorn at 6-7559 or at [Melinda.McLawhorn@fda.hhs.gov](mailto:Melinda.McLawhorn@fda.hhs.gov).

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

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/s/  
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MELINDA W MCLAWHORN  
05/30/2013

**Division of Neurology Products**

**REGULATORY PROJECT MANAGER LABELING REVIEW**

**Application:** NDA 22416

**Name of Drug:** Stedesa (eslicarbazepine acetate) 200 mg, 400 mg, 600 mg, and 800 mg tablets.

**Applicant:** Sunovion Pharmaceuticals Inc.

**Proposed Indication:** Adjunctive therapy in the treatment of partial onset seizures in patients with epilepsy 18 years and older.

**Labeling Reviewed**

**Submission Date:** February 8, 2013

**Receipt Date:** February 11, 2013

**Background and Summary Description:**

Original NDA 22416 was submitted on March 13, 2009, Complete Response Letter was issued on April 30, 2010.

NDA first resubmission on August 31, 2012, Acknowledge Incomplete Response (AIR) letter was issued on November 6, 2012.

NDA second resubmission on February 8, 2013, the resubmission is accepted as class 2 resubmission.

**Review**

Proposed draft label (submitted on August, 2012 and resubmitted on February 8, 2013) was reviewed.

**Recommendations**

1. Recent Major Changes Section

Please delete Recent Major Changes Section

***Comment:***

Recent Major Changes section is not needed this time since there is no prior approved PI previously

2. Highlight Limitation Statement:

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:*** Please insert **STEDES**A (eslicarbazepine Acetate)Tablets, for oral use

### 3. Product Title:

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

***Comment:*** Insert the PROPRIETARY NAME if it’s approved already. Insert the non-proprietary name if proprietary name is still under review.

Please consider 5 components for product name in the following order:

PROPRIETARY NAME (non-proprietary name), dosage form, route of administration, and controlled substance symbol if it’s controlled product

### 4. Indications and Usage:

Please insert Product Name

***Comment:*** STEDES

A is indicated for adjunctive therapy in the treatment of partial seizures in patients 18 years and older

### 5. Dosage Forms and Strengths:

Please use bulleted subheadings for each dosage form

***Comment:*** Tablets: 200mg (white oblong), 400mg (white circular), 600mg (white oblong), and 800mg (white oblong)

### 6. Adverse Reactions:

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 phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”. Only includes a U.S. phone number.

***Comment:*** Please insert Sunovion’s actual phone # and web address

### 7. Table of Contents (TOC):

a. A horizontal line must separate TOC from the FPI.

***Comment:*** Please insert a horizontal line between TOC and FPI.

b. Statement regard to section or subsection from 201.56(d)(1) is omitted from the FPI and TOC

***Comment:*** Please move the sentence, “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”, to end of TOC , not top of the FPI.

### c. Medication Guide:

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 at approval.

***Comment:*** Medication Guide need to be moved to at the end of FPI (not in section 17)

8. Full prescribing Information Details:

Patient Counseling Information

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:

***Comment:*** Delete (b) (4) from section 17 title

Please insert "See FDA-approved patient labeling (Medication Guide)" below section 17 title

9. Additional comments for sections 2 and 6.1

In your proposed prescribing information for eslicarbazepine acetate you include recommended dosage modifications due to drug interactions. According to the 2012 Drug *Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations* Guidance

(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf>) and the 2010 *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products - Content and Format* Guidance

(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075066.pdf>) all dosage modifications due to drug interactions should be included in Dosage and Administration. Therefore, revise Section 2 to include the recommended dosage modifications due to drug interactions.

In your proposed prescribing information for eslicarbazepine acetate you include a "laundry list" of adverse events in Phase III trials in patients with partial-onset seizures in Section 6.1.

However, only adverse reactions (untoward events with a possible causal relationship to eslicarbazepine acetate) should be included. "Exhaustive lists of every reported adverse event, including those that are infrequent and minor, commonly observed in the absence of drug therapy or not plausibly related to drug therapy should be avoided." See 21 CFR 201.57c(7) and the 2006 *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products - Content and Format* Guidance

(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075057.pdf>). Therefore, revise this section.

Su-Lin Sun, PharmD

04-14-2013

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Regulatory Project Manager

Date

Jacqueline H. Ware, Pharm.D, RAC

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Chief, Project Management Staff

Date

# Selected Requirements of Prescribing Information (SRPI) Revised

Selected Requirement of Prescribing Information Revised (SRPI-Revised) is a drop-down checklist of critical elements of the prescribing information (PI) used during labeling review. The SRPI-Revised replaces the SRPI and includes only PI format items.

For additional information concerning the content and format of the PI, see regulatory requirements (21 CFR 201.56 and 201.57), labeling guidances, and the Labeling Review Tool at: <http://inside.fda.gov:9003/downloads/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/UCM284987.doc>.

**Instructions:** There is one drop-down menu and one comment field for each item.

**Drop-Down Menu:** For each item, click on the word “**NO**” and choose one of three options (since **NO** is the default option, review each item and select the appropriate option):

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

**Comment Field:** Comments are optional. To insert a comment, click on the word “**Comment**” for a particular item and start typing.

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## Selected Requirements of Prescribing Information (SRPI) Revised

### 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:* none
- YES** 2. HL is one-half page or less than one-half page (the HL Boxed Warning does not count against the one-half page requirement). If longer than one-half page:  
  - Filing Period (Regulatory Project Manager Physicians’ Labeling Rule (PLR) Format Review): RPM has notified the Cross-Discipline Team Leader (CDTL).
  - End-of Cycle Period: A waiver has been or will be granted by the review division.*Comment:* none
- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.  
*Comment:* none
- YES** 4. White space must be present before each major heading in HL.  
*Comment:* none
- YES** 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:* none
- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• <b>Highlights Heading</b>	Required
• <b>Highlights Limitation Statement</b>	Required
• <b>Product Title</b>	Required
• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a Boxed Warning is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state “None.”)
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present**
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* See Recent Major Changes section below.

\*\* Virtually all product labeling should include at least one Warning and Precaution.

## Selected Requirements of Prescribing Information (SRPI) Revised

### Comment:

Recent Major Changes section is not needed this time since there is no prior approved PI previously

**YES**

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

Comment: none

### HIGHLIGHT 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: none

#### Highlights Limitation Statement

**NO**

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: Please insert STEDESA (eslicarbazepine Acetate)Tablets, for oral use

#### Product Title

**NO**

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

Comment: Insert the proprietary name if it’s approved already. Insert the non-proprietary name if proprietary name is still under review.

#### 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: The approval year will be inserted on action day

#### Boxed Warning

**N/A**

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

Comment: none

**N/A**

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: none

**N/A**

14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

Comment: none

**N/A**

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.*”)

## Selected Requirements of Prescribing Information (SRPI) Revised

**Comment:** none

- N/A** 16. Should use sentence case for summary (combination of uppercase and lowercase letters typical in a sentence).

**Comment:** none

### Recent Major Changes (RMC)

- N/A** 17. Other than these five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions, there are no other sections noted in RMC.

**Comment:** no needed since no prior PI approved previously.

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

**Comment:** none

- 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) --- 2/2010".

**Comment:** none

- 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:** none

### Indications and Usage

- NO** 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 class) indicated for (indication)]."

**Comment:** STEDESA is indicated for adjunctive therapy in the treatment of partial seizures in patients 18 years and older **(1.1)**

### Dosage Forms and Strengths

- NO** 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:** Tablets: 200mg (white oblong), 400mg (white circular), 600mg (white oblong), and 800mg (white oblong) **(3)**

### 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:** none

- NO** 24. Each contraindication is bulleted when there is more than one contraindication.

**Comment:** N/A

### Adverse Reactions

## Selected Requirements of Prescribing Information (SRPI) Revised

- NO** 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 phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”. Only includes a U.S. phone number.

**Comment:** Please insert Sunovion’s actual phone # and web address

**YES** **Patient Counseling Information Statement**

26. Must include one of the following **bolded** verbatim statements:

Product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

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:** none

**Revision Date**

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

**Comment:**

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## Contents: Table of Contents (TOC)

### GENERAL FORMAT

- NO** 28. A horizontal line must separate TOC from the FPI.

**Comment:** Please insert a horizontal line between TOC and FPI.

- 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:**

- N/A** 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:**

## Selected Requirements of Prescribing Information (SRPI) Revised

- 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:** Please move the sentence, “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”, to end of TOC , not top of the FPI.

### 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.

<b>Boxed Warning</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>
<b>8.4 Pediatric Use</b>
<b>8.5 Geriatric Use</b>
<b>9 DRUG ABUSE AND DEPENDENCE</b>
<b>9.1 Controlled Substance</b>
<b>9.2 Abuse</b>
<b>9.3 Dependence</b>
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
<b>12.1 Mechanism of Action</b>
<b>12.2 Pharmacodynamics</b>
<b>12.3 Pharmacokinetics</b>
<b>12.4 Microbiology (by guidance)</b>
<b>12.5 Pharmacogenomics (by guidance)</b>
<b>13 NONCLINICAL TOXICOLOGY</b>
<b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b>
<b>13.2 Animal Toxicology and/or Pharmacology</b>

## Selected Requirements of Prescribing Information (SRPI) Revised

14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

### Comment:

- NO** 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 at approval.

Comment: Medication Guide need to be moved to at the end of FPI (not in section 17)

- 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 (5.1)*].

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

- N/A** 42. All text is **bolded**.

Comment:

- N/A** 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:

- N/A** 44. Should use sentence case (combination of uppercase and lowercase letters typical 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:

## Selected Requirements of Prescribing Information (SRPI) Revised

*“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**

**NO**

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:** Delete  <sup>(b) (4)</sup> from section 17 title  
Please insert “ See FDA-approved patient labeling (Medication Guide)” below section 17 title

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SU-LIN SUN  
04/19/2013

JACQUELINE H WARE  
05/09/2013

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

**Pharmacovigilance Review**

**Date:** April 12, 2013

**Reviewer:** Monica Muñoz, Pharm.D., MS  
Safety Evaluator, Division of Pharmacovigilance I (DPV 1)

**Team Leader:** Cindy Kortepeter, Pharm.D.  
Safety Evaluator Team Leader, DPV 1

**Division Director:** Min Chen, MS, R.Ph.  
Division Director (acting), DPV 1  
Deputy Director, DPV 1

**Product Name:** Eslicarbazepine acetate

**Subject:** Abuse, misuse, overdose, psychiatric adverse events, suicidal behavior, homicides, and deaths

**Application Type/Number:** NDA 22416

**Applicant/Sponsor:** Sunovion Pharmaceuticals Inc

**OSE RCM #:** 2013-670

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## EXECUTIVE SUMMARY

The Office of Surveillance and Epidemiology (OSE) was consulted by the Office of the Center Director's Controlled Substance Staff (CSS) to review foreign databases for reports of adverse events associated with eslicarbazepine and related to abuse, misuse, overdose, psychiatric adverse events, suicidal behavior, homicides, and deaths. Eslicarbazepine acetate has not been approved in the United States, but is currently under evaluation by the Division of Neurology Products (DNP) for adjunctive treatment of partial onset seizure in adults with epilepsy.

FAERS was searched and four foreign cases associated with the events of interest were identified. All 4 cases reported eslicarbazepine as a co-suspect medication. Dizziness, syncope, orthostatic hypotension, and palpitations were reported in a 55 year old male on multiple medications. Aura associated with focal epileptic seizures was reported in a 31 year old female. One case reported adverse events related to depression and suicidal ideation in a 23 year old female on multiple potentially contributing medications. Finally, the death of a 64 year old female was reported without further details. At the time of her death she was on multiple antiepileptic medications.

The World Health Organization's (WHO) Individual Case Safety Report (ICSR) database, VigiBase, was searched for additional cases. The VigiBase search retrieved 191 reports of all adverse events reported with eslicarbazepine. Two reports of depression and two reports with the adverse event of death were retrieved. FAERS reports are included in VigiBase; therefore, there was one additional report for each of the adverse events death and depression identified in VigiBase. Additional adverse events reports not appearing in FAERS and containing adverse events possibly related to the events of interest include: altered state of consciousness (N=2), memory impairment (N=1), disturbance in attention (N=2), mental impairment (N=1), agitation (N=1), nervousness (N=1), aggression (N=3), delirium (N=1), sleep disorder (N=1), sudden death (N=2), completed suicide (N=2), suicide attempt (N=2), and overdose (N=1). Given the current small report count for these events (N<3), data mining VigiBase to identify potential safety signals is of low utility.

The cases in the FAERS database containing adverse event terms of interest also involved other co-suspect medications and/or comorbid disease states. Additional reports containing the adverse events of interest were identified in VigiBase; however, the strength of these cases and causality could not be assessed due to the inaccessibility of case details. The small number of reports and limited report details do not provide sufficient evidence to support an association between eslicarbazepine acetate and abuse, misuse, overdose, psychiatric adverse events, suicidal behavior, homicides, and deaths at this time using these data sources.

## 1 INTRODUCTION

The Office of Surveillance and Epidemiology (OSE) was consulted by the Office of the Center Director's Controlled Substance Staff (CSS) to review foreign databases for reports of adverse events associated with eslicarbazepine and related to abuse, misuse, overdose, psychiatric adverse events, suicidal behavior, homicides, and deaths. CSS provided a list of MedDRA terms suggesting abuse. (Appendix A)

### 1.1 BACKGROUND

Eslicarbazepine acetate has been submitted to the Division of Neurology Products (DNP) as NDA 22416. Eslicarbazepine acetate is being evaluated as adjunctive treatment of partial onset seizure in adults with epilepsy. The pharmacological activity of eslicarbazepine acetate is primarily exerted through its active metabolite, eslicarbazepine. The precise mechanism(s) by which eslicarbazepine exerts its anticonvulsant actions are not fully characterized. Electrophysiological studies indicate that eslicarbazepine stabilizes the inactivated state of voltage-gated sodium channels, preventing their return to the activated state resulting in an inhibition of repetitive neuronal firing. In addition, eslicarbazepine has been shown to inhibit T-type calcium channels which may contribute to its anticonvulsant effects.<sup>1</sup> Marketing authorization for eslicarbazepine acetate was granted by the European Commission on April 21, 2009 under the tradenames Zebinix<sup>®</sup> and Exalief<sup>®</sup>. Exalief<sup>®</sup> was not marketed anywhere in the EU for three consecutive years from the granting of the marketing authorization, therefore the marketing authorization of Exalief<sup>®</sup> has ceased to be valid. Exalief<sup>®</sup> was a duplicate application to Zebinix<sup>®</sup>, which is marketed in several EU countries. Eslicarbazepine acetate was also approved in India on March 7, 2011.

Relevant information contained in Zebinix<sup>®</sup>'s product leaflet includes the following:<sup>1</sup>

#### Warnings and Precautions

A small number of people being treated with anti-epileptics have had thoughts of harming or killing themselves. If at any time you have these thoughts, when taking Zebinix, contact your doctor immediately.

#### Side Effects

**Uncommon** (may affect 1 to 10 users in 1,000) side effects are:

- Difficulty in sleeping
- Crying, feeling depressed, nervous or confused, lack of interest or emotion
- Agitated
- Irritability
- Mood changes or hallucinations
- Feeling sleepy

Other antiepileptic drugs (AEDs), such as ezogabine and benzodiazepines, have been scheduled as controlled substances. The two other FDA approved members of the dibenzazepine family of AEDs, carbamazepine and oxcarbazepine, are not known to be associated with abuse.<sup>2,3</sup>

All approved AEDs, with the exception of those only indicated for short-term use, possess a warning regarding the risk of suicidal thoughts or behavior. The warning was included as a result of an FDA analysis of reports of suicidality from placebo controlled trials. The analysis found an increased risk of suicidal thoughts and behavior with antiepileptic drugs of varying mechanisms of action and across a range of indications.<sup>4</sup>

## 2 METHODS AND MATERIALS

### 2.1 FAERS SEARCH STRATEGY

The FDA Adverse Event Reporting System (FAERS) was searched with the strategy described in Table 1.

<b>Table 1. FAERS Search Strategy*</b>	
Date of search	March 14, 2013
Time period of search	April 21, 2009 <sup>^</sup> - March 14, 2013
Product Terms	Eslicarbazepine, eslicarbazepine acetate
MedDRA Search Terms	All SOCs, PTs

\* See Appendix B for description of the FAERS database.

<sup>^</sup> Date marketing authorization granted by the European Commission

### 2.2 WHO INDIVIDUAL CASE SAFETY REPORT DATABASE (VIGIBASE) SEARCH STRATEGY

VigiBase was searched with the strategy described in Table 2.

<b>Table 2. VigiBase Search Strategy*</b>	
Date of search	March 18, 2013
Time period of search	April 21, 2009 <sup>^</sup> - February 26, 2013 <sup>†</sup>
Product Terms	Eslicarbazepine, eslicarbazepine acetate
MedDRA Search Terms	All SOCs, PTs

\* See Appendix C for description of the WHO Individual Case Safety Report database, VigiBase.

<sup>^</sup> Date marketing authorization granted by the European Commission

<sup>†</sup> VigiBase data refresh date

## 3 RESULTS

### 3.1 FAERS CASE SELECTION

The FAERS search retrieved 11 reports, all of which were foreign. All cases reported eslicarbazepine as a co-suspect medication. Adverse events associated with abuse, misuse, overdose, psychiatric adverse events, suicidal behavior, homicides, and deaths are listed in Table 2.

<b>Table 2. Adverse Events Reports<sup>¶</sup> Containing PT Terms Associated with Events of Interest*</b>		
<b>System Organ Class (SOC)</b>	<b>Preferred Term</b>	<b>N<sup>^</sup></b>
General Disorders and Administration Site Conditions (N=3)		
	Crying	1
	Death	1
	Fatigue	1
Nervous System Disorders (N=7)		
	Aura	1
	Dizziness	5
	Syncope	4
Psychiatric Disorders (N=1)		
	Depressed Mood	1
	Depression	1
	Mood Altered	1
	Suicidal Ideation	1

<sup>¶</sup> Includes duplicates

\*Events of interest are related to abuse, misuse, overdose, psychiatric adverse events, suicidal behavior, homicides, and deaths (Appendix A)

<sup>^</sup> Reports may be coded with more than one adverse event

Of the 11 reports identified in FAERS, eight contained adverse events of interest. After removal of duplicates, four unique cases were identified:

1. Dizziness, syncope, orthostatic hypotension, and palpitations in a 55 year old male on multiple medications. (five duplicate reports)
2. Aura associated with focal epileptic seizures in a 31 year old female.
3. Depressed mood, depression, mood altered, suicidal ideation, crying, and fatigue in a 23 year old female.
4. Death of a 64 year old female.

Details of the four cases are described below.

*Dizziness, syncope*  
FAERS # 8038434v1

A 55 year-old male on mirtazepine 15 mg and eslicarbazepine 800 mg was hospitalized for dizziness, postural hypotension, collapse, palpitations, and shortness of breath. Concomitant medications include levetiracetam, citalopram, allopurinol, fluticasone, salmeterol, and albuterol. The action taken on mirtazepine and eslicarbazepine was unknown.

*Aura*

FAERS # 8042475v2

A 31 year old female experienced focal epileptic seizures and aura while on zonisamide (525 mg daily) and eslicarbazepine acetate (Zebinex 2400 mg daily). The female recovered from the seizures and auras were not noted on follow-up. No additional information was provided.

*Depressed mood, depression, mood altered, suicidal ideation, crying, fatigue*

FAERS #7724864v1

A physician in Denmark reported a case in which a 23 year old female experienced tiredness, suicidal thoughts, and depression. Suspect medications include levetiracetam, lamotrigine, valproic acid, clobazam, topiramate, and eslicarbazepine (Zebinix). The patient reportedly planned her suicide, but moved home with parents to have someone with her. Suicidal thoughts were present for 3 weeks, and then resolved after 1.5 months. At the time of reporting, the patient continued eslicarbazepine as monotherapy.

*Death*

FAERS #8292874v1

One case of death associated with eslicarbazepine was reported in the United Kingdom. Suspect medications include retigabine, lamotrigine, and eslicarbazepine. On an unknown date a 64 year-old female started taking lamotrigine 450 mg daily and eslicarbazepine (Zebinix) 800 mg at night. On November 7, 2011 the patient also started taking retigabine. On (b) (6) the patient missed a dose of retigabine and died the following day. No additional details of the cause or circumstances of her death were provided.

### 3.2 VIGIBASE CASE SELECTION

A search of VigiBase retrieved 191 reports for any adverse event reported with eslicarbazepine. Reports containing adverse event terms associated with abuse, misuse, overdose, psychiatric adverse events, suicidal behavior, homicides, and deaths are described in Table 3. Report narratives are not available in VigiBase.

<b>System Organ Class (SOC)</b>	<b>Preferred Term</b>	<b>N<sup>^</sup></b>
General Disorders and Administration Site Conditions		
	Sudden death	2
	Death	2
	Fatigue	5

Nervous System Disorders		
	Aura	1
	Altered state of consciousness	2
	Somnolence	4
	Dizziness	10
	Syncope	1
	Memory impairment	1
	Disturbance in attention	2
	Mental impairment	1
Psychiatric Disorders		
	Agitation	1
	Nervousness	1
	Aggression	3
	Delirium	1
	Depressed Mood	1
	Depression	2
	Mood Altered	1
	Sleep disorder	1
	Completed suicide	2
	Suicidal ideation	1
	Suicide attempt	2
Injury, poisoning and procedural complications		
	Overdose	1

\* Events of interest are related to abuse, misuse, overdose, psychiatric adverse events, suicidal behavior, homicides, and deaths (Appendix A)

^ Reports may be coded with more than one adverse event

#### 4 DISCUSSION

The FAERS search retrieved 11 foreign reports of all adverse events reported with eslicarbazepine. Four unique cases contained the adverse events of interest, 2 of which were related to psychiatric events or death. One report included the adverse events depression, depressed mood, mood altered, and suicidal ideation in a 23 year old female on multiple potentially contributing medications. Another reported the death of a 64 year old female on eslicarbazepine. The subject was on multiple antiepileptic medications at the time of her death and limited details were provided.

The Vigibase search retrieved 191 reports of all adverse events reported with eslicarbazepine. Two reports of depression and two reports of the adverse event death were retrieved. FAERS reports are included in Vigibase; therefore, there was one additional report for each of the adverse events death and depression identified in Vigibase. Additional adverse events reports not appearing in FAERS and containing adverse events possibly related to abuse include: altered state of consciousness (N=2), memory impairment (N=1), disturbance in attention (N=2), mental impairment (N=1), agitation (N=1), nervousness (N=1), aggression (N=3), delirium (N=1), sleep

disorder (N=1), sudden death (N=2), completed suicide (N=2), suicide attempt (N=2), and overdose (N=1). Given the small report count for these events (N<3), data mining VigiBase to identify potential safety signals is of low utility at this time.

Carbamazepine and oxcarbazepine, members of the same AED family as eslicarbazepine, are not known to have abuse potential. Due to the structural and mechanistic relationship to carbamazepine and oxcarbazepine, eslicarbazepine is likely to possess a similar suicidality risk given the results of the previous FDA analysis.<sup>4</sup>

## **5 CONCLUSION**

The four cases in the FAERS database containing adverse event terms of interest involved other co-suspect medications or concomitant medical conditions. Additional reports containing adverse events possibly relating to of the events of interest were identified in VigiBase; however, the strength of these cases and causality could not be assessed due to the lack of case details. The small number of reports and limited report details do not allow the association between eslicarbazepine acetate and abuse, misuse, overdose, psychiatric adverse events, suicidal behavior, homicides, and deaths to be assessed at this time using these data sources.

## **6 REFERENCES**

1. Zebinix : EPAR - Product Information. Last Updated: February 14, 2013. Available at: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/000988/WC500047225.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000988/WC500047225.pdf)
2. Tegretol [package insert] East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2013.
3. Trileptal [package insert] East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2013.
4. US Food and Drug Administration: Antiepileptic drugs and suicidality. May 23, 2008. Antiepileptic drugs and suicidality. Available at: <http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4372b1-01-FDA.pdf>.

## 7 APPENDICES

### 7.1 APPENDIX A. TERMS SUGGESTIVE OF ABUSE POTENTIAL

Terms suggestive of abuse potential:

- *EUPHORIA-RELATED TERMS:*

*Euphoric mood:* euphoria, euphoric, exaggerated well-being, excitement excessive, feeling high, felt high, high\*, high\* feeling, laughter. (\* Exclude terms that clearly are not related or relevant such as “high blood pressure,” etc.)

*Elevated mood:* mood elevate, elation.

*Feeling abnormal:* cotton wool in head, feeling dazed, feeling floating, feeling strange, feeling weightless, felt like a zombie, floating feeling, foggy feeling in head, funny episode, fuzzy, fuzzy head, muzzy head, spaced out, unstable feeling, weird feeling, spacey.

*Feeling drunk:* drunkenness feeling of, drunk-like effect, intoxicated, stoned, drugged.

*Feeling of relaxation:* Feeling of relaxation, feeling relaxed, relaxation, relaxed, increased well-being, excessive happiness.

*Dizziness:* dizziness and giddiness, felt giddy, giddiness, light headedness, light-headed, light-headed feeling, lightheadedness, swaying feeling, wooziness, woozy.

*Thinking abnormal:* abnormal thinking, thinking irrational, wandering thoughts.

*Hallucination* (auditory, visual, and all hallucination types), illusions, flashbacks, floating, rush, and feeling addicted.

*Inappropriate affect:* elation inappropriate, exhilaration inappropriate, feeling happy inappropriately, inappropriate affect, inappropriate elation, inappropriate laughter, inappropriate mood elevation.

- *SUBJECTIVE RESPONSE TERMS INDICATIVE OF IMPAIRED ATTENTION, COGNITION, MOOD, AND PSYCHOMOTOR EVENTS WHICH ARE OFTEN ASSOCIATED WITH DRUGS OF ABUSE):*

*Somnolence:* groggy, groggy and sluggish, groggy on awakening, stupor.

*Mood disorders and disturbances* (mental disturbance, depersonalization, psychomotor stimulation, mood disorders, emotional and mood disturbances, deliria, delirious, mood altered, mood alterations, mood instability, mood swings, emotional liability, emotional disorder, emotional distress, personality disorder, impatience, abnormal behavior, delusional disorder, irritability.

*Mental impairment disorders:* memory loss (exclude dementia), amnesia, memory impairment, decreased memory, cognition and attention disorders and disturbances, decreased concentration, cognitive disorder, disturbance in attention, mental impairment, mental slowing, mental disorders.

*Drug tolerance, Habituation, Drug withdrawal syndrome, Substance-related disorders*

- *DISSOCIATIVE/PSYCHOTIC* (TERMS OFTEN ASSOCIATED PCP, AND KETAMINE):

*Psychosis:* psychotic episode or disorder.

*Aggressive:* hostility, anger, paranoia

*Confusion and disorientation:* confusional state, disoriented, disorientation, confusion, disconnected, derealization, dissociation, detached, fear symptoms, depersonalization, perceptual disturbances, thinking disturbances, thought blocking, sensation of distance from one's environment, blank stare, muscle rigidity, non-communicative, sensory distortions, slow slurred speech, agitation, excitement, increased pain threshold, loss of a sense of personal identity.

## 7.2 APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

### **FDA Adverse Event Reporting System (FAERS)**

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

### **7.3 APPENDIX C. WORLD HEALTH ORGANIZATION'S (WHO) INDIVIDUAL CASE SAFETY REPORT (ICSR) DATABASE, VIGIBASE<sup>1</sup>**

VigiBase™ is the name of the WHO global ICSR database; it consists of reports of adverse reactions received from member countries since 1968. VigiBase is updated with incoming ICSRs on a continuous basis. National centers are recommended to send reports at least quarterly; most national centers adhere to these guidelines, and several report more frequently.

Uppsala Monitoring Centre (UMC) in its role as the WHO Collaborating Centre for International Drug Monitoring receives reports of suspected adverse reactions to medicinal products from National Centres in countries participating in the WHO pharmacovigilance network, the WHO Programme for International Drug Monitoring. Limited details about each suspected adverse reaction are received by the UMC. It is important to understand the limitations and qualifications that apply to this information and its use.

The reports submitted to UMC generally describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a specific medicinal product (rather than, for example, underlying illness or other concomitant medication) is the cause of an event. Reports submitted to National Centres come from both regulated and voluntary sources. Some National Centres accept reports only from medical practitioners; other National Centres accept reports from a broader range of reporters, including patients. Some National Centres include reports from pharmaceutical companies in the information submitted to UMC; other National Centres do not.

The volume of reports for a particular medicinal product may be influenced by the extent of use of the product, publicity, the nature of the reactions and other factors. No information is provided on the number of patients exposed to the product. Some National Centres that contribute information to VigiBase make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not. Time from receipt of a report by a National Centre until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from those obtained directly from National Centres.

For the above reasons interpretations of adverse reaction data, and particularly those based on comparisons between medicinal products, may be misleading. The supplied data come from a variety of sources. The likelihood of a causal relationship is not the same in all reports. Any use of this information must take these factors into account.

1. WHO Collaborating Centre for International Drug Monitoring. Caveat Document. Available online at: <http://www.who-umc.org/graphics/25300.pdf>

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MONICA MUNOZ  
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CINDY M KORTEPETER  
04/12/2013

MIN CHU CHEN  
04/13/2013

**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:** 11/21/12

**To:** Su-Lin Sun, PharmD  
Senior Regulatory Project Manager  
Division of Neurology Products (DNP)

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

**Subject:** NDA 022416 - Stedesa (eslicarbazepine acetate)

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We acknowledge receipt of your September 5, 2012, consult request for the proposed product labeling for Stedesa (eslicarbazepine acetate) tablets. DPDP notes that a Complete Response letter was issued on November 2, 2012 and final labeling negotiation was not initiated during the current review cycle. Therefore, DPDP requests that DNP submit a new consult request and we will provide comments regarding labeling for this application during the subsequent review cycle.

If you have any questions, please contact Quynh-Van Tran at 301-796-0185 or [quynh-van.tran@fda.hhs.gov](mailto:quynh-van.tran@fda.hhs.gov).

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QUYNH-VAN TRAN  
11/21/2012



**MEMORANDUM**  
**Department of Health and Human Services**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**

**Date:** July 27, 2010

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

**Through:** Michael Klein, Ph.D., Director  
Lori A. Love, M.D., Ph.D., Lead Medical Officer  
Controlled Substance Staff

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

**Subject:** **Indication:** Adjunctive therapy for the treatment of partial onset seizure in adults with epilepsy  
**Dosages:** 400, 600, 800 mg tablets for oral administration  
**Company:** Sepracor Inc.

**Materials reviewed:** Briefing Package for Meeting with sponsor July 30 2010 is located in the EDR

This is our response to the Sepracor Concept Protocol # SEP093-153 and Briefing Package from June 15, 2010 regarding Stedesa abuse potential assessment and a new human abuse potential study.

Sepracor questions will be provided (**bold, italics**) first, then our response (regular font).

***Sepracor: 4. Does CSS agree that the following features of the proposed study are adequate to determine an appropriate recommendation regarding abuse potential?***



(b) (4)

(b) (4)

### CSS Response

No, we do not agree that the submitted Concept Protocol No. SEP093-153 is adequate to evaluate the abuse potential of this drug. The proposed Concept Protocol is missing a number of important details that can influence the study results and interpretation. When the Sponsor officially submits a complete protocol to the IND, we will review this and provide feedback.

The Sponsor should be aware that data from the human abuse potential study will undergo a statistical analysis by Agency statisticians when it is submitted. This analysis will include an evaluation of whether the study is validated (as determined by statistical differentiation between placebo and positive control on primary measures) and will use Effect Maximum (Emax) values for all evaluation of subjective measures.

The details of abuse potential evaluation are described in Guidance for Industry Assessment of Abuse Potential of Drugs, January 2010:  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>

*Sepracor: 5. If the study results demonstrate that eslicarbazepine acetate does not show a potential for abuse are these data sufficient to support a recommendation to not schedule the product?*

### CSS Response

No.

Cumulative data from all pre-clinical and clinical studies, as well as the scientific literature and other postmarketing surveillance information are considered in the evaluation of the abuse potential of the drug.

*Sepracor: 6. Given this background information, does CSS concur that there are sufficient human data available to evaluate the potential for physical dependence?*

### CSS Response

No.

(b) (4)

. Consequently a two-week prospective evaluation of physical dependence is

necessary to adequately evaluate withdrawal and dependence. We note that besides providing information on this drug's abuse potential, this information supplies critical information for the label/labeling to assure safe use of the product in the indicated population.

We are available to evaluate the protocol design and provide feedback prior to the start of this study.

***Sepracor: 7. Will it be acceptable to re-code all adverse events from the clinical studies to MedDRA Version 12.1 to be used in the safety update?***

**CSS Response**

Yes, this is acceptable, as long the MedDRA terms are translated from verbatim descriptions.

***8. Given Sepracor's commitment to re-code all adverse events into a single MedDRA version and reanalyze the abuse related adverse events in a single cumulative table across all studies, does CSS agree with the methodology we have utilized to assure all terms are included in the table of adverse events? If not, please provide additional detail as to how we can address the concern that all terms are included?***

**CSS Response**

No.

Analyze abuse related adverse events (CSS list is included) of all studies broken down by the individual studies, and the dose of the drug in addition to providing a single cumulative table across all studies.

Please include the following abuse-related MedDRA terms: "psychosis: psychotic episode or disorder", and "aggression".

***Sepracor: 9. Does CSS concur that Study 2093-303 should be excluded from the abuse liability reanalysis since the Agency has determined that the study is not sufficient to support safety?***

**CSS Response**

No.

All data are included in our evaluation of safety, which includes the abuse potential of a drug.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22416	ORIG-1	SEPRACOR INC	SEP-0002093 ESLICARBAZEPINE ACETATE

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07/27/2010

**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**

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**CLINICAL INSPECTION SUMMARY**

DATE: April 7, 2010

TO: Dorothy Demczar, Regulatory Health Project Manager  
Teresa Podruchny, M. D., Medical Officer  
Division of Neurology Products

THROUGH: Tejashri Purohit-Sheth, M.D.  
Branch Chief  
Good Clinical Practice Branch II  
Division of Scientific Investigations

FROM: Antoine El-Hage, Ph.D.  
Regulatory Pharmacologist  
Good Clinical Practice Branch II  
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-416

APPLICANT: Sepracor, Inc.

DRUG: Stedesa (eslicarbazepine acetate)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION:  (b) (4)

CONSULTATION REQUEST DATE: June 19, 2009

DIVISION ACTION GOAL DATE: January 30, 2010 extended to 4/30/2010

PDUFA DATE: January 30, 2010 extended to 4/30/2010

## I. BACKGROUND:

The Applicant, Sepracor Inc. submitted a New Drug Application for the marketing approval of eslicarbazepine acetate (ESL) [REDACTED] (b) (4) [REDACTED]. Eslicarbazepine acetate (ESL) SEP-0002093 was developed as an adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy. Bial-Portela (BIAL) originally conducted the clinical trials under IND 67,466. A pre-NDA meeting was held with Bial on January 23, 2008, when Bial advised FDA that Sepracor would assume responsibility as the sponsor for the IND and for marketing the product in the U.S.; the transfer of ownership of the IND to Sepracor became effective April 10, 2008. Another pre-NDA meeting was held with both Bial and Sepracor on November 13, 2008.

The results of two pivotal studies were submitted in support of the application, Protocol BIA-2093-301: “Efficacy and safety of BIA-2093 as adjunctive therapy for refractory partial seizures in a double-blind, randomized, placebo-controlled, parallel-group, multicenter clinical study”; and BIA-2093-302: same title as above. Protocols 301 and 302 were double-blind placebo-controlled studies of similar design; however, Protocol 302 had no 4-week tapering-off period. The subjects were assigned to one of four treatment groups: ESL 400 mg once daily, ESL 800 mg once daily, ESL 1200 mg once daily, or placebo once daily.

Study Protocol BIA-2093-301 was a randomized double-blind, placebo and active controlled trial. At the end of the double-blind maintenance phase, patients were eligible to enter an open label extension study. The duration of the study for a given subject was 12-weeks. The treatment included male and female subjects over 18 years of age.

The primary objective of study Protocol BIA-2093-301 was to evaluate the efficacy of ESL administered once daily at doses of 400 mg, 800 mg and 1200 mg compared to placebo as adjunctive therapy in patients with refractory partial epilepsy over a 12-week maintenance period followed by a 4-week tapering-off period and over a 1 year open-label period.

The primary objective of study Protocol BIA-2093-302 was the same as above except there was no tapering-off period.

The review division requested inspection of Protocols BIA-2093-301 and BIA-2093-302. Four foreign clinical investigators and the sponsor, Sepracor, were targeted for inspection due to enrollment of a relatively large number of subjects with GCP issues that were discussed at NDA filing meeting of 5/13/09 and the fact that there were no domestic studies to support the application.

A third phase III study, Study 303, was conducted in support of the drug development program. However, prior to NDA submission, the sponsor declared that Study 303 will not be used for efficacy because of significant GCP violations. The study instead will be used in support of safety. At the NDA filing meeting, the DSI reviewer expressed concerns with the use of Study 303 for safety only in light of GCP violations. However, the review division did not request inspection of sites from Study 303.

**II. RESULTS (by protocol/site):**

<b>Name of CI, site # and location</b>	<b>Protocol and # of subjects</b>	<b>Inspection Dates</b>	<b>Final Classification</b>
Danilo Hodoba, M.D. Psychiatric Hospital Vrabe Bolnicka cesta 32 Zagreb, Croatia	Site#112-Protocol 301 Number of subjects listed 18	10/12-16/09	Preliminary classification OAI (untitled ltr.)*
Valerij Bitensky, M.D. Odessa Regional Hospital 9, Vorrobjova Str. 6500 odessa, Ukraine	Site# 213-Protocol 302 Number of subjects listed 28	9/28- 10/2/09	VAI (pending)
Cristine Baldauf, M.D. Hospital Brigadrio Avenida Brigardio Luis Antonio 2651, 4 andar. Sao Paulo, Brazil	Site #338-Protocol 302 Number of subjects listed 36	9/21-25/09	VAI (pending)
Carmen D.Obregon,M.D. Hospital Clinico San Carlos 28040 Madrid, Spain	Site#395-Protocol 302 Number of subjects listed 16	10/19-23/09	OAI (untitled ltr.)*
Sepracor Inc. 84 Waterford Drive Marlborough, MA 01752	Sites#338&395- Protocol 302 Number of total subjects at sites: 52	10/20/09	NAI (pending)
* The classifications for these are OAI untitled as 1) for Dr. Hodoba's site, issues pertinent to drug dispensation, the issue considered most significant to support an OAI classification, were not documented on the Form FDA 483 or the EIR and an addendum documenting the dispensation issues was requested; however, given the timeframe from receipt of the EIR to post-inspectional correspondence, it is unlikely that OCC would support a WL and 2) for Dr. Obregon's site, the issues were considered significant to warrant an OAI; however, Dr. Obregon is deceased, as such an OAI untitled letter was issued.			

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; EIR has not been received from the field and complete review of EIR is pending.

Protocol BIA-2093-301

1. **Danilo Hodoba, M.D.**  
**Zagreb, Croatia**

**a. What Was Inspected:** At this site, a total of 18 subjects were screened, and one subject was reported as screen failure. Seventeen (17) subjects were randomized and completed the study. Informed consent procedures, for all subject records reviewed, verified that subjects signed informed consent documents prior to enrollment.

A review of the medical records/source documents was conducted. The medical records for 17 subjects were reviewed in depth, including drug accountability records, vital signs, laboratory test results, IRB records, patients diaries, use of concomitant medications, and source documents were compared to case report forms and to data listings, including primary efficacy endpoints and adverse events.

**b. General observations/commentary:** The medical records reviewed disclosed major findings in terms of inadequate drug accountability records and inadequate record keeping. The medical charts and source documents consisted of EKGs, laboratory results, progress notes, which were typed not labeled or signed, and with handwritten notes and sticky notes. Some typed progress notes had newly handwritten entries added to them with no initials as to who made the entries. The progress notes were not in sequence which made it very difficult to follow the protocol required events. In general, the records reviewed were found to be out of sequence and difficult to verify. The fact that the study records were in foreign language was a limitation to this inspection.

The inspection identified the following significant issues with drug accountability:

- There was no identification of the investigational product kit assigned to the subject or lot numbers on the drug accountability log. There was no way to correlate which box of product was assigned to each subject from the records available at the site. For example, only an entry such as, “box# 1, 9 blisters” would be recorded on the log sheet. From this type of entry on the Investigational Drug Accountability record, the identification of the investigational drug kit assigned to a subject cannot be determined, making it difficult to verify adequate drug dispensation to subjects.
- All investigational drug products and related labeling, to include blister cards, had been destroyed prior to the inspection, therefore, a review and verification of the returned drug was not possible.
- The medical records reviewed disclosed significant inadequate drug accountability records in that there was a lack of documentation for the returned test article that would allow reconciliation of the amount of placebo or test article given to study

subjects. In addition, there was a lack of complete documentation and identification of the amount of investigational drug dispensed and returned. This led to errors in drug accountability and made reconciliation difficult to reconstruct retrospectively.

- Our investigation found instances where the number of tablets destroyed were greater than the number of tablets returned by the subjects. The certificate of destruction does not differentiate between the baseline (placebo) and double-blind phase of the study. For at least five subjects (1245, 1246, 1249, 1250 and 1251), the number of tablets returned by the subjects and the number destroyed by the site were different. For example, Subjects 1246 and 1251 returned 70 and 72 tablets respectively, however, the site documented that 84 and 94 tablets were destroyed which is 14 and 22 tablets more than what was returned by the respective subjects. In addition, we found an instance where a blister (12 tablets) of study drug assigned to Subject 1272 had been already dispensed to Subject 1269. Therefore, the study site does not know what the subject was receiving: a placebo or strength of active drug.

**Reviewer comments:** The issues with drug accountability records are quite significant at this site. The most significant issue was the inability to verify that subjects were appropriately dispensed the investigational drug product to which they were randomized. Without being able to verify that subjects received the appropriate randomized investigational product, reliability of the collected data cannot be confirmed. In addition, the condition/state of drug accountability source documents were discussed with the clinical investigator who agreed with the findings and stated that drug accountability records reflected errors that did not allow for complete accountability of the study drug, to include dispensation as well as reconciliation.

The inspection identified the following inadequate record keeping deficiencies:

- Our investigation found instances where the diaries were translated into English by an unidentified individual, and the seizure counts for certain visits experienced by Subjects 1249, 1250 and 1270 were not reported in the data listings. Specifically,
  - Subject 1250's diary collected at Visit 3 listed 21 seizures experienced between 12/1/04 and 1/11/05. The original diary pages (white sheets) were present in the CRF binder. There is an English translation of the diary pages, dated 2/21/05 and signed by the sub-investigator who could not recall who prepared the English translation. The seizure counts listed in the diary were not recorded in the data listings.
  - Subject 1249's diary collected at Visit 2 listed 29 seizures experienced between 12/2/04 and 1/9/05. The original diary pages (white sheets) were present in the CRF binder. There was an English translation of the diary pages, which was dated 2/21/05 and signed by the sub-investigator, who

could not remember who prepared the English translation. The number of seizures listed in the diary were not recorded in the data listing.

- Subject 1270's diary collected at Visit 4 listed 19 seizures experienced between 5/20/05 and 6/26/05. The original dairy pages (white sheets) were present in the CRF binder; however, the seizure counts listed in this diary were not recorded in the data listing.
- Our investigation found that Subject 1264 was terminated due to low level of white blood count (2.66) between Visit 4 and Visit 5. This adverse event (low WBC /leucopenia) was recorded as leucopenia in the adverse event section of the case report form. However, this adverse event was not recorded as leucopenia in the data listing but, rather as an unacceptable adverse event.

At the conclusion of the inspection, a 3 item Form FDA 483, Inspectional Findings was issued and discussed with Dr. Hodoba. Dr. Hodoba submitted a written response dated November 5, 2009. While he agreed with our findings, he provided no explanation or corrective action plan to address any of the significant issues identified. Therefore, his response is unacceptable.

c. **Assessment of Data Integrity:** The data generated from Dr. Hodoba's site revealed significant drug accountability issues and inadequate record keeping practices. The drug accountability issues were considered critical in the evaluation of data reliability, as these issues precluded the verification of adequate drug dispensation of randomized investigational drug product to subjects. Therefore, the data from this site are not considered reliable in support of the pending application.

## 2. Valerij Bitenskyy, M.D. Odessa, Ukraine

**a. What Was Inspected:** At this site, a total of 28 subjects were screened, one subject was reported as a screen failure, 27 subjects were randomized into the study, 18 subjects completed Part I and Part II, 14 subjects continued on Part III, and 12 subjects completed Part I through Part III of the study. Informed consent procedures, for all subject records reviewed, verified that subjects signed informed consent documents prior to enrollment.

The medical records/source data for 9 subjects were reviewed in depth, including drug accountability records, vital signs, laboratory results, IRB records, patients' diaries for inclusion/exclusion criteria, and source documents were compared to data listings for primary efficacy endpoints and adverse events. In addition, a limited review of all subjects enrolled was conducted for inclusion/exclusion criteria, endpoint data, adverse event reporting, and dosing.

**b. General Observations/Commentary:** Our investigation found 3 subjects with elevated laboratory results at screening, who did not meet eligibility criteria.

- Subject 90064 did not meet the protocol inclusion criteria, as the Visit 1 AST levels of 86 U/l were greater than twice the upper limit of normal, and no repeat testing was conducted prior to randomization.
- Subject 90033 was randomized into the study with an abnormally low hematology result at Visit 1, a history of alimentary anemia and an adverse event of anemia. No additional tests were performed prior to randomization.
- Subject 90296 was randomized into the study with elevated blood glucose of 16.8, 11.3, 8.8 and 17.7 mmol/l at Visits 1, 2, 4, and 5 respectively. At Visit 5, the elevated blood glucose was considered to be an adverse event and reported as increased blood glucose level. No waiver was obtained for the above subjects and no repeat testing was performed prior to randomization.

No additional significant violations were noted.

At the conclusion of the inspection, a 1 item Form FDA -483 was issued to Dr. Bitensky. The clinical investigator responded to the observations, in a letter dated October 20, 2009, agreeing with the findings noted on the Form FDA 483 and promised corrective action to prevent these type of errors in the future. The medical records reviewed disclosed no adverse finding that would reflect negatively on the reliability of the data. In general, the records reviewed were found to be in order and the data verifiable. There were no known limitations to this inspection.

**c. Assessment of Data Integrity**

Although regulatory violations were noted, these appear to be isolated occurrences, and are unlikely to importantly impact study outcome. The data from Dr. Bitensky's site are considered reliable and appear acceptable in support of the pending application.

**Protocol BIA 2093-302**

**3. Cristine Baldauf, M.D.  
Sao Paulo, Brazil**

**a. What Was Inspected:** At this site, a total of 36 subjects were screened, 7 subjects were reported as screen failures, 2 subjects were reported as lost to follow-up, 27 subjects were randomized, 16 subjects completed the study and 11 subjects were discontinued and reasons were documented (carbon copies maintained at the site were, at times, difficult to read). Informed consent procedures, for 11 subjects reviewed, verified that all subjects signed informed consent documents prior to enrollment.

The medical records/source documents for 11 subjects were reviewed in depth, including drug accountability records, vital signs, IRB files, laboratory test results, use of concomitant medications, and source documents were compared to case report forms and data listings for primary efficacy endpoints and adverse events.

**b. General Observations/Commentary:** Some regulatory violations were noted with respect to adherence to protocol.

- The medical records reviewed found that Subject 80156 did not meet the inclusion criteria for frequency of seizure count prior to randomization as required by the protocol.
- SAEs, as defined by the protocol, were not reported within the protocol required 24 hour time-frame, although they were reported to the sponsor later.
  - Subjects 80239, 80156, and 80157 had their last dose of study drug on 1/28/07, 11/26/06 and 1/15/07, respectively. These subjects underwent elective surgical procedures on [REDACTED] (b) (6) respectively. These elective surgical procedures were not reported as serious adverse events within the 24 hour time frames required by the protocol. The adverse events were reported 2-3 months later.
  - Subject 80164 had a pancreatic tumor removed on [REDACTED] (b) (6) at another hospital and the clinical investigator became aware of the procedure 5 months later when the subject returned to the clinic. The clinical investigator reported the SAE only after the post study visit stating he did not know if there was a need to report as SAE, as the patient completed the study. The protocol defines inpatient hospitalization as an SAE even if hospitalization occurred within 30 days after discontinuation.

At the conclusion of the inspection, a 1 item Form FDA-483 was issued to Dr. Baldauf/Cukiert. The clinical investigator agreed with the inspectional findings in her response dated October 15, 2009.

The medical records reviewed disclosed no adverse findings that would reflect negatively on the reliability of the data. In general, the records reviewed were found to be in order and the data verifiable. There were no known limitations to this inspection.

**c. Assessment of Data Integrity:** Although regulatory violations were noted, these are unlikely to importantly impact data integrity. The data from Dr. Baldauf/Cukiert's site are considered reliable and appear acceptable in support of the pending application.

**4. Carmen Diaz-Obregon, M.D.  
Martin Lagos, Madrid**

- a. **What was Inspected:** At this site, 16 subjects were screened, 3 subjects were reported as screen failures, 13 subjects were randomized, 2 were discontinued for adverse events (Subject 2230/exacerbation of seizure and stomach pain); (Subject 2480/exacerbation of seizure and rash); one subject withdrew consent, and 10 subjects completed the study. Informed consent procedures, for all subjects reviewed, verified that all subjects signed the informed consent documents prior to enrollment.

The medical records/source data for 15 subjects were reviewed in depth, including drug accountability records, vital signs, laboratory results, IRB files, patients' diaries for inclusion/exclusion criteria, the use of concomitant medications and

anti-epileptic drugs (AEDs), and source documents were compared to case report forms and to data listings for primary efficacy endpoint and adverse events.

- b. General Observations/Commentary:** The medical records reviewed disclosed significant protocol violations and inadequate record keeping. The medical charts and source documents consisted of laboratory results, EKG's, progress notes, single sheets in various sizes with handwritten entries and sticky notes used to record observation or to add what appear to be missing from the original progress notes. The progress notes do not contain information that identifies the person making the entries. Medical records relied upon as source documentation were also not well organized and difficult to follow with respect to sequence of events. The inspection team did not find any request for waivers to include ineligible subjects into the study. The fact that the study records were in foreign language was a limitation to this inspection.

The results of the inspection disclosed failure to adhere to the protocol and failure to maintain adequate and accurate case histories: 10 of the 15 subjects enrolled did not meet the inclusion criteria and case histories were inadequate with respect to study observations and medical history to confirm that the subjects met inclusion criteria.

The inspection noted the following significant protocol violations:

- The inspection found that at least 4 subjects (2265, 2268, 2152 and 2474) did not meet the inclusion criteria of having at least partial seizures in each 4-week period during the 8-week baseline period prior to randomization; however, these subjects were included in the study. In Dr. Matias-Guiu's response, he stated that waivers were requested, however, the waivers were approved after the subjects had already been enrolled into the study. Therefore, we consider the enrollment of these subjects in violation of the protocol inclusion criteria, to be significant and not acceptable. In addition, we found no documentation of the dates or during which 4-week period prior to screening, subjects experienced seizures to support meeting the inclusion criteria (Subjects 2265, 2266, 2268, 2229 and 2231). In his response, he did not provide source documentation to show specifically the number of seizures recorded in each 4-week period during the last 8-weeks prior to screening for these subjects. In the absence of source documents to support the number of seizures recorded in each 4-week period of the 8-week assessment period prior to screening, we cannot confirm that the subjects met inclusion criteria per protocol. Therefore, we cannot verify that these subjects were appropriately enrolled into the study.
- The protocol required each subject to be currently treated with 1-3 anti-epileptic drugs (AEDs), except oxcarbazepine or felbamate, in a stable dose regimen for at least 2 months before screening. Our investigation found no source documentation to support that the following 7 subjects met this inclusion criterion: Subjects 2151, 2152, 2477, 2478, 2479, 2229 and 2230. In

Dr. Matias-Guiu's response, he agreed that Subjects 2229 and 2478 did not meet the inclusion criterion, and he did not provide supporting documents or adequate explanation for the other subjects to justify their inclusion into the study.

- The protocol required that subjects could not have seizure-free intervals exceeding 21 days; however, Subjects 2479 and 2468 documented in their dairies a seizure-free period exceeding 21 days.

Our investigation found the following inadequate recordkeeping issues:

- There were significant issues with the status of the records, which in many instances precluded the verification of adequate conduct of the study. Source documentation related to seizure counts (the primary efficacy endpoint) were missing, making it difficult to verify the seizure counts provided in the NDA data listings. The source documentation was not available to verify the entries on the CRFs.
- discrepancies between source documents and case report forms for at least 3 subjects (2479, 2152 and 2477) were noted:
  - Subject 2479 had a discrepancy in the number of seizure episode recorded in the subject's diary and case report form (CRF). The subject's diary noted 7 seizure episodes, and the CRF documented 3 and 5 (total 8) seizure episode in each 4-week period prior to randomization, respectively.
  - Subject 2152 had discrepancies between source documents and CRFs for AEDs listed as concomitant medications. For 2 of the 3 AEDs listed on the subjects' CRFs, the doses recorded do not match those noted in the source document. The CRF notes a 600 mg bid dose of Topiramate while the source documentation indicates a dose of 400 mg; and the CRF notes 1 mg b.i.d dose of Loracepan but no dose is listed on the source document. In addition, Phenobarbital was not listed on the CRF, but was listed on the source document with no dose specified and no documentation showing that it was stopped. Therefore, we were unable to determine whether the subject was on a stable dose of AED regimen for at least 2 months prior to screening (date November 18, 2005), as required by the protocol.
  - Subject 2477 had a discrepancy between source documents dated July 11, 2005 and November 2005 regarding the dose of Loracepan.

**Reviewer's comments:** In general, the records reviewed were found to be out of sequence and difficult to verify. The medical charts and source documents consisted of EKGs, laboratory results, and progress notes, which were typed, but not labeled or signed and included handwritten notes and sticky notes. Note that the seizure counts were missing from subject diaries, which were considered the source documents for the primary efficacy variable, for most of the subjects. Some typed progress notes had

newly handwritten entries added to them with no initials as to who made the entries, or the rationale for the addition of new notes. The progress notes were not in sequence which made it very difficult to follow the protocol required events. The study related documents were in such disarray, that it was difficult to verify adequate conduct of the study, and as such, reliability of the data.

A Form FDA 483, Inspectional Observations, was issued at the end of the inspection. Since Dr. Diaz-Obregon had passed away in 2008 after the completion of the clinical trial, Dr. Jorge Matias-Guiu Guiu accepted the Form FDA 483 on behalf of Dr. Diaz-Obregon and responded to the items listed on the Form FDA 483 in a letter dated November 11, 2009. As discussed above, we do not consider his response acceptable.

- c. **Assessment of Data Integrity:** The most significant issues identified at this site were failing to adhere to the protocol and failing to maintain adequate and accurate records. Failure to adhere to the protocol led to the enrollment of 10 out of the 15 subjects who did not meet eligibility criteria. Enrollment of subjects who do not meet eligibility criteria may potentially compromise the safety and welfare of subjects as well as the interpretation and validity of the study endpoints. Although the review division may consider the clinical relevance of the specific issues related to enrollment of ineligible subjects on the impact of study outcome, it should be noted that this evaluation may be overshadowed by the significant deficiencies in overall maintenance of records. The nature and state of inadequate recordkeeping at this site undermines the confidence in the data generated by this site. Therefore, the data from Dr. Obregon’s site are considered unreliable and should be considered for exclusion from the final analyses.

**5. Sepracor, Inc.  
Marlborough, MA 01752**

The sponsor (Sepracor) inspection was limited to one day (reasons unknown to this reviewer). The field investigator reported “management to be very accommodating and allowed full access to requested records with no adverse findings”. The EIR did not contain any information on what records were requested or reviewed by the field investigator. DSI has contacted the field investigator for further clarification of the scope of this inspection, and are awaiting a response from the field. Without further information, DSI is unable to make any firm recommendations on data reliability at this time based on the inspection of Sepracor.

**III. Evaluation of audit reports submitted by Sepracor to the NDA application:**

**A. Background:**

Sepracor submitted audit reports with the NDA submission. DSI conducted a review of the provided audit summaries and audit reports. The audit reports disclosed GCP violations and noncompliance with commonly accepted good clinical practices and federal regulations. The audit reports are inconclusive due to evaluation of a limited number of clinical sites with inadequate number of enrolled subjects audited. The

number of subjects audited by the applicant in all three studies is not sufficient in scope or detail to allow for adequate assessment of data reliability.

- 1) Study 301 enrolled 402 subjects in Part I at 40 clinical sites. Twenty two of the 40 sites were audited which covered 54 out of 158 subjects that were enrolled in the 22 sites (approximately 50% of the sites). The study enrolled 314 subjects in Part II at 40 clinical sites. Twenty two sites were audited which covered 40 out of 123 subjects that were enrolled in the 22 sites. Twelve (12) out of the 22 sites audited only covered 1-3 subjects at each site; however, the number of subjects enrolled was not listed in the audit report. Nine sites out of the 22 audited enrolled 11 or more subjects. At these nine sites only 3 to 6 subjects' records were audited. The percentage of subjects audited compared to the total number enrolled shows that 13% (54/402; Part I) and 12.7% (40/314; Part II).
- 2) Study 302 enrolled 395 subjects in Part I at 44 clinical sites. Twelve out of 44 sites were audited which covered 44 subjects out of 191 enrolled. The study enrolled 325 subjects in Part II at 44 clinical sites. Twelve sites out of 44 sites were audited which covered 47 subjects out of 157 enrolled. Ten (10) out of the 12 sites audited covered a very small number of subjects (2-5). Two out of the 12 sites audited enrolled less than 10 subjects. The percentage of subjects audited compared to the total number of enrolled was 11% (44/395; Part I) and 14% (47/325; Part II).
- 3) Study 303 enrolled 253 subjects in Part I at 35 clinical sites. Ten out of 35 sites were audited which covered 35 subjects out of 147 enrolled. The study enrolled 314 subjects in Part II at 35 clinical sites. Eight out of 35 sites were audited which covered 23 subjects out of 104 enrolled. Of the 10 sites audited, only 2 to 6 subjects' records were audited. The percentage of subjects audited compared to the total number of enrolled shows that 13.8% (35/253; Part I) and 8% (23/194; Part II).

**B. Audit Findings:**

1. The audits revealed a broad range of violations regarding subject safety, inclusion criteria, poor source documentation, discrepancies between source documents and what was recorded in the case report forms in terms of adverse events, use of concomitant medications, and inadequate drug accountability records suggesting a systemic problem across all three studies (301, 302, and 303). The most common adverse events found across the three studies included, but were not limited to: headache, dizziness, depression, fever, nausea, blurred vision, sore back, insomnia, weight gain, constipation, nervousness, gastritis, and respiratory infection. For example:
  - a. Regarding Study 301, the audits, conducted by both, (b) (4) on behalf of Sepracor, and (b) (4) on behalf of Bial, of clinical sites in Study 301 found discrepancies involving adverse event (AE) reporting at 6 sites involving 11 /88 subjects covered by the audits. There were 20 AES cited by the audit reports as being discrepant (SD vs CRF) with respect to the 11 subjects. ONLY 5 events were resolved via the data query process; 15 events remain unresolved.

- b. Regarding Study 302, the audits, conducted by both, (b) (4) on behalf of Sepracor, and (b) (4) on behalf of Bial, of clinical sites in Study 302 found discrepancies involving adverse events (AE) reporting at 9 sites, involving 23 of the 107 subjects covered by the audits. There were 34 AEs cited in the audit reports as being discrepant (SD vs CRF) with respect to these 23 subjects. ONLY 3 events were resolved via the data query process; 31 events remain unresolved.
- c. Regarding Study 303, the audits, conducted by both, (b) (4) on behalf of Sepracor, and (b) (4) on behalf of Bial, of clinical sites in Study 303 found discrepancies involving adverse events (AEs) reporting at 7 sites, involving 24/58 subjects covered by the audits. There were 44 AEs cited in the audit reports as being discrepant (SD vs CRF) with respect to these 24 subjects. ONLY 11 events were resolved via the data query process; 33 events remain unresolved.

**Reviewer's Comments:**

DSI recommends that the review division take into consideration the discrepancies in AE reporting as described above between SD and CRFs in evaluation of safety and the impact of the remaining unresolved events for each of the above referenced study.

2. The audit reports submitted by Sepracor to the NDA do not assure confidence in the data, as the audits do not appear to be sufficient in scope or detail to allow for an adequate assessment to determine the overall impact on the reliability and the use of the data. For example,

For Study 301, Site #112, Dr. Hodoba's site, audits were conducted by both Bial and Sepracor. The Sepracor audit reports for this site shows that only 3 out of 18 subject records were sampled and reviewed, although the audit report documented issues with drug accountability (dispensation and reconciliation) as well as inaccurate records in these 3 subjects. It doesn't appear from the audit reports whether the applicant took any actions to ensure that similar issues were not noted in any of the other subject records that were not evaluated, nor does there appear any specific conclusion as to the impact of the findings on the outcome of the study.

3. With respect to Study 303, the sponsor and applicant were aware of several issues in the conduct of this study based on the audits. Recognizing the issues identified, the applicant has appropriately chosen to exclude the data from efficacy analyses; however, still would like to use the safety data. In light of this, it is not clear what action(s) the applicant, Sepracor, took to account for inadequate monitoring procedures and non compliant clinical investigators involved in Study 303 to support the use of the safety data in the application.

**C. Conclusion:** Based on the audit reports submitted in the application by the applicant as well as the results of the clinical site inspections, DSI is concerned that Bial did not exercise adequate oversight over the investigator sites and the CROs involved in monitoring the sites of the studies submitted in support of the application. Although

Sepracor reviewed Bial audit reports and conducted some of their own audits after acquisition of the rights to eslicarbazepine acetate, the audit reports do not assure confidence in the data submitted in support of the application. In light of the fact that FDA audits noted significant issues with study conduct in 50% of audited sites, the audit reports submitted by the applicant are not considered sufficient in scope or detail to support the integrity of the application.

We recommend that the applicant provide additional information regarding Bial quality assurance (QA) audit program, their interaction with oversight of the contract research organizations hired by Bial to monitor the clinical sites, and perform a 3<sup>rd</sup> party comprehensive audits of the clinical sites that enrolled subjects in the three studies used in support of safety and efficacy of the investigational drug. These measures are necessary to provide assurance and confidence in the integrity of the data submitted in support of the application.

#### **IV. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS**

Four foreign clinical investigators and the sponsor were inspected in support of this application. The inspections of Drs. Bitensky and Baldauf/Cukiert revealed no significant problems that would adversely impact data acceptability. However, the inspections of Drs. Hodoba and Obregon revealed significant noncompliance with federal regulations and commonly acceptable good clinical practices. Considering the nature and state of the records at these two sites, in addition to the inspectional findings noted during the inspections, this DSI reviewer does not have confidence in the data generated from Sites 112 and 395. Therefore, it is recommended that Sites 112 and 395 be excluded from the final analyses. Because 50% of the clinical sites inspected by FDA had significant issues, we are concerned about data integrity at other sites not inspected.

In light of the issues noted during FDA audits, the audit reports submitted by Sepracor to the NDA are not considered sufficient in scope and detail to assure confidence of the data submitted in support of the application. The issues identified in the sponsor/applicant audit reports do not provide confidence in the data as several violations were noted in the audit reports, especially with respect to under-reporting of adverse events.

Therefore, we recommend that the review division consider requesting the applicant to provide some measure of confidence in the data from the other sites that were not inspected by FDA. This may include consideration by the Review Division for 1) additional FDA clinical site inspections for a) Studies 301 and 302, b) clinical sites from Study 303 because the sponsor proposes to use the data from this study to support safety, c) re-inspection of the sponsor, as a comprehensive inspection doesn't appear to have been conducted, and d) the CROs responsible for monitoring the studies; and 2) a 3<sup>rd</sup> party audit organized by the Applicant with a request that the Agency review and comment upon the audit plan prior to the audit to ensure that a sufficient number of subjects and sites are audited, and a request that full audit reports are provided to the Agency for review.

**Note:** Observations noted above for Dr. Bitensky, Dr. Cukiert (formerly Baldauf), Dr. Hodoba and Sepracor are based on the Form FDA 483 and communications with the field

investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

*{See appended electronic signature page}*

Antoine El-Hage, Ph.D.  
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Division of Scientific Investigations

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22416	ORIG-1	SEPRACOR INC	SEP-0002093 ESLICARBAZEPINE ACETATE

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/s/

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ANTOINE N EL HAGE  
04/08/2010

TEJASHRI S PUROHIT-SHETH  
04/09/2010



**MEMORANDUM**  
**Department of Health and Human Services**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**

**Date:** March 19, 2010

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

**Through:** Michael Klein, Ph.D., Director  
Lori A. Love, M.D., Ph.D., Lead Medical Officer  
Controlled Substance Staff

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

**Subject:** **Indication:** Adjunctive therapy for the treatment of partial onset seizure in adults with epilepsy  
**Dosages:** 400, 600, 800 mg tablets for oral administration  
**Company:** Sepracor Inc.

**Materials reviewed:** NDA 22-416 (March 29, 2009) is located in the EDR, Sponsor's letter from Feb 10 2010

This memorandum addresses the Sepracor letter of February 10, 2010, in which the sponsor responds to CSS comments of January 4 and 13, 2010.

The sponsor discusses preclinical and clinical study data related to the abuse potential of Stedesa (eslicarbazepine acetate).<sup>1</sup>

In this memorandum, CSS provides further details about study deficiencies in response to the sponsor's comments.

### **CONCLUSIONS**

The February 10, 2010 Sepracor response to CSS comments of January 4 and 13, 2010 provided additional information regarding preclinical abuse studies conducted with eslicarbazepine. However, these data did not provide convincing evidence of the absence of abuse potential of eslicarbazepine.

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<sup>1</sup> In this memorandum, eslicarbazepine is referred to by various designations (SEP-0002093, BIA 2-093, and ESL) assigned to the drug during development.

## **RECOMMENDATIONS**

In order to provide adequate data for the assessment of whether eslicarbazepine has abuse potential, CSS recommends that the Sponsor:

1. Conduct an appropriate and well designed human abuse potential study with eslicarbazepine. CSS is available to evaluate the protocol design and provide feedback prior to the start of the study.
2. Conduct a two-week prospective evaluation of physical dependence at the conclusion of the new clinical efficacy study. CSS is available to evaluate the protocol design and provide feedback prior to the start of this phase of the study.
3. Update the reporting of adverse events in clinical studies to the most recent version of MedDRA used in the NDA (i.e., MedDRA 10.0) by using the verbatim descriptions that occurred during clinical trials.
4. Provide an analysis of all abuse related AEs, using the terms provided previously by CSS.

## **CSS RESPONSES TO SPONSOR-SUBMITTED INFORMATION**

In this memorandum, the original CSS comments of January 4, 2010 will be provided first, followed second by the sponsor's response from February 10, 2010, and then followed third by the present CSS response to the information submitted by the sponsor.

### **1. Original CSS Comment (Jan. 4, 2010):**

**There are limitations in the design of pre-clinical abuse studies. These studies do not provide enough data to fully assess the abuse potential of eslicarbazepine acetate. Eslicarbazepine acetate has anxiolytic, sedative, and muscle relaxant properties, impairs memory and co-ordination and produces physical dependence, as evidenced by the occurrence of withdrawal symptoms upon abrupt withdrawal. This particular profile resembles sedative-hypnotic drugs and in particular benzodiazepines, that are currently scheduled in the Controlled Substance Act.**

### **1A. Sepracor Response (Feb. 10, 2010, page 4-5/42):**

#### **Preclinical Anxiolysis**

(b) (4)

Preclinical Sedation

(b) (4)

Preclinical Muscle Relaxation

(b) (4)

**1A. CSS Response (Mar. 19, 2010):**

(b) (4)

In the Irwin Test in mice (Study # 093-850, page 24-25/79 and Table 1), eslicarbazepine produced a sedative-hypnotic behavioral profile.

The 250 mg/kg dose of eslicarbazepine produced:

- \* moderate-to-marked sedation in all 6 mice (100%)
- \* decreased muscle tone in all 6 mice (100%).
- \* decreased fear and reactivity to touch in 3 of 6 mice (50%)
- \* abnormal gait in 6 of 6 mice (100%)

When the dose was increased to 500 mg/kg, eslicarbazepine produced:

- \* marked sedation in all 6 mice (100%)
- \* reduction in fear in all 6 mice (100%),
- \* decreased muscle tone in 5 mice (83%).
- \* abnormal gait in all 6 mice (100%)

The sponsor acknowledges this sedative-hypnotic behavioral profile on page 17 of the submitted response to CSS in the following statement:

*“ .... a previously completed CNS safety study investigating the potential adverse effects of SEP-0002093 administration in mice (Sepracor Document No. 093-850) demonstrated that at doses higher than 100 mg/kg, **marked to moderate sedation, abnormal gait, decreased muscle tone and loss of grasping/traction were seen**”.*

Sepracor documents also note the observation of the same behavioral profile:

*High doses of SEP-0002093 in mice **caused impaired coordination and muscle tone** (as noted by decreased rotarod performance, abnormal gait, loss of*

*grasping, loss of traction and decreased muscle tone) and **caused** sedation/hypoactivity/hyporesponsiveness (Sepracor Document Nos. 093-408 and 093-850).*

Thus, the data submitted clearly show evidence of anxiolytic activity, sedation and muscle relaxation in preclinical studies resulting from eslicarbazepine administration.

**Best Available Copy**

EFFECTS OF BIA 2-093  
IN THE PRIMARY OBSERVATION (IRWIN) TEST  
IN THE MOUSE  
(6 MICE PER GROUP)

DOSES (mg/kg, p.o.)			
50	100	250	500
No change	Hypothermia + 30' 60'	Sedation ++ (6/6) at 60' +++ (6/6) at 120' ++ (3/6) at 180' +++ (3/6) at 180'  Abnormal gait (rolling) (6/6) at 60' (3/6) at 180'  Fear (3/6) 60' 180'  Reactivity to touch (6/6) 60' 120' (3/6) at 180'  Muscle tone (6/6) 60' 180'  Loss of grasping (1/6) at 120'  Loss of traction (5/6) at 60' (6/6) at 120' (3/6) at 180'  Hypothermia + at 15' +++ 30' 180'  Mydriasis + at 60' + at 48h	Convulsions (1/6) 0 15' (1/6) at 30' (1/6) at 60'  Straub tail (1/6) 30' 60'  Sedation + (6/6) at 15' ++ (6/6) at 30' +++ (6/6) 60' 180'  Abnormal gait (rolling) (1/6) 0 15' (3/6) at 15' (6/6) at 30'  Fear (6/6) 30' 180'  Reactivity to touch (2/6) at 30' (6/6) 60' 180'  Muscle tone (5/6) at 30' (6/6) 60' 180'  Loss of grasping (1/6) at 30' (6/6) at 60' (3/6) 120' 180'  Loss of traction (3/6) at 30' (6/6) 60' 120' (3/6) at 180'  Hypothermia +++ 15' 180'

**1B. Sepracor Response (Feb. 10, 2010, page 5/42):**

Preclinical Memory Impairment



(b) (4)

**1B. CSS Response (Mar. 19, 2010):**

The doses of eslicarbazepine selected for the mouse cognition study are too low to appropriately evaluate the effect of the drug on memory. Given that the 220 mg/kg dose of eslicarbazepine is necessary to produce a full anti-seizure response in mice (see below Table 8, study # 093-408, page 21), the doses used in the mouse cognition study (30 and 100 mg/kg) are only a fraction of the functionally efficacious dose in mice against seizures. (Abbreviations: CBZ – carbazepine; OXC – oxcarbazepine; MES-seizure - Maximal Electroshock Seizure- induced seizure)

Additionally, no information was provided regarding the plasma levels produced by the doses used in the cognition study and how they relate to the human plasma levels produced by the proposed therapeutic doses. Thus, the negative results in the mouse cognition study cannot be validated because the dose cannot be justified.

**Table 8.** Protective effects of increasing doses of BIA 2-093, CBZ and OXC against MES-induced tonic seizures in mice. Animals were given increasing doses of test drugs by i.p. injection. Results are means ± S.E.M. (n=10).

mg/kg	% of protection		
	BIA 2-093	CBZ	OXC
0	0.0±5.9	0.0±5.9	0.0±5.9
5	N.D.	-26.8±5.1	N.D.
6	N.D.	54.4±19.0	N.D.
7.5	N.D.	91.3±8.7	N.D.
15	-20.3±14.9	100.0±0.0	50.1±30.8
7.5	N.D.	N.D.	N.D.
30	N.D.	N.D.	100.0±0.0
45	-3.6±12.4	N.D.	N.D.
75	N.D.	N.D.	100.0±0.0
90	60.1±16.5	N.D.	N.D.
120	72.5±11.7	N.D.	N.D.
180	91.3±8.7	N.D.	N.D.
220	100.0±0.0	N.D.	N.D.

N.D. – Not determined

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**1C. Sepracor response (Feb. 10, 2010, page 5/42):**

**Clinical Memory Impairment**



**1C. CSS Response (Mar. 19, 2010):**

(b) (4)  
After reviewing the clinical data, we conclude that eslicarbazepine produces memory impairment in humans.

In fact, this conclusion is affirmed by the sponsor in the study report for Study #2093-123 in the following statements:

*“In conclusion, the administration of ESL was associated with slower motor reaction times, **diminished recognition memory**, and lower digit detection sensitivity as compared to Placebo. At the highest dose, ESL was associated with diminished reaction time as compared to Placebo.” (page 9)*

*“The chronic administration of ESL (800 mg QD over 7 days and 1200 mg QD over 7 days) revealed some dose-dependent differences in cognitive abilities as compared to Placebo. ESL was associated with diminished psychomotor speed at both the low and high doses. The administration of ESL was also associated with a **reduction in the ability to recall digits** as compared to the Placebo condition. Both doses of the ESL were associated with **diminished word retrieval abilities**...Finally, the administration of ESL was associated with a reduction in the ability to detect digits as compared to the Placebo condition.” (page 10)*

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**1D. Sepracor Response (Feb. 10, 2010, page 6/42):**

Abnormal coordination

(b) (4)

**1D. CSS Response (Mar. 19, 2010):**

(b) (4)

Abnormal coordination was the fourth most commonly-reported neurological AE in clinical trials and its occurrence could present a serious safety risk, especially when it occurs in the presence of dizziness and somnolence. Given that most AEDs produce a similar AE profile in this regard, the addition of eslicarbazepine as an adjunct therapy could compound this neurological response.

As depicted below in Table 4.14.4-1 (from page 60 of the ISS, representing pooled Study #2093-301, Study #2093-302, and Study #2093-303), abnormal coordination was seen in 35 of 760 eslicarbazepine-treated patients (4.6%) and in 6 of 289 placebo-treated patients

(2.1%). The sponsor acknowledges that the rate of abnormal coordination in eslicarbazepine-treated patients is twice that of placebo-treated patients.

**Table 4.1.4.4-1: Treatment-Emergent Adverse Events by Overall Treatment Group for Part 1 of the Phase III Studies (2093-301 and 2093-302 Pooled vs 2093-303) (Safety Population)**

MedDRA* SYSTEM ORGAN CLASS Preferred term	Studies 2093-301 and 2093-302 Pooled			Study 2093-303		
	Placebo (N=202)	Total ESL (N=595)		Placebo (N=87)	Total ESL (N=165)	
	Subjects n (%)	Subjects n (%)	Difference <sup>b</sup> %	Subjects n (%)	Subjects n (%)	Difference <sup>b</sup> %
AT LEAST 1 TEAE	101 (50.0)	395 (66.4)	16.4	36 (41.4)	95 (57.6)	16.2
NERVOUS SYSTEM DISORDERS	48 (23.8)	260 (43.7)	19.9	26 (29.9)	70 (42.4)	12.5
Dizziness	12 (5.9)	127 (21.3)	15.4	9 (10.3)	41 (24.8)	14.5
Somnolence	19 (9.4)	78 (13.1)	3.7	8 (9.2)	23 (13.9)	4.7
Headache	15 (7.4)	71 (11.9)	4.5	10 (11.5)	13 (7.9)	-3.6
Abnormal coordination	5 (2.5)	29 (4.9)	2.4	1 (1.1)	6 (3.6)	2.5

Additionally, abnormal coordination experienced during administration of eslicarbazepine led to discontinuation of 19 of 760 patients (2.5%) from part 1 of pooled studies Studies #2093-301, 2093-302 and 2093-303.

Finally, the abnormal coordination observed in clinical trials is consistent with observations from the preclinical studies, as discussed above.

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**1E. Sepracor Response (Feb. 10, 2010, page 7/42):**

**Withdrawal**

[Redacted] (b) (4)

**1E. CSS Response (Mar. 19, 2010):**

[Redacted] (b) (4)

We reviewed CRFs provided for patients listed in the Table 22.1.1-1, Listing of subjects with new adverse events during a 2-week period after eslicarbazepine was abruptly discontinued in subjects not continuing into Part 2 (Module 5.3.5.3 ISS, page 442/582). Both the study methodology and the quality of the data provided prevent an adequate assessment for physical dependence.

Therefore, we request that the sponsor conduct a new evaluation of physical dependence with eslicarbazepine at the conclusion of the new clinical efficacy study. This phase of the study should prospectively evaluate whether eslicarbazepine produces classic withdrawal-like physiological and psychiatric changes, using daily measurements.

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**1F. Sepracor Response (Feb. 10, 2010, page 7/42):**

(b) (4)

**1F. CSS Response (Mar. 19, 2010):**

As noted above, data from the studies conducted in mice show that eslicarbazepine produces anxiolysis, muscle relaxation, and abnormal coordination in addition to sedation. Additionally, AE data from clinical studies show that eslicarbazepine produces abnormal coordination, cognitive impairment (including memory impairment), somnolence, dizziness and motor impairment. Taken in the context of assessing the abuse potential of eslicarbazepine, these data demonstrate that eslicarbazepine produces behavioral responses similar to that of sedative-hypnotics, a pharmacological class that includes benzodiazepines.

In order to determine whether eslicarbazepine has abuse potential similar to that of benzodiazepines or other CNS depressants which are scheduled, CSS recommends that the sponsor conduct a human abuse potential study in which eslicarbazepine is compared directly to a benzodiazepine with a similar pharmacokinetic profile or another appropriate CNS depressant that is scheduled.

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**2. Original CSS Comment (Jan. 13, 2010):**

**The receptor binding studies do not provide  $K_i$  parameters for GABA<sub>A</sub> receptors for  $\alpha_1$ ,  $\alpha_2$ ,  $\alpha_3$ ,  $\alpha_4$ ,  $\alpha_5$ , and  $\alpha_6$  subunits and TBOB site (chloride channel).**

**2A. Sepracor Response (Feb. 10, 2010, page 7/42):**

(b) (4)

**2A. CSS Response (Mar. 19, 2010):**

Receptor binding studies are conducted as part of an abuse potential assessment in order to provide guidance for conducting appropriate behavioral studies and to provide an explanation of abuse-related AEs observed in clinical studies. However, the mechanism of action of a drug may be unknown, even after binding studies are complete.

As noted above, CSS recommends that the sponsor conduct a human abuse potential study with eslicarbazepine to appropriately characterize its behavioral profile compared to drugs that function at GABA sites, including benzodiazepines.

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**2B. Sepracor Response (Feb. 10, 2010, page 7/42):**

*Functional studies completed with eslicarbazepine, (R)-licarbazepine, and oxcarbazepine confirm that none of these compounds potentiate or inhibit GABA-evoked currents from the benzodiazepine-sensitive  $\alpha 1$ ,  $\alpha 2$ ,  $\alpha 3$  and  $\alpha 5$  containing GABA<sub>A</sub> receptors even at multiples of clinically relevant concentrations.*

**2B. CSS Response (Mar. 19, 2010):**

We have no further comments.

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**2C. Sepracor Response (Feb. 10, 2010, page 8/42):**

[Redacted]

(b) (4)

**CSS Response (Mar. 19, 2010):**

We have no further comments.

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**2D. Sepracor Response (Feb. 10, 2010, page 8/42):**

[Redacted]

(b) (4)

**2D. CSS Response (Mar. 19, 2010):**

We do not agree with this interpretation of the data, as discussed below on Question 7.

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**3. Original CSS Comment (Jan. 13, 2010):**

**The majority of functional studies evaluating drug effects on motor performance and behavior were conducted in rats, a species exhibiting very different metabolism of the drug than humans.**

**3A. Sepracor Response (Feb. 10, 2010, pages 13-14/42):**



**3A. CSS Response (Mar. 19, 2010):**

We do not agree with the sponsor on the interpretation of the animal behavioral data. In the mice studies, muscle relaxation was produced by 250 mg/kg of eslicarbazepine, a dose that was fully protective against maximal electric shock-induced seizure (see Table below from the in vivo study in mice (Study # 093-408).

Table 9 shows the dose dependent increase of protective effects of increasing doses of BIA 2-093 (oral route) against MES-induced tonic seizures. As shown in this table, the maximal protective effect of 100% was achieved at doses greater than 120 mg/kg. The administration of BIA 2-093 (by gastric tube) conferred a dose-dependent protection of NMRI mice against MES-induced seizures.

**Table 9.** Protective effect of increasing doses of BIA 2-093 against MES-induced tonic seizures in NMRI mouse, 1 hour after the administration of the test substance. Results are means  $\pm$  S.E.M.

Dose (mg/kg)	% Protection		
	Mean	S.E.M.	n
0	0.00	2.39	37
1	-5.16	6.81	8
3	2.29	4.55	8
10	0.43	3.71	8
30	20.59	3.14	21
40	44.91	9.81	10
70	83.62	10.59	10
90	97.21	2.79	8
120	100	0	10
200	100	0	10

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**4. Original CSS Comment (Jan. 13, 2010):**

**Study # 093-873 evaluating effects of the drug on cognition in mice does not provide relevant plasma levels of the drug to enable comparison with human doses and to evaluate adequacy of the doses used.**

**4A. Sepracor Response (Feb. 10, 2010, page 16/42):**



**4A. CSS Response (Mar. 19, 2010):**

The 30 and 100 mg/kg (i.p.) doses are too low to evaluate the cognitive effects of eslicarbazepine, based on data (presented in tables above) showing that the fully protective dose of eslicarbazepine against maximal electrical shock-induced seizures in mice is 220 mg/kg (i.p.) and the dose that induces sedation in mice is 250 mg/kg (p.o.).

Additionally, the evaluation of abuse potential in animal models is typically based on utilizing doses in animals that produce plasma levels of the drug that are equivalent to, and 2-3 times greater than, the plasma levels produced in humans at the highest proposed therapeutic doses, which in this case would be 50-70  $\mu$ g/mL. Since no information was provided in this study regarding the plasma levels of eslicarbazepine in the species tested after i.p. administration of the drug, it is not possible to perform an adequate comparison.

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**4B. Sepracor Response (Feb. 10, 2010, page 16/42):**

*The effects of SEP-0002093 on cognition and psychomotor function in humans were evaluated in a directed clinical trial at clinically relevant doses (BIA-2093-123, Submitted to NDA 22-416 in Serial No. 007)*

**4B. CSS Response (Mar. 17, 2010):**

See the discussion regarding this study in Question 1C.

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**5. Original CSS Comment (Jan. 13, 2010):**

**The toxicity studies in rats (#093-809) and beagle dogs (# 093-817), which evaluated withdrawal symptoms, were performed in species having very different metabolism of the drug than humans.**

**5. Sepracor Response (Feb. 10, 2010, page 18):**

*While the metabolic fate of SEP-0002093 in rats is different from that in humans, the metabolism of SEP-0002093 in the dog is similar to humans. Therefore, the dog is an appropriate species in which to evaluate the potential withdrawal symptoms following repeated administration of SEP-0002093.*

**5. CSS Response (Mar. 19, 2010):**

We have no further comments.

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**6. Original CSS Comment (Jan. 13, 2010):**

**The discrimination study in monkeys is invalid due to methodological defects that result in data that is not generalizable to humans. The design of the study, in particular the choice of the training drug, timing of drug administration, and different route of drugs administration raises concerns.**

**Midazolam is an ultra short-acting benzodiazepine, which in humans has Tmax of ~ 0.51 +/- 0.18 h and half-life of ~3.2 +/- 1 h after subcutaneous injection. The sponsor did not provide matching values in monkeys. However, after oral administration in cynomolgus monkeys Tmax was ~ 0.5-3 h.**

**6. Sepracor Response (Feb. 10, 2010, page 20/42):**

*It was agreed that Sepracor will conduct the nonclinical abuse studies suggested by CSS (a receptor binding study with data provided as Ki values, and a drug discrimination study comparing eslicarbazepine to midazolam).*

**6. CSS Response (Mar. 19, 2010):**

We have no further comments. .

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**7. Original CSS Comment (Jan. 13, 2010):**

**Eslicarbazepine plasma concentrations following oral dose of SEP-0002093 in the two separate monkeys used for evaluation of PK parameters in this experiment had plasma peak values in range of 1 to 24 hours. Because of the individual variability noted, peak plasma values for eslicarbazepine can not be predicted for the four monkeys used in this time dependent drug discrimination paradigm; this fact is of particular concern because it invalidates the study.**

**7. Sepracor Response (Feb. 10, 2010, page 24/42):**

 (b) (4)

**7. CSS Response (Mar. 19, 2010):**

We reiterate that the high variability in Tmax and Cmax across animal subjects precludes the acceptance of the drug discrimination study as valid.

 (b) (4)

Thus, because of inter-animal and intra-animal variability of Tmax and Cmax, the validity of the drug discrimination study cannot be confirmed. Thus, data from this study cannot be used as part of a drug abuse assessment.

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**8. Original CSS Comment (Jan. 4, 2010):**

**There are significant problems in the methodology and conduct of the clinical studies that prevent an accurate and adequate assessment of abuse potential. These include:**

**\* Serious under-reporting of all adverse events, particularly in the pivotal safety and efficacy trials 2093-301, 2093-302 and 2093-303, which even the sponsor recognized.**

**\* Inadequate and inaccurate information by which to assess abuse related AEs:**

**a. Not including in the integrated table of abuse related AEs from pooled clinical studies all abuse related MedDRA terms provided to the sponsor by CSS (communication from Nov 28, 2008).**

**b. Omitting and minimizing number of AEs potentially related to abuse.**

**8. Sepracor Response (Feb. 10, 2010, page 26/42):**

*To address the CSS concern that AEs potentially related to abuse were omitted or minimized, we repeated our thorough review of the term selection for inclusion in the integrated assessment on abuse related terms provided in Table 9.*

**8. CSS Response (Mar. 19, 2010):**

There are numerous examples in the submission where the AEs reported during clinical trials were not adequately provided or were under-reported in the integrated summary table (Table 5.4.2-1). For example:

\* There was an omission of psychiatric symptoms coded in MedDRA terms under "Psychosis: psychotic episode or disorder", including cases in the pivotal studies 2093-301, 2093-302 and 2093-303 of "psychotic disorder" (3), "acute psychosis" (1),

“delusion” (1), “delusional disorder” (1), “schizoaffective disorder” (1), “conversion disorder” (1) (Module 5.3.5.3 ISS and individual study reports).

\* There was an omission in some studies of AE terms suggestive of stimulant effect, such as “energy increased” (1) and “attention deficit hyperactivity disorder” (2) (part 1 of pooled studies #301-303), “restlessness” (2) (study # 2093-203), and “psychomotor agitation” (1) (study #2093-202). Although these terms could have been coded as “psychomotor hyperactivity”, this does not appear to be the case. There were only 2 cases of “psychomotor hyperactivity” listed in study #2093-301, part 2, but there were actually 3 cases of “psychomotor hyperactivity” in that study plus 1 additional case of “psychomotor hyperactivity” in part 2 of study #2093-302.

\* There was an omission of mood-related AE cases, especially in Study # 2093-120. In this study, there were 5 cases of “euphoria” and 3 cases of “mood altered”, but the table cites only 4 cases and 2 cases (respectively) for these AEs.

\* There was an omission regarding “hallucinations”, with 3 cases reported in the clinical studies (1 in part 2 of Study #2093-302 study, 1 in part 2 of Study #2093-303 and 1 in Study #2093-02), but only 2 cases listed in the table.

\* Finally, in Study # 2093-123 the sponsor uses the term “any event” for all SOCs but this terms is not further defined and does not match the numbers provided.

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#### **9. Original CSS Comment (Jan. 4, 2010):**

**Use of different versions of MedDRA (Versions 4.0 to 10.0) throughout the drug development potentially could underestimate abuse related adverse events and makes the interpretation of these data difficult.**

#### **9. Sepracor Response (Feb. 10, 2010, page 36/42):**

*Table 9 above identifies the mapping of CSS-identified terms of potential abuse to searched codes for all MedDRA versions (4.0 to 10.0) utilized throughout the development of SEP-0002093. Each and every unique term was searched for the integrated dataset, ensuring that the use of various versions of MedDRA would not have any impact on the estimation of abuse term frequency. Further, it is apparent from this table that there are few terms that changed over time. Therefore, Sepracor does not believe that the use of different MedDRA versions would contribute to any difficulty in interpretation of these data.*

#### **9. CSS Response (Mar. 19, 2010):**

CSS will review the submitted data regarding MedDRA search terms to evaluate their completeness in conversion

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22416	ORIG-1	SEPRACOR INC	SEP-0002093 ESLICARBAZEPINE ACETATE

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/s/

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ALICJA LERNER  
03/19/2010

LORI A LOVE  
03/19/2010

MICHAEL KLEIN  
03/19/2010

**NDA/BLA REGULATORY FILING REVIEW**  
(Including Memo of Filing Meeting)

<b>Application Information</b>		
NDA # <b>022416</b> BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Stedesa Established/Proper Name: Eslicarbazepine Dosage Form: Tablet Strengths: 400, 600 and 800 mg		
Applicant: Sepracor Agent for Applicant (if applicable):		
Date of Application: 3/29/2009 Date of Receipt: 3/30/2009 Date clock started after UN:		
PDUFA Goal Date: 1/30/2010		Action Goal Date (if different):
Filing Date: 5/29/2009 Date of Filing Meeting: 5/13/2009		
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed Indication(s): Adjunctive therapy in the treatment of partial-onset seizures in adults with epilepsy.		
Type of Original NDA: AND (if applicable)		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
Type of NDA Supplement:		<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>Refer to Appendix A for further information.</i>		
Review Classification:		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i>		<input type="checkbox"/> Tropical disease Priority review voucher submitted
Resubmission after withdrawal?	<input type="checkbox"/>	
Resubmission after refuse to file?	<input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> 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): 067466	
PDUFA and Action Goal dates correct in tracking system?  <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system?  <i>If not, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Application Integrity Policy</b>	
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> <a href="http://www.fda.gov/ora/compliance_ref/aiplist.html">http://www.fda.gov/ora/compliance_ref/aiplist.html</a>  If yes, explain:  If yes, has OC/DMPQ been notified of the submission?  Comments:	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>User Fees</b>	
Form 3397 (User Fee Cover Sheet) submitted	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
User Fee Status  Comments:	<input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i>	
<b>Exclusivity</b>	

<p>Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at: <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a></i></p> <p><b>If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?</b></p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES # years requested: 5 <input type="checkbox"/> NO
<p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>):</p> <p>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)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>	<input checked="" type="checkbox"/> Not applicable  <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b>	
<ol style="list-style-type: none"> <li>1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>2. 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 less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).</li> <li>3. 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))?</li> </ol>	<input type="checkbox"/> Not applicable  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i></p>	
--	--

<p>4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <i>Check the Electronic Orange Book at: <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a></i></p>		<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO																
<p>If yes, please list below:</p> <table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>			Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration												
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration															
<p><i>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.</i></p>																		
<p><b>Format and Content</b></p>																		
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p> <p><b>Comments:</b></p>		<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)																
<p><b>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</b></p>																		
<p><b>If electronic submission:</b>  <u>paper</u> forms and certifications signed (non-CTD) or <u>electronic</u> forms and certifications signed (scanned or digital signature)(CTD)?</p> <p><i>Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p> <p><b>Comments:</b></p>		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO																
<p><b>If electronic submission, does it follow the eCTD guidance?</b>  (<a href="http://www.fda.gov/cder/guidance/7087rev.pdf">http://www.fda.gov/cder/guidance/7087rev.pdf</a>)</p> <p><b>If not, explain (e.g., waiver granted):</b></p>		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO																

<p><b>Form 356h:</b> Is a signed form 356h included?</p> <p><i>If foreign applicant, <b>both</b> the applicant and the U.S. agent must sign the form.</i></p> <p>Are all establishments and their registration numbers listed on the form?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>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:</p> <p><input checked="" type="checkbox"/> legible  <input checked="" type="checkbox"/> English (or translated into English)  <input checked="" type="checkbox"/> pagination  <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>Controlled substance/Product with abuse potential:</b></p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>BLAs/BLA efficacy supplements only:</b></p> <p>Companion application received if a shared or divided manufacturing arrangement?</p> <p><b>If yes, BLA #</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	
<p>Patent information submitted on form FDA 3542a?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Debarment Certification</b>	
<p>Correctly worded Debarment Certification with authorized signature?</p> <p><i>If foreign applicant, <b>both</b> the applicant and the U.S. Agent must</i></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><b>sign the certification.</b></p> <p><i>Note: Debarment Certification should use wording in FD&amp;C Act 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...”</i></p> <p><b>Comments:</b></p>	
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	
<p>Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</i>)</p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<p><input checked="" type="checkbox"/> Not Applicable (<i>electronic submission or no CMC technical section</i>)</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<b>Financial Disclosure</b>	
<p>Financial Disclosure forms included with authorized signature?</p> <p><i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<b>Pediatrics</b>	
<p><b><u>PREA</u></b></p>	
<p><i>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 &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	
<p>Are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES</p> <p><input checked="" type="checkbox"/> NO</p>
<p>If no, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?</p>	<p><input type="checkbox"/> YES</p> <p><input checked="" type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• <i>If no, request in 74-day letter.</i></li> <li>• <b>If yes</b>, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</li> </ul>	<p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p><b>Comments:</b> Will request pediatric plan in 74 day letter</p>	

<b><u>BPCA (NDAs/NDA efficacy supplements only):</u></b>	
Is this submission a complete response to a pediatric Written Request?  <i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i>  <b>Comments:</b>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b>Prescription Labeling</b>	
Check all types of labeling submitted.  <b>Comments:</b>	<input type="checkbox"/> Not applicable <input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use <input checked="" type="checkbox"/> MedGuide <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)
Is electronic Content of Labeling submitted in SPL format?  <i>If no, request in 74-day letter.</i>  <b>Comments:</b>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Package insert (PI) submitted in PLR format?  <b>If no</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If before</b> , what is the status of the request?  <i>If no, request in 74-day letter.</i>  <b>Comments:</b>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?  <b>Comments:</b>	<input type="checkbox"/> YES <input type="checkbox"/> NO
MedGuide or PPI (plus PI) consulted to OSE/DRISK? ( <i>send WORD version if available</i> )  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
REMS consulted to OSE/DRISK?  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP?  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<b>OTC Labeling</b>	
<p>Check all types of labeling submitted.</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> <b>Not Applicable</b> <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)
<p>Is electronic content of labeling submitted?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Are annotated specifications submitted for all stock keeping units (SKUs)?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>If representative labeling is submitted, are all represented SKUs defined?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP?</p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Meeting Minutes/SPA Agreements</b>	
<p>End-of Phase 2 meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO
<p>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p><b>Comments:</b> Sponsor also provided mtg min response</p>	<input checked="" type="checkbox"/> YES Date(s): Jan. 23, 2008: Nov. 13, 2008 <input type="checkbox"/> NO
<p>Any Special Protocol Assessment (SPA) agreements?</p> <p><i>If yes, distribute letter and/or relevant minutes before filing meeting.</i></p> <p><b>Comments:</b> also a preIND meeting minutes Jul. 21, 2006</p>	<input checked="" type="checkbox"/> YES Date(s): Feb. 4, 2009 <input type="checkbox"/> NO

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** May 13, 2009

**NDA/BLA #:** 22416

**PROPRIETARY/ESTABLISHED NAMES:** Stedesa (eslicarbazepine acetate)

**APPLICANT:** Sepracor

**BACKGROUND:**

This is a NME NDA application submitted by Sepracor. All clinical studies were conducted outside the United States with the exception of two Phase I studies which were conducted under IND 67,466. Eslicarbazepine acetate was developed by BIAL-Portela. Bial originally submitted IND 67,466 during November 2006. In December 2007, Bial and Sepracor entered into an agreement authorizing Sepracor to develop and market eslicarbazepine acetate in the United States and Canada. Bial completed a transfer of ownership of the IND to Sepracor effective April 10, 2008.

**REVIEW TEAM:**

<b>Discipline/Organization</b>	<b>Names</b>		<b>Present at filing meeting? (Y or N)</b>
Regulatory Project Management	RPM:	Dorothy Demczar	Y
	CPMS/TL:	Robbin Nighswander	Y
Cross-Discipline Team Leader (CDTL)	Norman Hershkowitz		Y
Clinical	Reviewer:	Teresa Podruchny	Y
	TL:	Norman Hershkowitz	Y
OSE (DMEPA)	Reviewer:	Latoya Toombs	Y
	TL:	Carlos Mena-Grillasca	Y

Clinical Pharmacology	Reviewer:	Veneeta Tandon	Y
	TL:		
Biostatistics	Reviewer:	Xiang Ling	Y
	TL:	Kun Jin	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Christopher Toscano	Y
	TL:	Lois Freed	N
Statistics, carcinogenicity	Reviewer:	Steven Thomson	N
	TL:	Karl Lin	N
Product Quality (CMC)	Reviewer:	Charles Jewel	Y
	TL:	Martha Heimann	Y
Facility ( <i>for BLAs/BLA supplements</i> )	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:	Tony El Hage	Y
	TL:		
Pharmacometrics	Hao Zhu		Y
Controlled Substance Staff	Reviewer:	Alicja Lerner	Y
	TL:	Lori Love	Y

**OTHER ATTENDEES:** Dan Brounstein, OSE PM; Ellis Unger, Robert Temple, Eric Bastings

505(b)(2) filing issues?  <b>If yes, list issues:</b>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
Per reviewers, are all parts in English or English translation?  <b>If no, explain:</b>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><b>Electronic Submission comments</b></p> <p><b>List comments:</b></p>	<input type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>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</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason: Need for AC meeting discussed. No unique or significant safety or efficacy issues identified. However, AC meeting tentatively scheduled in January 2010 if need arises, as the review progresses.
<ul style="list-style-type: none"> <li>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?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

<b>Comments:</b>	<input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>BIOSTATISTICS</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>Comments:</b>	
<b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>Comments:</b>	
<b>PRODUCT QUALITY (CMC)</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input checked="" type="checkbox"/> Review issues for 74-day letter
<b>Comments:</b>	
<ul style="list-style-type: none"> <li>Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Establishment(s) ready for inspection?</li> </ul> <ul style="list-style-type: none"> <li>Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Sterile product?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO

<p><b>If yes, was Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>FACILITY (BLAs only)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<b>REGULATORY PROJECT MANAGEMENT</b>	
<p><b>Signatory Authority:</b> Robert Temple, MD (ODE 1 Office Director)</p> <p><b>GRMP Timeline Milestones:</b></p> <p><b>Comments:</b></p>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <ul style="list-style-type: none"> <li><input type="checkbox"/> No review issues have been identified for the 74-day letter.</li> <li><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</li> <li><input checked="" type="checkbox"/> Standard Review</li> <li><input type="checkbox"/> Priority Review</li> </ul>
<b>ACTIONS ITEMS</b>	
<input checked="" type="checkbox"/>	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
<input type="checkbox"/>	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.
<input type="checkbox"/>	If BLA or priority review NDA, send 60-day letter.
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

## 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.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22416	ORIG-1	SEPRACOR INC	SEP-0002093 ESLICARBAZEPINE ACETATE

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/s/

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DOROTHY J DEMCZAR  
03/16/2010



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: February 25, 2010

To: Russell Katz, MD, Director  
Division of Neurology Products

Through: Carlos M. Mena-Grillasca, RPh, Team Leader  
Denise Toyer, PharmD, Deputy Director  
Carol Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis

From: LaToya Shenee' Toombs, PharmD, Safety Evaluator  
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Stedesa (Eslicarbazepine Acetate) Tablets  
400 mg, 600 mg, and 800 mg

Application Type/Number: NDA 022416

Applicant/sponsor: Sepracor

OSE RCM #: 2009-996

## 1 INTRODUCTION

This review was written in response to a request from the Division of Neurology Products to evaluate the container labels, carton and package insert labeling for the product Stedesa (NDA 22-416), for areas that could lead to medication errors.

## 2 METHODS AND MATERIALS

DMEPA used Failure Mode and Effects Analysis (FMEA)<sup>1</sup> in our evaluation of the Stedesa carton labeling and container labels received March 29, 2009 and February 12, 2010 and the insert labeling received February 12, 2010. (see Appendix A thru E).

## 3 RECOMMENDATIONS

Our evaluation of the proposed container labels, carton and insert labeling noted areas of needed improvement in order to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 3.1 *Comments to the Division* for discussion during the labeling meetings. Section 3.2 *Comments to the Applicant* contains our recommendations for the container label and carton labeling. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

### 3.1 COMMENTS TO THE DIVISION

#### A. HIGHLIGHTS OF PRESCRIBING INFORMATION

##### Dosage Forms and Strengths

The dosage form is not presented in this section. Modify the statement to include the dosage form (i.e. tablets). In addition, indicate whether or not the tablets are scored.

#### B. FULL PRESCRIBING INFORMATION

##### 1. Section 2.2- Patients with Renal Impairment

(b) (4)

We recommend specific instructions on how much to increase and in what timeframe be added, for example, “dose may be increased by XX mg per day in weekly intervals based on individual response.”

### 3.2 COMMENTS TO THE APPLICANT

#### A. General Comments (All Labels and Labeling)

We note the proprietary name is presented in all-caps. Consider revising the proprietary name to appear in title case (i.e. Stedesa). Words set in upper and lower case form recognizable shapes, making them easier to read than the rectangular shape that is formed by words set in all-caps. In addition, consider revising the presentation of the dosage form to appear in title case (i.e. Tablets).

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

**B. Container Labels: 30 count bottle (400 mg and 800 mg)**

1. De-bold the net quantity statement so it appears less prominent than the product strength to avoid confusion and misinterpretation of these numbers.
2. Revise the statement, [REDACTED] (b) (4) to read “Usual Dosage: See package insert for dosage information.”

**C. Container Labels: 60 count bottle (600 mg)**

1. See Comments B.1- B.2 above

**D. Container Labels: 90 count bottle (600 mg and 800 mg)**

1. See Comments B.1- B.2 above
2. We note that although the 90 count bottle may be a unit-of-use container, it may also be used for more than one patient. Ensure a sufficient number of medication guides are provided.

**E. Professional Samples (Carton labeling): 7 count (400 mg); 10 count (600 mg, 800 mg)**

1. See Comment B.2. above
2. To ensure the entire contents of the carton is not misinterpreted as one single dose, revise the presentation of the strength through either of the following statements, “XX mg per tablet”, “XX mg/tablet” or “Each tablet contains 100 mg.”

**F. Professional Samples (Blister Card): 7 count (400 mg); 10 count (600 mg, 800 mg)**

Ensure that the established name is at least ½ the size of the proprietary name and the established name shall have a prominence commensurate with the prominence with which such proprietary name appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features per 21 CFR 201.10(g)(2). Revise accordingly.

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22416	ORIG-1	SEPRACOR INC	SEP-0002093 ESLICARBAZEPINE ACETATE

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/s/

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Latoya S TOOMBS  
02/25/2010

CARLOS M MENA-GRILLASCA  
02/26/2010

DENISE P TOYER  
02/28/2010

CAROL A HOLQUIST  
02/28/2010

MEMORANDUM

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

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DATE: January 20, 2010

TO: Russell Katz, M.D.  
Director  
Division of Neurology Products (DNP)

FROM: John A. Kadavil, Ph.D.  
Division of Scientific Investigations (HFD-48)

THROUGH: Martin K. Yau, Ph.D. \_\_\_\_\_  
Acting Team Leader (Bioequivalence)  
Division of Scientific Investigations (DSI)

SUBJECT: Review of EIR Covering NDA 22-416, Stedesa  
(eslicarbazepine acetate) 400, 600 and 800 mg  
tablets, Sponsored by Sepracor, Inc.

At the request of DNP, the Division of Scientific Investigations conducted an audit of the clinical and analytical portions of the following bioequivalence study supporting NDA 22-416:

**Study Number:** BIA-2093-122

**Study Title:** "Single Dose Crossover Comparative Bioavailability Study of Eslicarbazepine Acetate 400 mg, 600 mg and 800 mg Tablets Clinical Trial Formula (CTF) versus the To-Be-Marketed Formulation (TBM) in Healthy Male and Female Volunteers/ Fasting State"

The clinical portion of Study BIA-2093-122 was conducted at two Algorithmme Pharma Inc. sites in Quebec, Canada: Montreal and Mount-Royal. The Montreal facility is no longer in operation; hence the clinical audit took place at the Mount-Royal site. The analytical portion was conducted at  (b) (4)

Following the inspection at Algorithmme Pharma, Mount-Royal (November 30 - December 4, 2009, and December 14-18, 2009),

Page 2 - NDA 22-416, Stedesa (eslicarbazepine acetate) 400, 600 and 800 mg tablets

Form FDA-483 was issued. Following the inspection at [REDACTED] (b) (4) Form FDA-483 was issued. [REDACTED] (b) (4)

**Algorithmme Pharma, Inc., Mount-Royal, Quebec, Canada**  
**(Clinical Site)**

- 1. The firm failed to assure complete drug accountability following drug dispensation and prior to subject dosing.**

The firm's pharmacist dispensed test and reference tablets into vials 2 to 3 days prior to subject dosing at the Mount-Royal site. These vials were then transferred to and stored in a Temporary Drug Room (TDR) at the Montreal clinical site. However, the shipping slip did not list how many vials were received at the TDR and whether they were sealed. Additionally, when vials were removed from the TDR on dosing days, the identities of the individual tablets inside the vials were not confirmed.

Although the firm should improve their drug accountability practices, this finding should not affect study outcome. The firm's response notes that products used for dosing were confirmed by visual check at dosing as documented on case report forms. DSI accepts this as confirmation that subjects received the correct drug product.

The firm's response also indicated that they have since implemented corrective actions in their drug accountability documentation practices.

[REDACTED] (b) (4) **(Analytical Site)**

- 1. The firm failed to document whether subject plasma samples were evaluated for hemolysis.**

Specifically, sample receipt logs and sample processing forms did not provide information on the assessment of plasma samples for hemolysis.

In their response, the firm acknowledged this finding and stated that corrective actions will be implemented.

Page 3 - NDA 22-416, Stedesa (eslicarbazepine acetate) 400, 600 and 800 mg tablets

Although the firm should assess hemolysis to assure sample integrity, the inspection did not find any aberrations in the raw analytical data to suggest compromised sample integrity. Therefore, DSI accepts that this finding does not significantly impact study outcomes.

**Conclusion:**

Following DSI's evaluation of the inspectional findings (b) (4) DSI recommends that the inspected clinical and analytical portions be accepted for review.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

John A. Kadavil, Ph.D.  
Pharmacologist

**Final Classification:**

Algorithme Pharma, Inc., Mount-Royal, Quebec, Canada - VAI  
(b) (4) - VAI

CC:

OC DSI GLPBB/Yau/Kadavil/Rivera-Lopez/CF

OND ODEI DNP/Demczar

Draft: JAK 1/13/10

Edit: MFS 1/19/10

DSI: 5974; O:\BE\EIRCover\22416sep.esl.doc

FACTS 1067568

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22416	ORIG-1	SEPRACOR INC	SEP-0002093 ESLICARBAZEPINE ACETATE

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/s/

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JOHN A KADAVIL  
01/20/2010

MICHAEL F SKELLY  
01/20/2010  
Skelly signed on behalf of Martin Yau.

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

<b>NDA</b>	22,416
<b>Brand Name</b>	Eslicarbazepine Acetate
<b>Generic Name</b>	Eslicarbazepine Acetate
<b>Sponsor</b>	Sepracor
<b>Indication</b>	Treatment of Epilepsy
<b>Dosage Form</b>	Tablet
<b>Drug Class</b>	Voltage-gated sodium channel blocker
<b>Therapeutic Dosing Regimen</b>	800 mg, 1200 mg po QD (adjunctive to other anti-epileptic drugs)
<b>Duration of Therapeutic Use</b>	Chronic
<b>Maximum Tolerated Dose</b>	2400 mg (monotherapy)
<b>Submission Number and Date</b>	N 000 / 29 Mar 2009
<b>Review Division</b>	DNP / HFD 120

**1 SUMMARY**

**1.1 OVERALL SUMMARY OF FINDINGS**

No significant QT prolongation effect of eslicarbazepine acetate (1200 mg and 2400 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between eslicarbazepine acetate (1200 mg and 2400 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the  $\Delta\Delta QTcI$  for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 4, indicating that assay sensitivity was established. Overall summary of findings is presented in Table 1

**Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Eslicarbazepine Acetate (1200 mg and 2400 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)**

<b>Treatment</b>	<b>Time (hour)</b>	<b><math>\Delta\Delta QTcI</math> (ms)</b>	<b>90% CI (ms)</b>
Eslicarbazepine Acetate 1200 mg	12	1.5	(-1.0, 3.9)
Eslicarbazepine Acetate 2400 mg	23.5	1.4	(-1.2, 4.1)
Moxifloxacin 400 mg*	2	12.0*	(9.5, 14.5)

\* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 6 timepoints is 8.3 ms.

Dose selection is acceptable; the 2400-mg dose is the maximum tolerated dose. Eslicarbazepine acetate (BIA2-093) is rapidly and extensively metabolized to eslicarbazepine (BIA2-194), which represents about 95% of total systemic drug exposure to active moieties. (R)-licarbazepine (BIA2-195) and oxcarbazepine are minor active metabolites, corresponding to approximately 5% and 1% of systemic exposure, respectively. The suprathreshold dose (2400 mg) produces concentrations of 2-fold higher than those with the therapeutic dose (1200 mg). Mean eslicarbazepine  $C_{max}$  was increased 31% in mild, 5.4% in moderate, and 4.8% in severe renal impairment; mean  $AUC_{0-\infty}$  was increased 61% in mild, 11% in moderate, and 154% in severe renal impairment. Moreover, there were no relevant changes in  $C_{max}$  and AUC in patients with mild to moderate hepatic impairment compared to healthy volunteers.

In this randomized, double-blind, placebo-controlled and open label active-controlled, four-period crossover study, 67 subjects were enrolled in this study and randomized to one of the four treatment sequences that consists of the following four treatments: eslicarbazepine acetate 1200 mg once daily  $\times$  5 days, eslicarbazepine acetate 2400 mg once daily  $\times$  5 days, an active-control, moxifloxacin 400 mg  $\times$  1 dose on Day 5 (with placebo on Days 1-4), and placebo once daily  $\times$  5 days. All randomized subjects were treated with at least one dose of study medication and a total of 55 (82.1%) completed the study. Twelve subjects discontinued from treatment; 10 subjects withdrew because of an adverse event and two subjects withdrew consent.

## **2 PROPOSED LABEL**

The sponsor did not provide the language statement on TQT. We propose the following description of study results is included in section 12.2 of the label.

### **12.2 Cardiac Electrophysiology**

The effect of eslicarbazepine acetate on cardiac repolarization was evaluated in a randomized, double-blind, placebo- and active-controlled 4-period crossover trial in healthy adult men and women. Subjects received eslicarbazepine acetate 1200 mg once daily  $\times$  5 days, eslicarbazepine acetate 2400 mg once daily  $\times$  5 days, an active-control, moxifloxacin 400 mg  $\times$  1 dose on Day 5, and placebo once daily  $\times$  5 days. At both doses of eslicarbazepine, no significant effect on the QTc interval was detected.

## **3 BACKGROUND**

### **3.1 PRODUCT INFORMATION**

SEP-0002093 (eslicarbazepine acetate, BIA 2-093) is a third-generation, single-enantiomer member of the long-established family of first-line dibenz[b,f]azepine antiepileptic drugs (AEDs) represented by carbamazepine (first-generation) and oxcarbazepine (second-generation). It behaves as a voltage-gated sodium channel (VGSC) blocker that competitively interacts with site 2 of the inactivated state of the channel, preventing its return to the active state and inhibiting repetitive neuronal firing. SEP-0002093 is rapidly and extensively metabolized to eslicarbazepine, the pharmacologically active moiety, and (R)-licarbazepine in a 24:1 ratio; systemic exposure to the parent drug is negligible in humans.

### 3.2 MARKET APPROVAL STATUS

SEP-0002093 is not approved for marketing in any country..

### 3.3 PRECLINICAL INFORMATION

From NDA 22416 (module 2, overview of safety pharmacology)

“The safety pharmacology of SEP-0002093 and its metabolites [eslicarbazepine, (R)-licarbazepine and licarbazepine] has been examined in vivo in mice, rats, and dogs, and in several in vitro studies. SEP-0002093, licarbazepine, eslicarbazepine, and (R)-licarbazepine had minimal effects (< 20% inhibition) on hERG channel current at concentrations up to 100 µg/mL. In a study in canine Purkinje fibers, SEP- 0002093, licarbazepine, and oxcarbazepine had effects that suggested inhibition of cardiac sodium channel current at concentrations ≥ 10 µg/mL. The effects of oxcarbazepine were more pronounced than those of either SEP-0002093 or licarbazepine.

“Characterization of the pharmacological and kinetic interactions of SEP-0002093 with voltage-gated Na<sup>+</sup> channels in the mouse neuroblastoma cell line N1E-115 was extended by comparison with the major metabolite, eslicarbazepine, as well as with (R)-licarbazepine, licarbazepine (racemic mixture), oxcarbazepine, and carbamazepine. The whole-cell voltage patch-clamp technique was used to investigate the effects of SEP- 0002093, its major metabolite (eslicarbazepine), (R)-licarbazepine, licarbazepine, oxcarbazepine, and the chemically related carbamazepine at concentrations of 10, 50, 100, 250, and 500 µM.

“The influence of holding potential (-100 mV, -80 mV, and -60 mV) on inhibitory potency was assessed. In addition, the affinities of test articles (250 µM) for the resting (KR) and inactivated (KI) states were determined by examining the functional effects on Na<sup>+</sup> currents evoked by a 10 ms pulse to 0 mV immediately after 15 seconds of a conditioning prepulse ranging from -120 mV to -40 mV. To determine the kinetics of dissociation, the cells were held at -100 mV in the presence of compound (250 µM) and the Na<sup>+</sup> channels were inactivated by a 30 second depolarization to 0 mV. Then the cells were reactivated by stepping back to -100 mV for a duration of 0.5 seconds for 1-20 seconds (1 second interval) followed by a 10 ms test pulse to 0 mV.

“Carbamazepine, oxcarbazepine, licarbazepine, SEP-0002093, eslicarbazepine, and (R)-licarbazepine inhibited voltage-gated Na<sup>+</sup> channels. The inhibitory potencies of all tested compounds increased as the holding potential was made less negative, which is a characteristic of agents interacting with the inactivated state of the Na<sup>+</sup> channel (Table 4). Based on IC<sub>50</sub> values relative to carbamazepine at -100 mV, oxcarbazepine, licarbazepine, SEP-0002093, eslicarbazepine, and (R)-licarbazepine were approximately 2.4, 4.8, 4.8, 13.1, and 18.6-fold less potent than carbamazepine, respectively.

**Table 4: IC<sub>50</sub> Values at Different Holding Potentials**

Test Article	IC <sub>50</sub> Values (μM)		
	V <sub>hold</sub> = -100 mV	V <sub>hold</sub> = -80 mV	V <sub>hold</sub> = -60 mV
SEP-0002093	3,977 ± 694 μM	741 ± 130 μM	207 ± 31 μM
Eslicarbazepine	10,818 μM*	3,106 ± 624 μM	563 ± 103 μM
(R)-Licarbazepine	15,304 ± 7,661 μM	1,014 ± 97 μM	531 ± 106 μM
Licarbazepine	3,970 μM*	1,123 ± 213 μM	306 ± 53 μM
Oxcarbazepine	2,000 ± 200 μM	806 ± 123 μM	173 ± 35 μM
Carbamazepine	823 ± 50 μM	399 ± 55 μM	109 ± 4 μM

Results are expressed as mean ± SEM; n=3-7

\* = Obtained from fit of averaged experiments

“In conscious dogs, SEP-0002093 had no significant effect on blood pressure or heart rate following oral administration at 40 or 80 mg/kg. A slight increase in heart rate was seen at 210 mg/kg which resulted in a slightly shorter QT-interval. No treatment-related arrhythmias or other changes in the morphology of the ECG were noted. In anesthetized dogs, SEP-0002093 had no significant effect on cardiovascular or respiratory parameters following intraduodenal administration at doses up to 160 mg/kg.”

*Reviewer’s comments: SEP-0002093 and eslicarbazepine induced less than 20% blockade of hERG with concentration up to 2 times the MTD C<sub>max</sub> exposure. SEP-0002093 and eslicarbazepine interact with the inactivated state of the Na<sup>+</sup> channel with an IC<sub>50</sub> ≥ 10 times the MTD C<sub>max</sub> exposure.*

### 3.4 PREVIOUS CLINICAL EXPERIENCE

Summary of Clinical Safety and Integrated Summary of Safety (Modules 2.7.4 and 5.3.5.3 respectively).

“The clinical program of eslicarbazepine acetate (ESL, BIA 2-093, or SEP-0002093) consisted of 30 trials including more than 2,000 subjects.

“The clinical studies in this program utilized single or multiple doses of ESL as adjunctive or monotherapy between 20 mg and 3600 mg per day.

“ESL was well tolerated at doses up to 2400 mg in Phase I studies.

“The safety profile observed in Phase II and III studies were consistent, reproducible, and demonstrated adverse events (AEs) that were compatible with the known pharmacology of ESL and the AED class. The most common events included dizziness, somnolence, headache, nausea, vomiting, diplopia, and abnormal coordination. All demonstrated a clear dose response. These effects are easily monitored and represent tolerability issues rather than serious or life-threatening problems.

“There was no notable impact of ESL on electrocardiograms (ECGs), including QTc effects, or vital signs, including orthostatic effects.

“In addition to standard safety evaluations [adverse events (AEs), vital signs, electrocardiograms (ECGs), and clinical laboratory parameters (hematology,

coagulation, thyroid function, and serum chemistry)], evaluations of electroencephalograms (EEG) (Studies 2093-101 and 2093-102), cardiac safety, and concomitant AEDs were also performed.

“12-lead ECGs were captured during all Phase II and III studies conducted in subjects with epilepsy and bipolar disorder. During Part 1 of the Phase III epilepsy studies, 12-lead ECGs were obtained at screening, study baseline, and Week 14 of treatment. During the Phase II epilepsy and bipolar disorder studies, ECGs were obtained at baseline, during the treatment phase, and at the end of the study.

“Overall, no clinically significant changes from baseline in ECG parameters were observed among subjects in the Phase II bipolar disorder studies. In Studies 2093-203 and 2093-204, no treatment-emergent ECG abnormalities were considered by the Investigator to be clinically relevant, and none were reported as AEs. In Study 2093-205, AEs associated with ECG parameters included sinus tachycardia in 2 subjects (6%) in the ESL 300 mg dose group and 1 subject (4%) in the 900 mg ESL dose group. These events were assessed by the Investigator as mild or moderate in severity, and all were unrelated to treatment. The event of sinus tachycardia in the 900 mg ESL dose group, which was moderate in severity and required no treatment, led to discontinuation of treatment (Subject 531/203081); no other adverse events were reported in this subject. The only other treatment-emergent clinically relevant ECG abnormality reported in this study was sinus bradycardia in 1 subject (2093-205-535-203086) in the ESL 300 mg dose group; this abnormality was not reported as an AE (Study 2093-203 CSR Section 13.5.3.3, Study 2093-204 CSR Table 14.3-5, and Study 2093-205 CSR Table 14.3-7 and Appendix 16.2 Listings 16.3-1, 16.3-2, and 16.3-10).”

*Reviewer’s comments: Single or multiple doses up to 3600 mg were studied in the SEP-0002093 clinical program. No syncope, sudden death or ventricular arrhythmias were reported in these studies. There are no reports of QTc prolongation in these studies. Episodes of tachycardia and bradycardia were reported in subjects treated with SEP-0002093.*

### **3.5 CLINICAL PHARMACOLOGY**

Appendix 6.1 summarizes the key features of eslicarbazepine’s clinical pharmacology.

## **4 SPONSOR’S SUBMISSION**

### **4.1 OVERVIEW**

The QT-IRT reviewed the protocol prior to conducting this study under IND 67,466. The sponsor submitted the study report *bia-2093-116a-legacy.pdf* for the study drug, including electronic datasets and waveforms to the ECG warehouse.

#### **4.1.1 Title**

A randomized, double-blind, placebo-controlled and open label active-controlled, 4-period crossover trial to evaluate the effect of eslicarbazepine acetate on cardiac repolarization in healthy adult men and women

#### **4.1.2 Protocol Number**

SFB/BIA-2093-116

#### **4.1.3 Study Dates**

Study Initiation Date: 23 March 2007

Study Completion Date: 27 June 2007

#### **4.1.4 Objectives**

The primary objective of the study was to evaluate the effect of therapeutic and supra-therapeutic doses of eslicarbazepine acetate on the placebo corrected time-matched change from baseline using individually corrected QT (QTcI) interval durations in adult healthy volunteers.

Secondary objectives were as follows:

- To evaluate the effect of therapeutic and supra-therapeutic doses of eslicarbazepine acetate on time-averaged QTcI, uncorrected QT, fixed exponent corrected QT (Bazett [QTcB] and Fridericia [QTcF]), heart rate (HR), PR, and QRS intervals, and electrocardiograph (ECG) waveform morphology.
- To correlate any observed effect of eslicarbazepine acetate on QTcI, QTcB, and QTcF to plasma concentrations of eslicarbazepine.
- To assess the safety and tolerability of therapeutic and supra-therapeutic doses of eslicarbazepine acetate.

#### **4.1.5 Study Description**

##### **4.1.5.1 Design**

This thorough QT/QTc study employed a randomized, double-blind, placebo-controlled and open-label active-controlled, 4-period crossover design to assess the effect of eslicarbazepine acetate on cardiac conduction and repolarization in healthy adult male and female subjects. Subjects received each of the 4 study treatment regimens during the 4 periods according to a randomized sequence. The 4 treatments include eslicarbazepine acetate 1200 mg once daily  $\times$  5 days, eslicarbazepine acetate 2400 mg once daily  $\times$  5 days, an active-control, moxifloxacin 400 mg  $\times$  1 dose on Day 5 (with placebo on Days 1-4), and placebo once daily  $\times$  5 days. A 7-day washout separated treatment in each period. Subjects underwent screening assessments within 21 days of the first dosing period. During each study period, eligible subjects reported to the clinical site on Day -2 (run-in day) prior to dosing and remained in the clinic until clinic discharge on Day 6.

##### **4.1.5.2 Controls**

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

##### **4.1.5.3 Blinding**

The dispensing pharmacist was unblinded and allocated treatments according to the randomization code. During the eslicarbazepine acetate and placebo treatment periods, the Investigator and other members of staff involved with the study remained blinded to

the actual treatment received. Moxifloxacin was administered in an open-label fashion. The interpretation of Holter ECG data was performed in a blinded manner without knowledge of therapy or treatment sequence.

#### 4.1.6 Treatment Regimen

##### 4.1.6.1 Treatment Arms

Study drug administered in this study consisted of eslicarbazepine acetate tablets, moxifloxacin (active control), or matching placebo. The treatment regimens used in this trial are described in Table 2.

**Table 2: Treatment Regimens**

<b>Treatment Code</b>	<b>Treatment Description</b>	<b>Treatment Regimen</b>
A	Eslicarbazepine acetate 1200 mg once daily × 5 days	2 × 600 mg eslicarbazepine acetate tablets and 2 matching placebo tablets on Days 1–5
B	Eslicarbazepine acetate 2400 mg once daily × 5 days	4 × 600 mg eslicarbazepine acetate tablets on Days 1–5
C	Moxifloxacin 400 mg × 1 dose	Placebo tablet on Days 1 to 4, and 1 × 400 mg moxifloxacin tablet on Day 5
D	placebo once daily × 5 days	4 placebo tablets on Days 1–5

A total of 65 subjects each were to be randomized in roughly equal proportions to one of the four sequences following a William square design for four treatments.

##### 4.1.6.2 Sponsor’s Justification for Doses

“The therapeutic dose of eslicarbazepine acetate for the treatment of epilepsy is 1200 mg. The guidance covering Thorough QT Trials recommends that both therapeutic and suprathreshold doses of the investigational drug be administered to characterize the concentration-response relationship for QT/QTc interval prolongation. The guidance further suggests that the suprathreshold dose should represent a minimum 3-fold increase over the therapeutic dose. Accordingly, the starting dose in the previous dose-finding study was set at 3600 mg, 3 times the therapeutic dose. Following administration of 3600 mg to the first cohort, tolerability issues were noted, and the next cohort was dosed at 3000 mg. When tolerability issues were again observed in the second cohort, the sponsor made the decision to discontinue the study and declared a dose of 2400 mg to be the maximum tolerated dose. For this reason, the doses of eslicarbazepine acetate used in this study were 1200 mg (therapeutic dose) and 2400 mg (suprathreshold dose).”

*Reviewer’s Comment: The doses are acceptable because although the mean C<sub>max</sub> and AUC<sub>∞</sub> values after suprathreshold dose (2400 mg) were only 2-times higher than those at a therapeutic dose of 1200 mg as the sponsor identified maximum tolerated dose.*

#### **4.1.6.3 Instructions with Regard to Meals**

Subjects received a standard breakfast and fasted from at least 1 hour prior to dosing until 4 hours following dosing. Fasting was not required on Days 1 through 4, and subjects were given breakfast at approximately one hour following dosing on those days.

*Reviewer's Comment: It is acceptable as there is negligible effect with /without food.*

#### **4.1.6.4 ECG and PK Assessments**

On Day 5 of each treatment period, samples of venous blood for analysis of eslicarbazepine and its metabolites were obtained in 4 mL lithium-heparin tubes 30 minutes prior to dose administration (0 hours, pre-dose), and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, and 24 hours postdose.

Continuous 12-lead Holter ECG data were obtained in triplicate at the following 13 specified time points at baseline (Day -1) and at 13 matched time points on Day 5 using a Mortara Instrument H12+ Digital ECG Recorder : -30 minutes (pre-dose), and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, and 23.5 hours post-dose.

When the timing of Holter ECG assessments and plasma sampling coincided, the Holter reading was performed before plasma sampling.

*Reviewer's Comment: The sampling times are acceptable. ECGs measurements were collected frequently enough to monitor the effects of eslicarbazepine. The mean  $T_{max}$  is approximately 2-3 hours for eslicarbazepine and 6 hour for (R)-licarbazepine . The sponsor has collected ample ECG measurements before, around, and after the  $T_{max}$ .*

#### **4.1.6.5 Baseline**

The baselines used for the time-matched analyses (primary) were the arithmetic mean of the 3 ECGs at each of the time points on Day -1 providing a single ECG interval value for each pre-treatment time point.

The baseline used for the time-averaged analysis (secondary) was the arithmetic mean of the ECG results across 12 time points on Day -1 (each time point reflects the arithmetic mean of the 3 ECGs at that time point).

#### **4.1.7 ECG Collection**

Continuous 12-lead Holter ECG data were obtained in triplicate at the following 13 specified time points at baseline (Day -1) and at 13 matched time points on Day 5 using a Mortara Instrument H12+ Digital ECG Recorder. On Day -1 and Day 5 when ECG data were collected, the environmental conditions were controlled to the extent possible to minimize intrasubject variability. Subjects remained in a supine position for 10 minutes before the ECG data collection. Each subject wore the recorder and the 12-Lead ECGs were captured continuously during that period according to the collection period outlined above. The ECG signals were recorded on 1000 Hz flash memory cards (flash cards) provided to the site. The ECGs were stored continuously on a flash memory card about every 10 seconds and were not available for review until the flash card was received by the central core ECG laboratory and analyzed. Three digital ECGs were taken and the values of these were all averaged to estimate the ECG variables. The ECGs were

downloaded just prior to the scheduled PK blood sample collection (maximum of 5 minutes). A total of 39 ECGs were analyzed at baseline (3 ECGs at 13 time points).

A Holter transmittal form labeled with the subject’s unique identification number and demographic information was submitted along with the flash card to the central core laboratory, (b) (4) via overnight courier. The high resolution measurement of the cardiac intervals and morphological assessment were carried out at (b) (4) by qualified personnel blinded to study treatment.

A standard safety 12-lead electrocardiogram was obtained at screening and 2 hours after dose administration on Day 5 during each treatment period. The safety ECG was available immediately for the Investigator or study physician to review.

#### 4.1.8 Sponsor’s Results

##### 4.1.8.1 Study Subjects

Sixty-seven (67) subjects (approximately equal numbers of males and females) 18 to 45 years of age with a BMI within the range of 18 to 30 kg/m<sup>2</sup> were enrolled.

##### Exclusion criteria concerning ECGs:

An abnormal screening ECG indicating a second- or third-degree AV block, or one or more of the following: QRS > 110 milliseconds (ms), QTc (Fridericia correction) > 450 ms, PR interval > 240 ms. Any rhythm other than sinus rhythm, which was interpreted by the Investigator to be clinically significant.

All randomized subjects were treated with at least one dose of study medication and a total of 55 (82.1%) completed the study. Twelve subjects discontinued from treatment; 10 subjects due to an adverse event and 2 subjects withdrew consent.

**Table 3: Table summary of subject disposition**

	Treatment Sequence				All Subjects N = 67 n (%)
	ABCD N = 17 n (%)	BDAC N = 17 n (%)	CADB N = 17 n (%)	DCBA N = 16 n (%)	
Subjects Randomized	17	17	17	16	67
Subjects Treated	17 (100)	17 (100)	17 (100)	16 (100)	67 (100)
Subjects Completed	16 (94.1)	13 (76.5)	12 (70.6)	14 (87.5)	55 (82.1)
Subjects Discontinued	1 (5.9)	4 (23.5)	5 (29.4)	2 (12.5)	12 (17.9)
Reason for Discontinuation					
Adverse Event(s)	1 (5.9)	3 (17.6)	5 (29.4)	1 (6.30)	10 (14.9)
Withdrew Consent	0 (0.0)	1 (5.9)	0 (0.0)	1 (6.3)	2 (3.0)
Safety Population	17 (100)	17 (100)	17 (100)	16 (100)	67 (100)
ECG Analysis Population	17 (100)	15 (88.2)	17 (100)	16 (100)	65 (97.0)

Data Source: Table 15.1.1, Listing 16.2.1.

Sixty-seven (67) were analyzed for safety and 65 were included in the ECG analysis population.

##### 4.1.8.2 Statistical Analyses

##### 4.1.8.2.1 Primary Analysis

The primary analysis for the QT/QTc data was based on the time-matched analysis of QTcI at Day 5. The time-matched analysis was based upon the change from baseline (Day -1) in the QTcI interval and was calculated for each of the 12 separate post dose time points. For each post baseline time point, an upper one-sided 95% pair-wise comparison to placebo confidence intervals (CI) was derived from the analysis of variance (ANOVA) model with sequence, period, gender, and treatment group as factors, QTc baseline as a covariate, where subject was a random effect nested with sequence. If at all time points, the upper one-sided 95% CI was below 10 ms, then  $H_0$  was rejected, and it would be concluded that the drug does not have a QT prolonging effect.

If the time-matched change in QTcI duration from baseline for moxifloxacin was >5 ms greater than placebo, and the upper one-sided bound of the time-matched 95% CI at Day 5 for the eslicarbazepine acetate dose groups versus placebo fell below 10 ms, it would be concluded that eslicarbazepine acetate does not prolong the QTc interval to a clinically significant degree.

The sponsor's results are presented in Table 4. LS mean difference between the eslicarbazepine acetate groups and the placebo group in the time-matched QTcI change from baseline was less than 1.54 ms at all post-dose time points, and the corresponding upper one-sided 95% confidence bound around the differences were all less than 10 ms. The LS mean differences between the moxifloxacin and placebo groups in time-matched QTcI change from baseline ranged from 1.59 to 12.04 msec. The upper one-sided 95% confidence intervals about the differences were 10 ms or greater at 3 time points (2, 3, and 4 hours).

**Table 4: Analysis of Time-Matched Placebo-Corrected QTcI Change from Baseline**

Treatment Group	LS Mean (Upper One-Sided 95% CI) Difference from Placebo in QTcI Change from Baseline (msec)		
	1200 mg Eslicarbazepine Acetate	2400 mg Eslicarbazepine Acetate	Moxifloxacin
Time (hr)	Difference (Upper CI)	Difference (Upper CI)	Difference (Upper CI)
0.5	-3.28 (-0.6676)	-1.67 (0.9750)	1.59 (4.2034)
1	-5.45 (-2.9464)	-3.83 (-1.3106)	7.56 (10.0410)
1.5	-4.54 (-1.7277)	-4.49 (-1.6395)	9.30 (12.1097)
2	-3.96 (-1.4483)	-2.96 (-0.3891)	11.96 (14.4609)
3	-4.88 (-2.1513)	-5.19 (-2.4246)	11.55 (14.2626)
4	-5.58 (-2.6390)	-4.11 (-1.1550)	12.04 (14.9555)
5	-3.05 (-0.4563)	-1.04 (1.5841)	8.28 (10.8667)
6	-1.37 (1.3440)	0.21 (2.9499)	9.10 (11.8017)
8	-1.23 (1.6511)	0.06 (2.9735)	7.20 (10.0602)
12	1.48 (3.9111)	1.54 (4.0066)	7.14 (9.5626)
16	-1.92 (1.1856)	-2.92 (0.2008)	6.58 (9.6567)
23.5	-1.59 (1.0264)	1.43 (4.0736)	4.27 (6.8802)

Source: Sponsor's CSR Table 7 on Page 58.

*Reviewer's Comments: The sponsor did not provide the lower bounds of the two-sided 95% confidence intervals for the moxifloxacin group. The assessment of the assay sensitivity cannot be made based on the provided results. However, by the rule of symmetry of confidence bounds, the assay sensitivity seems established in this study. We will provide our independent analysis results in section 5.2.*

#### **4.1.8.2.2 Categorical Analysis**

A categorical analysis of ECG abnormalities was performed. The categorical analyses were by subject and summarized based on the number and percentage of study subjects meeting or exceeding the pre-specified categories (outliers) for each treatment.

The baseline used for the categorical outlier analysis was the arithmetic mean of the 3 ECGs at each of the 13 time points to define a single ECG interval value for each pre-treatment time point. The triplicate ECGs at each of the 12 post-dose time points on Day 5 were averaged to define a single ECG interval value for each on-treatment time point. Each baseline value was compared to the value at matched time point on Day 5 and the maximum observed change was used to categorize each subject as having met or not met an outlier criterion. If a subject met more than one outlier criterion for each ECG interval, that subject was counted only once using the largest or worst case value. Subjects identified as having outliers were profiled in a listing. The sponsor's results of the categorical analyses are provided in Table 5.

**Table 5: Summary of Categorical ECG Outliers**

Treatment Group Parameter	N (%) of Subjects			
	1200 mg Eslicarbazepine Acetate (N=64)	2400 mg Eslicarbazepine Acetate (N=66)	Moxifloxacin (N=62)	Placebo (N=64)
<b>QTcI (msec)</b>				
Change <30	60 (93.8%)	55 (83.3%)	55 (88.7%)	60 (93.8%)
30 ≤ Change ≤60	1 (1.6%)	3 (4.5%)	6 (9.7%)	4 (6.3%)
Change >60	0 (0%)	0 (0%)	0 (0%)	0 (0%)
New onset QTcI ≥500	0 (0%)	0 (0%)	0 (0%)	0 (0%)
New onset QTcI ≥480	0 (0%)	0 (0%)	0 (0%)	0 (0%)
New onset QTcI ≥450	0 (0%)	1 (1.5%)	6 (9.7%)	4 (6.3%)
<b>QTcB (msec)</b>				
Change <30	55 (85.9%)	48 (72.7%)	37 (59.7%)	54 (84.4%)
30 ≤ Change ≤60	6 (9.4%)	10 (15.2%)	24 (38.7%)	10 (15.6%)
Change >60	0 (0%)	0 (0%)	0 (0%)	0 (0%)
New onset QTcB ≥500	0 (0%)	0 (0%)	0 (0%)	0 (0%)
New onset QTcB ≥480	0 (0%)	0 (0%)	0 (0%)	0 (0%)
New onset QTcB ≥450	3 (4.7%)	8 (12.1%)	11 (17.7%)	7 (10.9%)
<b>QTcF (msec)</b>				
Change <30	61 (95.3%)	54 (81.8%)	60 (96.8%)	62 (96.9%)
30 ≤ Change ≤60	0 (0%)	4 (6.1%)	1 (1.6%)	2 (3.1%)
Change >60	0 (0%)	0 (0%)	0 (0%)	0 (0%)
New onset QTcF ≥500	0 (0%)	0 (0%)	0 (0%)	0 (0%)
New onset QTcF ≥480	0 (0%)	0 (0%)	0 (0%)	0 (0%)
New onset QTcF ≥450	0 (0%)	0 (0%)	3 (4.8%)	0 (0%)
<b>Heart rate (bpm)</b>				
25% decrease and resultant value <50	0 (0%)	0 (0%)	0 (0%)	0 (0%)
25% increase and resultant value >100	2 (3.1%)	4 (6.1%)	3 (4.8%)	0 (0%)
<b>PR (msec)</b>				
25% increase when resultant PR >200	0 (0%)	0 (0%)	0 (0%)	0 (0%)
<b>QRS (msec)</b>				
25% increase when resultant QRS >100	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Analysis based on maximum time-matched change from baseline on Day 5

Source: Sponsor's CSR Table 10 on Page 64.

#### **4.1.8.2.3 Additional Analyses**

The sponsor also performed the secondary analysis for the ECG interval data that was based on the arithmetic mean of all post baseline time points on Day 5 (Time-averaged). For each subject, the arithmetic mean of all baseline time points was subtracted from the arithmetic mean of all post-baseline, post-treatment time points for Day 5. The statistical analysis was based upon this summary measure. This time-averaged change from baseline corrected for placebo was analyzed using an analysis of variance (ANCOVA) model with sequence, period, gender, and treatment group as factors, QTc baseline as a covariate, where subject was a random effect nested with sequence. Upper one-sided 95% CIs were derived for pair-wise mean differences between treatments using the residual error of the ANCOVA (i.e., comparing each active treatment vs placebo). Each treatment group including the positive control was compared to the placebo group using a pair-wise comparison derived from the ANCOVA model. An upper one-sided 95% CI

was displayed for Day 5. All 95% CIs for this time-averaged analysis were considered as a descriptive summary. The sponsor's results are provided in Table 6.

**Table 6: Analysis of Time-Averaged Placebo-Corrected Change from Baseline QTc on Day 5**

Treatment Group	LS Mean (Upper One-Sided 95% CI) Difference from Placebo in Change from Baseline QTc (msec)		
	1200 mg Eslicarbazepine Acetate	2400 mg Eslicarbazepine Acetate	Moxifloxacin
Parameter			
QTcI (msec)	-3.11 (-1.4379)	-2.02 (-0.3192)	8.11 (9.7811)
QTcB (msec)	-1.08 (0.6766)	1.71 (3.4825)	9.60 (11.3482)
QTcF (msec)	-3.54 (-1.8460)	-2.48 (-0.7664)	8.05 (9.7355)

ANCOVA model: change from baseline = baseline period sequence gender treatment

Source: Sponsor's CSR Table 9 on Page 63

#### 4.1.8.3 Safety Analysis

The majority of adverse events overall (86.6%) were considered treatment related. A greater number of subjects had one or more treatment-related adverse event(s) during treatment with the 1200- or 2400-mg doses of eslicarbazepine acetate (59.4% and 84.8%, respectively), compared to 17.7% and 28.1% in the moxifloxacin and placebo groups, respectively. The majority of adverse events were mild or moderate; one subject receiving eslicarbazepine acetate 1200 mg and three subjects receiving eslicarbazepine acetate 2400 mg experienced severe adverse events. No serious adverse events were reported.

Discontinuations due to adverse events were most frequent in subjects receiving eslicarbazepine acetate 2400 mg (8/66 or 12.1%), while 2/64 (3.1%) subjects discontinued while being treated with the eslicarbazepine acetate 1200-mg dose, and 1/64 (1.6%) discontinued from treatment while receiving placebo.

The adverse events most commonly associated with discontinuations were vomiting and rash (three subjects each). Two subjects each discontinued from treatment due to nausea, dizziness, oral paraesthesia, and somnolence; and one subject each discontinued due to abdominal distension, upper abdominal pain, constipation, depressed level of consciousness, headache, pruritus, blurred vision, fatigue, increased blood pressure, back pain, and vasodilation. The majority of the 10 subjects who discontinued due to adverse events did so following treatment with eslicarbazepine acetate 2400 mg. One subject with rash and one subject with rash and pruritus discontinued following treatment with eslicarbazepine acetate 1200 mg.

No deaths occurred during this study.

### 4.1.8.4 Clinical Pharmacology

#### 4.1.8.4.1 Pharmacokinetic Analysis

Eslicarbazepine acetate (BIA2-093) is rapidly and extensively metabolized to eslicarbazepine (BIA2-194), which represents about 95% of total systemic drug exposure to active moieties. (R)-licarbazepine (BIA2-195) and oxcarbazepine are minor active metabolites, corresponding to approximately 5% and 1% of systemic exposure, respectively.

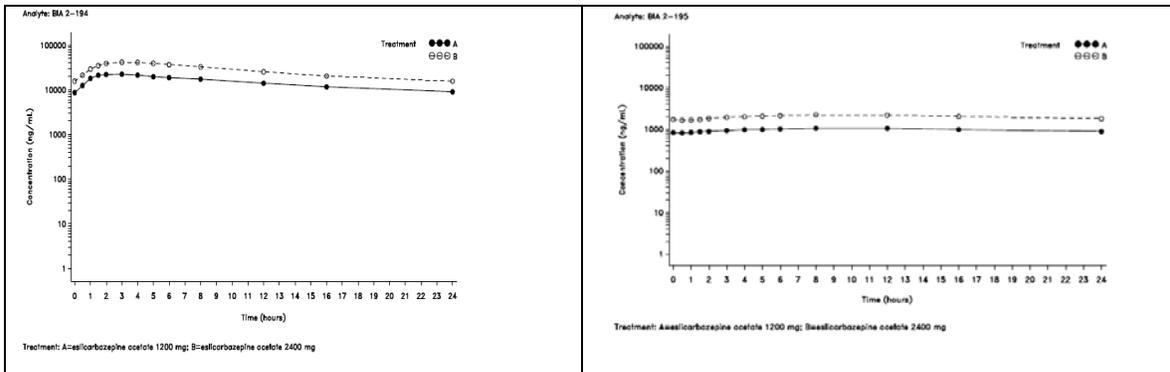
The pharmacokinetics of eslicarbazepine acetate and metabolites appears to be linear after 1200 mg and 2400 mg once daily dose. Summary statistics of the pharmacokinetics of eslicarbazepine are provided in Table 6. The mean C<sub>max</sub> and AUC<sub>∞</sub> values after supratherapeutic dose (2400 mg qd) were 2 times higher, when compared to therapeutic dose (1200 mg qd).

**Table 7: Summary Statistics of Eslicarbazepine acetate and metabolites Pharmacokinetics Parameters in Healthy Volunteers at Day 5**

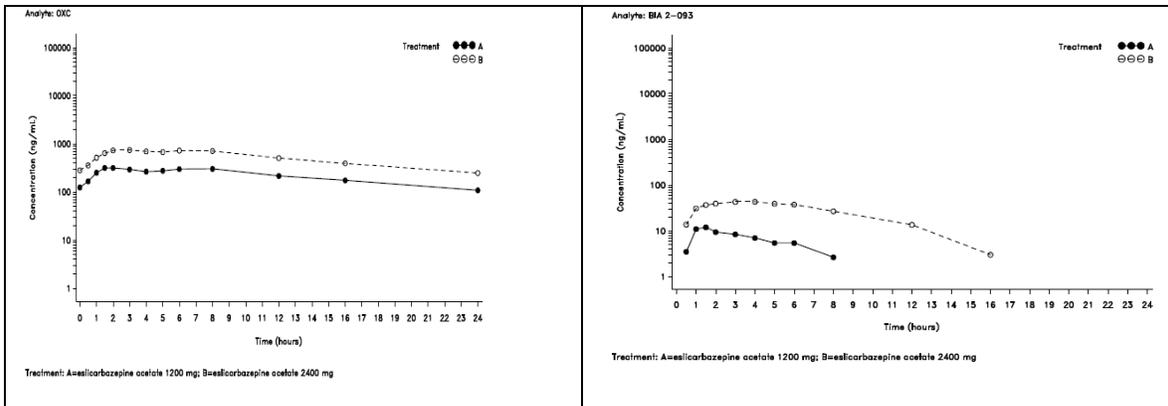
Parameter	Arithmetic Mean (SD)							
	1200 mg Eslicarbazepine Acetate				2400 mg Eslicarbazepine Acetate			
	BIA 2-194	BIA 2-195	Oxcarbazepine	BIA 2-093	BIA 2-194	BIA 2-195	Oxcarbazepine	BIA 2-093
C <sub>max</sub> (µg/mL)	24.71 (5.688) n=61	1.12 (0.278) n=61	0.37 (0.107) n=61	0.02 (0.028) n=61	45.15 (7.959) n=58	2.35 (0.551) n=58	0.89 (0.277) n=58	0.05 (0.0432) n=58
t <sub>max</sub> <sup>a</sup> (hour)	2.10 (1.10-6.10) n=61	8.10 (1.60-16.10) n=61	2.10 (1.10-8.10) n=61	1.35 (0.60-3.10) n=16	3.10 (1.10-5.10) n=58	8.10 (4.10-24.00) n=58	3.10 (1.10-8.10) n=58	2.10 (0.60-6.10) n=36
AUC <sub>0-24</sub> (µg·hr/mL)	351.7 (67.278) n=61	23.36 (5.841) n=61	5.182 (1.3494) n=61	0.8708 (0.25427) n=9	638.4 (113.25) n=58	48.45 (10.769) n=58	12.13 (3.377) n=58	1.159 (0.3148) n=34

<sup>a</sup> = median (range);  
Data Source: Table 15.2.3

**Figure 1: Mean (SD) eslicarbazepine acetate and metabolites Concentration-time Profiles – Day 5: BIA2-194, BIA2-195, Oxcarbazepine and BIA2-093 clockwise.**



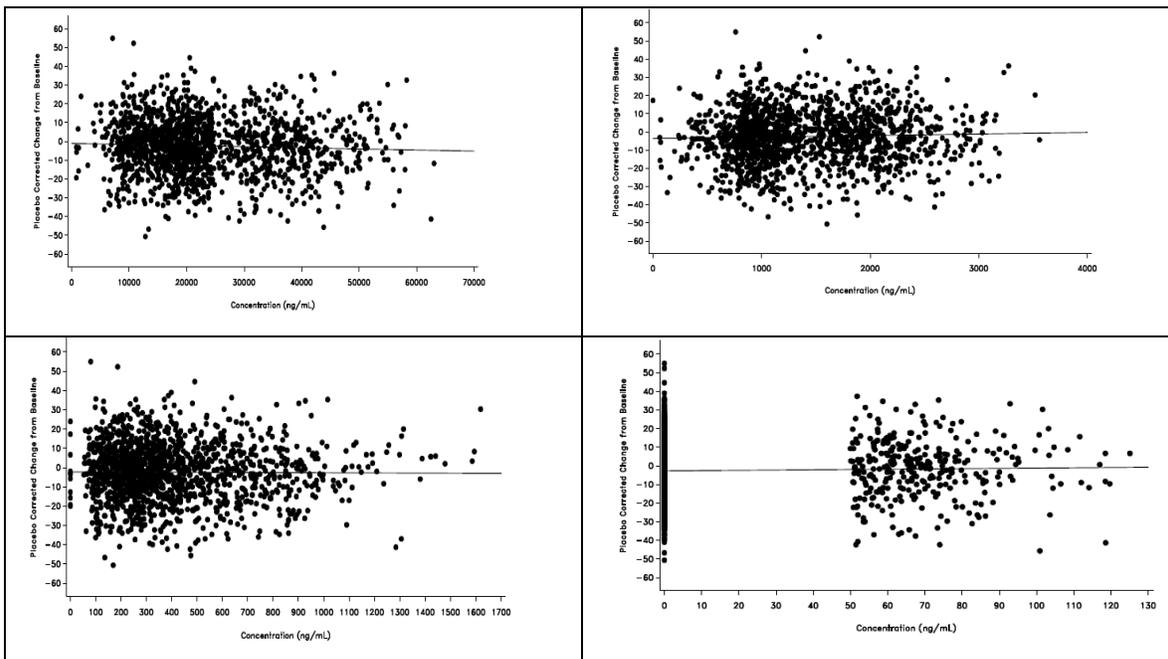
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#### 4.1.8.4.2 Exposure-Response Analysis

Figure 2 presents a scatter plot of the relationship between the time-matched QTcI change from baseline and plasma concentrations on Day 5. The QTcI change from baseline for each subject in the PK population at each of the 12 time points on Day 5 is plotted against each corresponding time-matched BIA 2-194, BIA 2-195, oxcarbazepine and BIA 2-093 plasma concentrations. The solid line shows the estimated regression of concentration against change from baseline in QTcI. The slope of the regression line for eslicarbazepine and metabolite plasma concentrations and mean change in QTcI was essentially 0, suggesting that there is no relationship between eslicarbazepine acetate exposure and QTcI.

**Figure 2: Plot of Placebo-Corrected Time-Matched Change in QTcI .vs. Concentrations at 12 Time Points on Day 5: BIA2-194, BIA2-195, Oxcarbazepine and BIA2-093 clockwise.**



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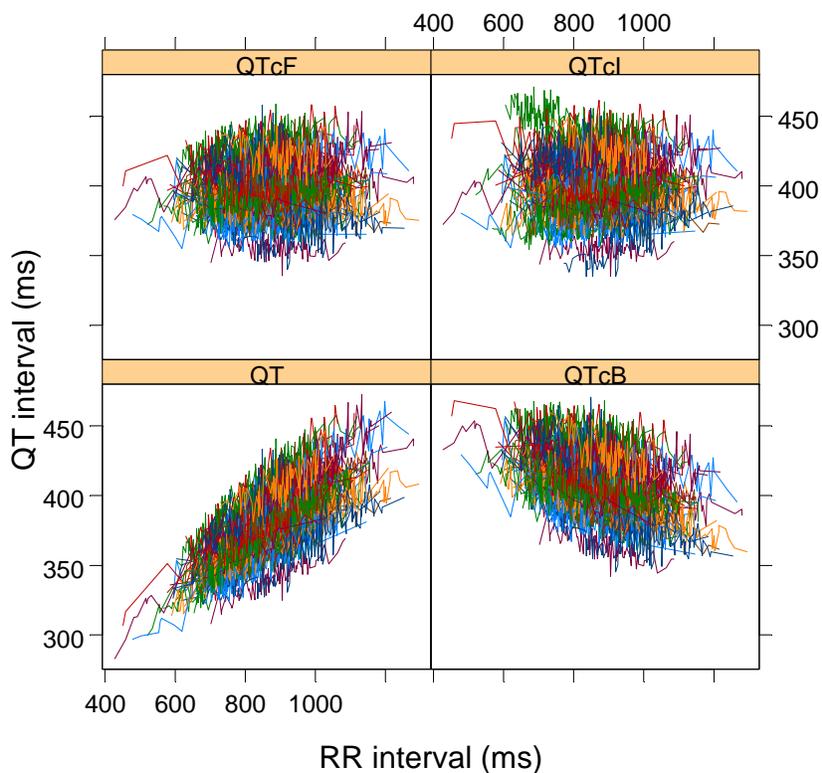
Reviewer's Comments: The sponsor's analysis is acceptable. The reviewer's additional analysis is focused on BIA2-194 (active compound) and is presented in section 5.3.

## 5 REVIEWERS' ASSESSMENT

### 5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The QT-RR interval relationship is presented in Figure 3 together with the Bazett's (QTcB), Fridericia (QTcF), and individual correction (QTcI).

**Figure 3: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)**



We evaluated the appropriateness of the correction methods (QTcF and QTcI). Baseline values were excluded in the validation. Ideally an “unbiased” correction for QT would not be affected by changes in RR intervals. We used the mixed model of the pooled post-dose data of QTcF and QTcI distinguished by an indicator of correction method to evaluate the linear relationships between different correction methods and RR. The model included gender, baseline, RR, correction type (QTcF or QTcI), and the interaction term of RR and correction type. The slopes of QTcF and QTcI versus RR are compared in absolute magnitude as well as statistical significance in difference. As shown in Table 8, it appears that QTcI had smaller absolute slopes than QTcF and therefore is a better correction method for the study data.

We also confirmed this conclusion by another approach, where we used the mean sum of squared slopes (MSSS) from individual regressions of QTc values versus RR as the criterion. The smaller this value is, the better the correction. Based on the results listed in Table 9, it also appears that QTcI is the best correction method. Therefore, this statistical reviewer used QTcI for the primary statistical analysis. This is consistent with the sponsor’s choice of QTcI for their primary analysis.

**Table 8: Comparison of QTcF and QTcI Using the Mixed Model**

Treatment Group	Slope of QTcF	Slope of QTcI	p_value (difference)
All	0.0170	-0.0073	0.0000
Eslicarbazepine Acetate 1200 mg	0.0118	-0.0158	0.0000
Eslicarbazepine Acetate 2400 mg	-0.0127	0.0097	0.0006
Moxifloxacin 400 mg	0.0194	-0.0156	0.0000
Placebo	0.0074	-0.0120	0.0002

**Table 9: 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
All	64	0.0070	64	0.0031	64	0.0028
Eslicarbazepine Acetate 1200 mg	61	0.0116	61	0.0032	61	0.0040
Eslicarbazepine Acetate 2400 mg	58	0.0106	58	0.0022	58	0.0025
Moxifloxacin 400 mg	61	0.0063	61	0.0026	61	0.0022
Placebo	64	0.0377	64	0.0316	64	0.0352

## 5.2 STATISTICAL ASSESSMENTS

### 5.2.1 QTc Analysis

#### 5.2.1.1 The Primary Analysis for Eslicarbazepine Acetate and Assay Sensitivity

The statistical reviewer used mixed model to analyze the  $\Delta$ QTcI effect. The model included TIME, SEQUENCE, and PERIOD as fixed effects and SUBJECT as a random effect. The model also included the time-matched baseline and gender as covariates. The analysis results are presented in Table 10. The largest upper bounds of the two-sided 90% CI for the mean difference between eslicarbazepine acetate 1200 mg and placebo, and between eslicarbazepine acetate 2400 mg and placebo were 3.9 ms and 4.1 ms, respectively.

For the moxifloxacin group, the largest lower bound of the unadjusted 90% confidence interval is 9.5 ms. By considering Bonferroni multiple endpoint adjustment, the largest

lower bound also exceeds 5 ms, which indicates that an at least 5 ms QTcI effect due to moxifloxacin can be detected from the study.

**Table 10: Analysis Results of  $\Delta$ QTcI and  $\Delta\Delta$ QTcI**

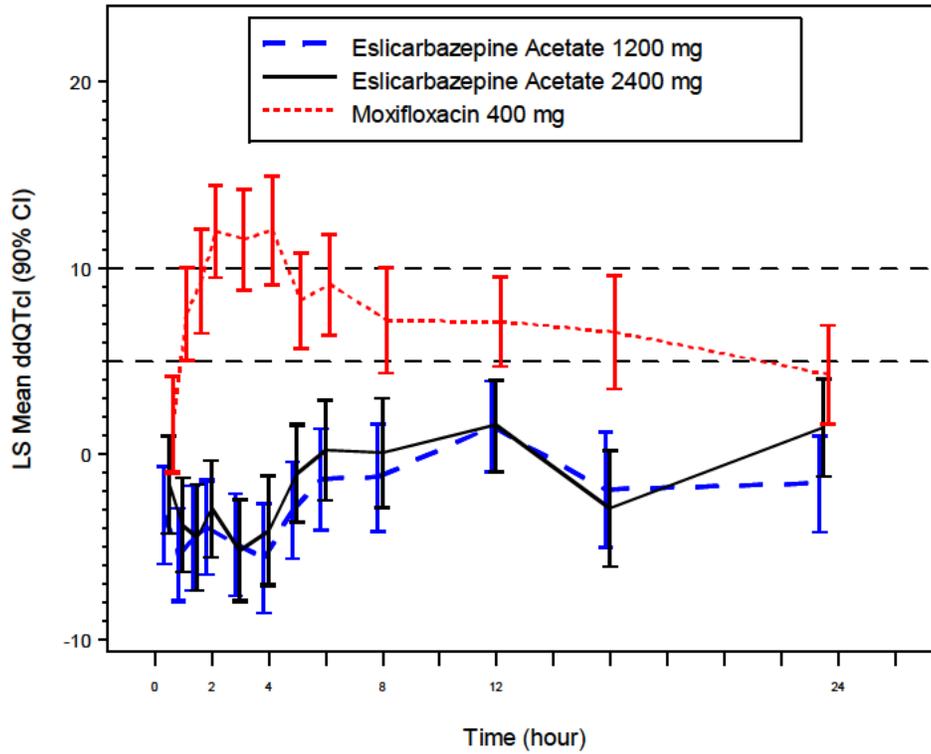
Time (hrs)	Placebo	Eslicarbazepine Acetate 1200 mg			Eslicarbazepine Acetate 2400 mg			Moxifloxacin 400 mg		
	$\Delta$ QTcI	$\Delta$ QTcI	$\Delta\Delta$ QTcI		$\Delta$ QTcI	$\Delta\Delta$ QTcI		$\Delta$ QTcI	$\Delta\Delta$ QTcI	
	LS Mean	LS Mean	Diff LS Mean	90% CI	LS Mean	Diff LS Mean	90% CI	LS Mean	Diff LS Mean	90% CI
0.5	-4.8	-8.0	-3.3	(-5.9, -0.7)	-6.4	-1.7	(-4.3, 1.0)	-3.2	1.6	(-1.0, 4.2)
1	-4.2	-9.6	-5.5	(-8.0, -2.9)	-8.0	-3.8	(-6.4, -1.3)	3.4	7.6	(5.1, 10.0)
1.5	-4.4	-9.0	-4.5	(-7.4, -1.7)	-8.9	-4.5	(-7.3, -1.6)	4.9	9.3	(6.5, 12.1)
2	-5.6	-9.5	-4.0	(-6.5, -1.4)	-8.5	-3.0	(-5.5, -0.4)	6.4	12.0*	(9.5, 14.5)
3	-3.5	-8.4	-4.9	(-7.6, -2.2)	-8.7	-5.2	(-7.9, -2.4)	8.1	11.5	(8.8, 14.3)
4	-2.4	-8.0	-5.6	(-8.5, -2.6)	-6.5	-4.1	(-7.1, -1.2)	9.7	12.0	(9.1, 15.0)
5	-1.0	-4.0	-3.0	(-5.6, -0.5)	-2.0	-1.0	(-3.7, 1.6)	7.3	8.3	(5.7, 10.9)
6	-3.3	-4.7	-1.4	(-4.1, 1.3)	-3.1	0.2	(-2.5, 2.9)	5.8	9.1	(6.4, 11.8)
8	-1.7	-2.9	-1.2	(-4.1, 1.7)	-1.6	0.1	(-2.8, 3.0)	5.5	7.2	(4.3, 10.1)
12	-1.4	0.0	1.5	(-1.0, 3.9)	0.1	1.5	(-0.9, 4.0)	5.7	7.1	(4.7, 9.6)
16	-1.9	-3.8	-1.9	(-5.0, 1.2)	-4.8	-2.9	(-6.0, 0.2)	4.7	6.6	(3.5, 9.7)
23.5	-1.8	-3.4	-1.6	(-4.2, 1.0)	-0.4	1.4	(-1.2, 4.1)	2.4	4.3	(1.7, 6.9)

\*The lower bound of the 90% CI is 8.3 ms after Bonferroni adjustment for 6 time points.

### 5.2.1.2 Graph of $\Delta\Delta$ QTcI Over Time

The following figure displays the time profile of  $\Delta\Delta$ QTcI for different treatment groups.

**Figure 4: Mean and 90% CI  $\Delta\Delta$ QTcI Timecourse**



### 5.2.1.3 Categorical Analysis

Table 11 and Table 12 present the categorical analysis results for the absolute QTcI and  $\Delta$ QTcI, respectively. There were no subjects with QTcI above 480 ms. Nor were there any subjects with  $\Delta$ QTcI above 60 ms.

**Table 11: Table 12: Categorical Analysis for QTcI**

Treatment Group	N	QTcI $\leq$ 450 ms	450 ms $<$ QTcI $\leq$ 480 ms
Baseline	67	62 (92.5%)	5 (7.5%)
Eslicarbazepine Acetate 1200 mg	61	59 (96.7%)	2 (3.3%)
Eslicarbazepine Acetate 2400 mg	58	57 (98.3%)	1 (1.7%)
Moxifloxacin 400 mg	61	55 (90.2%)	6 (9.8%)
Placebo	64	60 (93.8%)	4 (6.3%)

**Table 13: Categorical Analysis of  $\Delta$ QTcI**

Treatment Group	N	$\Delta$ QTcI $\leq 30$ ms	$30$ ms $< \Delta$ QTcI $\leq 60$ ms
Eslicarbazepine Acetate 1200 mg	61	60 (98.4%)	1 (1.6%)
Eslicarbazepine Acetate 2400 mg	58	56 (96.6%)	2 (3.4%)
Moxifloxacin 400 mg	61	55 (90.2%)	6 (9.8%)
Placebo	64	60 (93.8%)	4 (6.3%)

**5.2.2 PR Analysis**

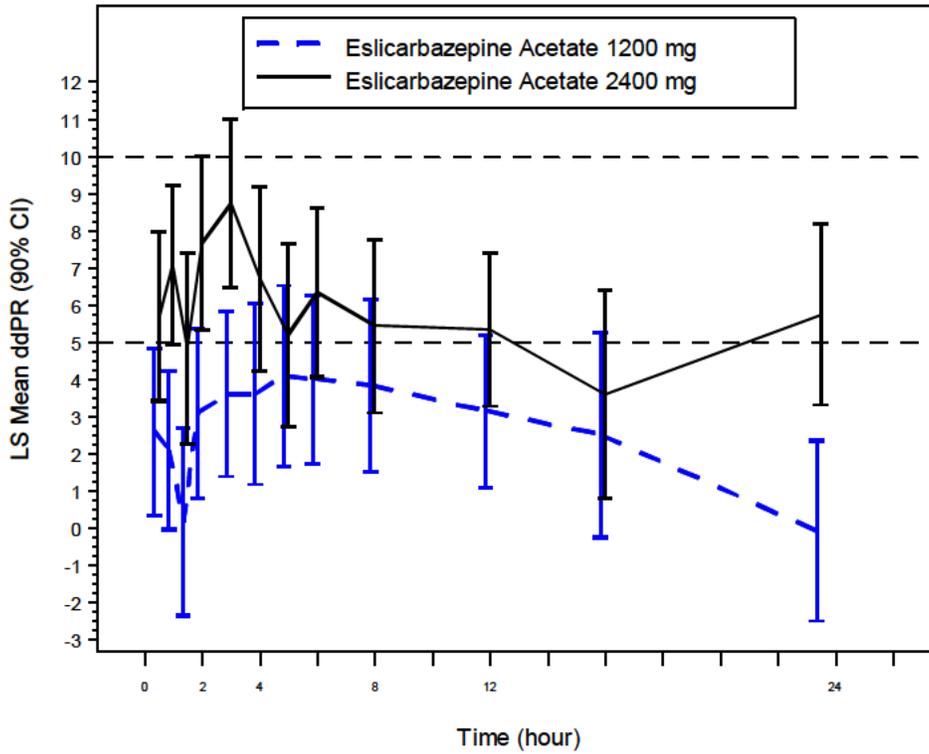
The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 14 and Figure 5. The largest upper limits of 90% CI for the PR mean differences between eslicarbazepine acetate 1200 mg and placebo, and between eslicarbazepine acetate 2400 mg and placebo are 6.5 ms and 11.0 ms, respectively.

The outlier analysis results for PR are presented in Table 15. A listing of the subjects with PR intervals of 200 ms or above post the eslicarbazepine acetate treatment is given in Table 14.

**Table 14: Analysis Results of  $\Delta$ PR and  $\Delta\Delta$ PR**

Time (hrs)	Placebo	Eslicarbazepine Acetate 1200 mg			Eslicarbazepine Acetate 2400 mg		
	$\Delta$ PR	$\Delta$ PR	$\Delta\Delta$ PR		$\Delta$ PR	$\Delta\Delta$ PR	
	LS Mean	LS Mean	Diff LS Mean	90% CI	LS Mean	Diff LS Mean	90% CI
0.5	0.9	3.5	2.6	(0.3, 4.9)	6.6	5.7	(3.4, 8.0)
1	2.1	4.2	2.1	(-0.0, 4.2)	9.2	7.1	(4.9, 9.2)
1.5	3.4	3.6	0.2	(-2.4, 2.7)	8.3	4.9	(2.3, 7.4)
2	2.0	5.1	3.1	(0.8, 5.4)	9.6	7.7	(5.3, 10.0)
3	2.2	5.8	3.6	(1.4, 5.8)	10.9	8.7	(6.5, 11.0)
4	2.3	5.9	3.6	(1.2, 6.1)	9.0	6.7	(4.2, 9.2)
5	2.2	6.3	4.1	(1.7, 6.5)	7.4	5.2	(2.7, 7.7)
6	2.2	6.2	4.0	(1.8, 6.3)	8.6	6.3	(4.0, 8.6)
8	1.9	5.7	3.9	(1.5, 6.2)	7.3	5.4	(3.1, 7.8)
12	3.8	6.9	3.2	(1.1, 5.2)	9.2	5.4	(3.3, 7.4)
16	0.8	3.3	2.5	(-0.3, 5.3)	4.4	3.6	(0.8, 6.4)
23.5	1.2	1.1	-0.1	(-2.5, 2.3)	7.0	5.8	(3.3, 8.2)

**Figure 5: Mean and 90% CI  $\Delta\Delta$ PR Timecourse**



**Table 15: Categorical Analysis for PR**

Treatment Group	N	PR < 200 ms	PR $\geq$ 200 ms
Baseline	67	65 (97.0%)	2 (3.0%)
Eslicarbazepine Acetate 1200 mg	61	58 (95.1%)	3 (4.9%)
Eslicarbazepine Acetate 2400 mg	58	55 (94.8%)	3 (5.2%)
Moxifloxacin 400 mg	61	58 (95.1%)	3 (4.9%)
Placebo	64	61 (95.3%)	3 (4.7%)

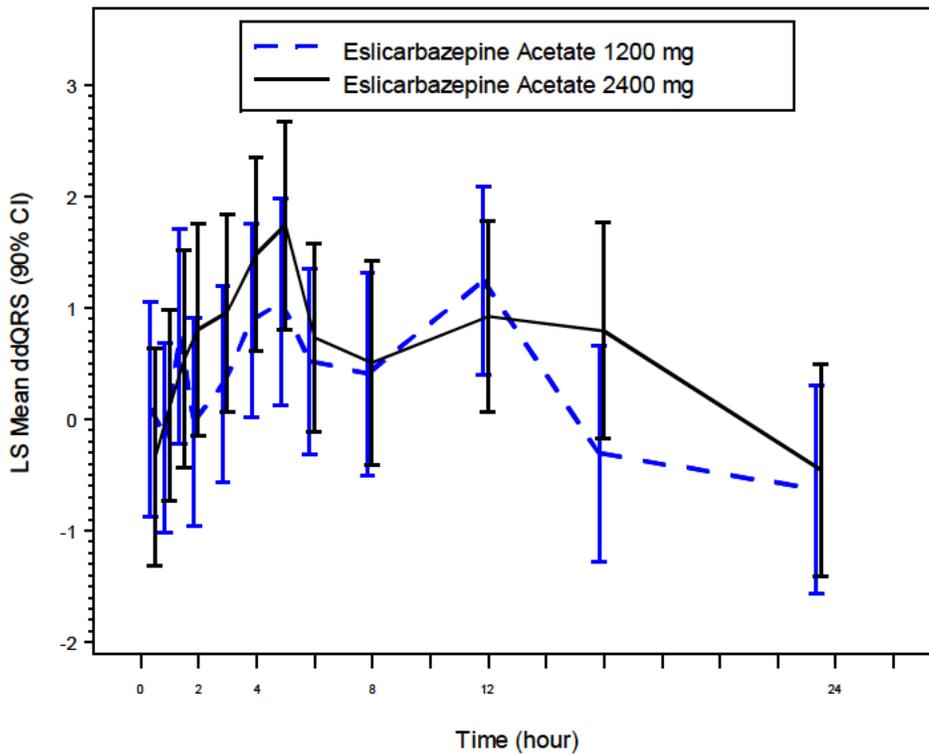
### 5.2.3 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 16 and Figure 6. The largest upper limits of 90% CI for the QRS mean differences between eslicarbazepine acetate 1200 mg and placebo, and between eslicarbazepine acetate 2400 mg and placebo are 2.1 ms and 2.7 ms, respectively. There are no subjects who experienced absolute QRS interval greater than 120 ms in either of the eslicarbazepine acetate groups.

**Table 16: Analysis Results of  $\Delta$ QRS and  $\Delta\Delta$ QRS**

Time (hrs)	Placebo	Eslicarbazepine Acetate 1200 mg			Eslicarbazepine Acetate 2400 mg		
	$\Delta$ QRS	$\Delta$ QRS	$\Delta\Delta$ QRS		$\Delta$ QRS	$\Delta\Delta$ QRS	
	LS Mean	LS Mean	Diff LS Mean	90% CI	LS Mean	Diff LS Mean	90% CI
0.5	0.8	0.9	0.1	(-0.9, 1.1)	0.5	-0.3	(-1.3, 0.6)
1	0.8	0.7	-0.2	(-1.0, 0.7)	1.0	0.1	(-0.7, 1.0)
1.5	0.5	1.2	0.8	(-0.2, 1.7)	1.0	0.5	(-0.4, 1.5)
2	0.8	0.8	-0.0	(-1.0, 0.9)	1.6	0.8	(-0.1, 1.8)
3	0.7	1.1	0.3	(-0.6, 1.2)	1.7	1.0	(0.1, 1.8)
4	0.1	1.0	0.9	(0.0, 1.8)	1.6	1.5	(0.6, 2.4)
5	-0.0	1.0	1.1	(0.1, 2.0)	1.7	1.7	(0.8, 2.7)
6	0.3	0.9	0.5	(-0.3, 1.4)	1.1	0.7	(-0.1, 1.6)
8	0.4	0.8	0.4	(-0.5, 1.3)	0.9	0.5	(-0.4, 1.4)
12	-0.2	1.1	1.2	(0.4, 2.1)	0.8	0.9	(0.1, 1.8)
16	-0.3	-0.6	-0.3	(-1.3, 0.7)	0.5	0.8	(-0.2, 1.8)
23.5	0.2	-0.5	-0.6	(-1.6, 0.3)	-0.3	-0.5	(-1.4, 0.5)

**Figure 6: Mean and 90% CI  $\Delta\Delta$ QRS Timecourse**

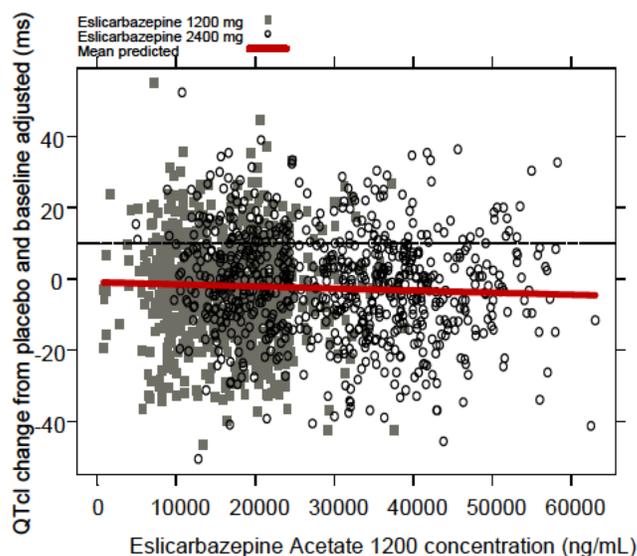


### 5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

Eslicarbazepine acetate (BIA2-093) is rapidly and extensively metabolized to eslicarbazepine (BIA2-194), which represents about 95% of total systemic drug exposure to active moieties. (R)-licarbazepine (BIA2-195) and oxcarbazepine are minor active metabolites, corresponding to approximately 5% and 1% of systemic exposure, respectively. Therefore, the reviewer's analysis is focused on main active compound, BIA2-194.

The relationship between  $\Delta\Delta\text{QTcI}$  and Eslicarbazepine 1200 mg concentrations is visualized in Figure 7 with no evident exposure-response relationship.

**Figure 7:  $\Delta\Delta\text{QTcI}$  vs. Eslicarbazepine concentration**



### 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, 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 96% of the ECGs were annotated in the primary lead II, with less than 0.08 % 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

There were no clinically relevant effects on the PR and QRS intervals. Five subjects had a post-dose PR over 200 ms but none of them experienced a change from baseline > 25%.

## 6 APPENDIX

### 6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

#### Highlights of Clinical Pharmacology: SEP-0002093 (Eslicarbazepine Acetate)

Note to the reviewer: SEP-0002093 is rapidly and extensively biotransformed to eslicarbazepine by first-pass hydrolytic metabolism.

Therapeutic dose	800 mg, 1200 mg po QD (adjunctive to other anti-epileptic drugs)	
Maximum tolerated dose	2400 mg (monotherapy)	
Principal adverse events	<p>The most common treatment emergent adverse events identified in the eslicarbazepine acetate (SEP-0002093) development program were dizziness, somnolence, headache, nausea, diplopia, vomiting and abnormal coordination. A dose response relationship was established for all of these except vomiting.</p> <p>Dose limiting toxicity was established at a dose of 3000 – 3600 mg and was manifest by dizziness, nausea and vomiting (Study 2093-118). In the majority of subjects dizziness occurred within 2 to 4 hours following the first dose, which corresponds to the approximate time peak plasma concentrations were reached. Dizziness generally persisted for more than 24 hours and was accompanied by nausea and vomiting, both of which occurred at about 4 to 6 hours following dosing. Vomiting led to discontinuation of dosing for 50% in both dose groups, therefore, the 2400 mg dose was chosen for Study 2093-116.</p> <p>In Study 2093-116 the most frequently observed adverse events were dizziness, somnolence, nausea and vomiting which led to discontinuation in 10 out of 67 subjects.</p>	
Maximum dose tested	Single Dose	SEP-0002093 3600 mg (Study 2093-118)
	Multiple Dose	SEP-0002093 2400 mg QD x 5 days (Study 2093-116)

Distribution	Vd/F or Vd	Eslicarbazepine Vd/F: Mean (SD) = 87.01 (14.93) L (from CL/F/k <sub>el</sub> ) (Studies 2093-119, 2093-120, and 2093-121)
	% bound	< 40 % binding of eslicarbazepine to plasma proteins over the concentration range of 1-100 µg/mL (Sepracor Document No. 093-525)
Elimination	Route	Renal excretion is the main elimination pathway for eslicarbazepine: 67% in the unchanged form, and 33% after conjugation with glucuronic acid.  Unchanged eslicarbazepine and its glucuronide form corresponds to 92% of drug material excreted in urine. (Study 2093-111)
	Terminal t <sub>1/2</sub>	Mean (% CV) t <sub>1/2</sub> values of eslicarbazepine under steady-state conditions: SEP-0002093 400 mg : 9.5 (18.8) h SEP-0002093 800 mg: 12.3 (22.9) h SEP-0002093 1200 mg: 13.1 (20.1) h (Study 2093-102)
	CL/F or CL	Eslicarbazepine CL/F: Mean (SD) = 3.14 (0.41) L/h (Studies 2093-119, 2093-120, and 2093-121)

Exposures achieved at maximum tested dose	Single Dose	SEP-0002093 3600 mg: Mean (SD) C <sub>max</sub> 54.66 (11.49) µg/mL and AUC <sub>0-∞</sub> 2237 (995.8) µg·hr/mL eslicarbazepine (Study 2093-118)
	Multiple Dose	SEP-0002093 2400 mg : Mean (SD) C <sub>max</sub> 45.15 (7.96) µg/mL and AUC <sub>0-24</sub> 638.4 (113.25) µg·hr/mL eslicarbazepine (Study 2093-116)
Range of linear PK	Linear PK has been documented for eslicarbazepine following administration of SEP-0002093 400 to 1200 mg QD. While statistical assessment has not been performed, PK at the 2400 mg dose level appears to be consistent with this range. (Studies 2093-102, 2093-301 PK sub-study)	
Accumulation at steady state	Mean accumulation ratio (% CV) after 400 mg, 800 mg, and 1200 mg QD x 8 days is 1.36 (28.3), 1.70 (11.4), 1.70 (10.8), respectively. (Study 2093-102)	
Metabolites	Relative systemic exposure to metabolite after SEP-0002093 800 mg: Eslicarbazepine (active): 94% (R)-licarbazepine (active): 5% Oxcarbazepine (active): 1% (Study 2093-111)	
Absorption	Absolute/Relative Bioavailability	N/A
	T <sub>max</sub>	Median (range) eslicarbazepine t <sub>max</sub> values under steady-state conditions: SEP-0002093 400 mg: 3 (0.5-7) h SEP-0002093 800 mg: 2.5 (1-7) h SEP-0002093 1200 mg: 3 (0.5-6) h (Study 2093-102)

Intrinsic Factors	Age*	<p>Mean eslicarbazepine <math>C_{max}</math> was 12.1% lower in elderly; mean <math>AUC_{0-\infty}</math> was &lt;1% higher</p> <p><math>C_{max}</math> and <math>AUC_{0-\infty}</math> were not significantly different between the young and elderly subjects. (Study 2093-105)</p>
	Sex*	<p>Mean eslicarbazepine <math>C_{max}</math> was 10% higher in females; mean <math>AUC_{0-\infty}</math> was 1% higher</p> <p><math>C_{max}</math> and <math>AUC_{0-\infty}</math> were not significantly different between male and female subjects. (Study 2093-105)</p>
	Race	<p>No apparent impact of race upon the pharmacokinetics of eslicarbazepine. (report: <a href="#">EMFFR2007/13/00ESLEPI32</a>)</p>
	Hepatic & Renal Impairment*	<p><u>Hepatic:</u></p> <p>Mean eslicarbazepine <math>C_{max}</math> was 5.3% lower in moderate hepatic impairment; mean <math>AUC_{0-24}</math> was 1.1% lower.</p> <p>Overall, there were no statistically significant pharmacokinetic differences between liver-impaired and healthy subjects. (Study 2093-111)</p> <p><u>Renal:</u></p> <p>Mean eslicarbazepine <math>C_{max}</math> was increased 30.7% in mild, 5.4% in moderate, and 4.8% in severe renal impairment; mean <math>AUC_{0-\infty}</math> was increased 61.1% in mild, 111.1% in moderate, and 153.6% in severe renal impairment</p> <p><math>AUC_{0-\infty}</math> was significantly increased in the renal impairment groups, dose adjustment with creatinine clearance below 50 mL/min is recommended. (Study 2093-112)</p>

Extrinsic Factors	Drug interactions*	<p><u>Lamotrigine:</u></p> <p>Eslicarbazepine mean <math>C_{max}</math> was 4.5% lower; mean <math>AUC_{0-24}</math> was 3.9% lower with concurrent lamotrigine</p> <p>Lamotrigine mean <math>C_{max}</math> was 12.2% lower; mean <math>AUC_{0-24}</math> was 14.4% lower with concurrent eslicarbazepine acetate</p> <p>The 90% CI for <math>C_{max}</math> and <math>AUC_{0-24}</math> were within the bioequivalence acceptable range [80.00%; 125.00%] and, therefore, it was concluded that the bioavailability of eslicarbazepine at steady-state was essentially bioequivalent to eslicarbazepine in the presence of lamotrigine, and the bioavailability of lamotrigine at steady-state is bioequivalent to lamotrigine in the presence of eslicarbazepine. (Study 2093-119)</p> <p><u>Topiramate:</u></p> <p>Eslicarbazepine mean <math>C_{max}</math> was 13.4% lower; mean <math>AUC_{0-24}</math> was 7.2% lower with concurrent topiramate</p> <p>Topiramate mean <math>C_{max}</math> was 19.0% lower; mean <math>AUC_{0-24}</math> was 18.1% lower with concurrent eslicarbazepine acetate</p> <p>The 90% CI for eslicarbazepine <math>C_{max}</math> and <math>AUC_{0-24}</math> fell within the bioequivalence acceptable range. Therefore, the bioavailability of eslicarbazepine at steady-state is essentially bioequivalent to eslicarbazepine in the presence of topiramate.</p> <p>The 90% CI for topiramate <math>AUC_{0-24}</math> were borderline, and those for topiramate <math>C_{max}</math> fell outside the bioequivalence range. Therefore, the bioavailability of topiramate at steady-state is not formally bioequivalent to topiramate in the presence of</p>
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	<p>eslicarbazepine acetate. This modest decrease in exposure to topiramate is not considered to be clinically relevant. (Study 2093-120)</p> <p><u>Phenytoin:</u></p> <p>Eslicarbazepine mean <math>C_{max}</math> was 31.1% lower; mean <math>AUC_{0-24}</math> was 32.4% lower with concurrent phenytoin</p> <p>Phenytoin mean <math>C_{max}</math> was 37.2% higher; mean <math>AUC_{0-24}</math> was 41.8% higher with concurrent eslicarbazepine acetate</p> <p>The 90% CI for <math>C_{max}</math> and <math>AUC_{0-24}</math> fell outside the bioequivalence acceptable range both for eslicarbazepine and phenytoin. Therefore, the bioavailability of eslicarbazepine at steady-state is not bioequivalent to eslicarbazepine in the presence of phenytoin, and the bioavailability of phenytoin at steady-state is not bioequivalent to phenytoin in the presence of eslicarbazepine acetate. The dose of eslicarbazepine acetate may need to be increased and the dose of phenytoin may need to be decreased. (Study 2093-121)</p> <p><u>Digoxin:</u></p> <p>Digoxin mean <math>C_{max}</math> was 18.8% lower; mean <math>AUC_{0-24}</math> was 5.7% lower with concurrent eslicarbazepine acetate</p> <p>The lower bound of the 90% CI for <math>C_{max}</math> fell outside the bioequivalence acceptable range for digoxin, however the 90% CI for <math>AUC_{0-24}</math> was within the acceptable limits. This decrease in digoxin <math>C_{max}</math> in the presence of eslicarbazepine acetate is not expected to be clinically significant. (Study 2093-107)</p> <p><u>Warfarin:</u></p> <p>(S)-warfarin mean <math>C_{max}</math> was 17.6% lower; mean <math>AUC_{0-24}</math> 21.1% lower with</p>
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		<p>concurrent eslicarbazepine acetate (R)-warfarin mean <math>C_{max}</math> was 3.3% lower; mean <math>AUC_{0-24}</math> was &lt;1% lower with concurrent eslicarbazepine acetate</p> <p>The lower bound of the 90% CI for (S)-warfarin <math>C_{max}</math> and <math>AUC_{0-24}</math> fell outside the bioequivalence acceptable range, however the 90% CI for both parameters for (R)-warfarin were within the acceptable range. There was no clinically or statistically significant change in steady-state prothrombin time ratios (INR). (Study 2093-108)</p> <p><u>Oral Contraceptive:</u></p> <p>Levonorgestrel mean <math>C_{max}</math> was 14% lower; mean <math>AUC_{0-\infty}</math> was 38.7% lower with concurrent eslicarbazepine acetate</p> <p>Ethinyl estradiol mean <math>C_{max}</math> was 17.9% lower; mean <math>AUC_{0-\infty}</math> was 40.9% lower with concurrent eslicarbazepine acetate</p> <p>The 90% CI for <math>AUC_{0-\infty}</math> and the lower bound of the 90% CI for <math>C_{max}</math> for levonorgestrel and ethinyl estradiol were not within the bioequivalence acceptable range. An alternative method of non-hormonal contraception is recommended during treatment with eslicarbazepine acetate. (Study 2093-114)</p>
	Food Effects*	<p>Negligible differences (&lt; 1%) were observed for mean eslicarbazepine <math>C_{max}</math> between fasting and fed conditions using a standard meal; mean <math>AUC_{0-\infty}</math> was 3% lower in the fed state.</p> <p>For <math>C_{max}</math> and <math>AUC_{0-\infty}</math>, the 90% CI fell within the pre-defined accepted range [80.00%; 125.00%] and therefore bioequivalence is assumed. (Study 2093-117)</p>

Expected High Clinical Exposure Scenario	<p>No significant inhibition of eslicarbazepine clearance has been observed in the completed DDI studies. At steady-state conditions for SEP-0002093 1200 mg, eslicarbazepine mean (SD) <math>AUC_{(0-24)} = 351.7 (67.28) \mu\text{g}\cdot\text{h}/\text{mL}</math> and mean (SD) <math>C_{max} = 24.71 (5.69) \mu\text{g}/\text{mL}</math>. For example, if drug clearance were to decrease by 50%, resulting mean plasma eslicarbazepine concentrations (<math>AUC_{0-24}</math> approximately 703 <math>\mu\text{g}\cdot\text{h}/\text{mL}</math> and <math>C_{max}</math> approximately 49 <math>\mu\text{g}/\text{mL}</math>) are anticipated to be less than those observed in the subject with the highest concentrations at the 2400 mg dose level (<math>AUC_{(0-24)} = 989.21 \mu\text{g}\cdot\text{h}/\text{mL}</math>, <math>C_{max} = 63.04 \mu\text{g}/\text{mL}</math>). (Study 2093-116)</p>
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\*Presented as % difference based on group means rather than individual data

## 6.2 TABLE OF STUDY ASSESSMENTS

Table 2 Study Assessments and Procedures

STUDY PHASE	Screen	Treatment Periods 1, 2, 3, and 4									
		DAY	-21	-2	-1	1	2	3	4	5	6
Medical History	X										
Informed Consent	X										
Assess Eligibility	X										
Physical Examination	X	X (e)									X(e)(f)
Safety 12-lead ECG	X								X (b)		
Clinical Lab Tests	X	X									X
Vital Signs	X				X (g)						
Serology	X										
Body Weight	X										
Serum Pregnancy Test	X	X									
Urine Drug Screen	X	X									
Clinic Admission		X									
Randomization (a)				X							
Medication Dose					X (h)	X (h)	X (h)	X (h)	X		
Plasma Samples									X (c)		
24-hour Holter				X (d)					X (d)		
Assessment of AEs		X	X	X	X	X	X	X	X	X	X
Clinic Discharge											X

a. Period 1 only  
b. 2 hours post dose administration  
c. Plasma sample times: -30 (pre-dose) 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, and 24 hours post-dose.  
d. Holter applied 30 minutes prior to scheduled dose. QT interval determinations made in triplicate at -30 (pre-dose) 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, and 23.5 hours post-dose  
e. Brief physical examination  
f. Period 4 or early termination only  
g. Routine vital signs, including pulse rate, respiration, blood pressure, and temperature were obtained in conjunction with the physical examination at screening, prior to dosing and at 2 hours following dosing on Days 1 to 5, and prior to clinic discharge on Day 6 of each treatment period.  
h. During the moxifloxacin period, placebo administered on Days 1 to 4 and 400 mg moxifloxacin administered on Day 5

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22416	ORIG-1	SEPRACOR INC	SEP-0002093 ESLICARBAZEPINE ACETATE

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/s/

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