CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202810Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template for Oxcarbazepine ER
PMR # 1938-1

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

PMR/PMC Description: The Sponsor is to develop an age appropriate extended release formulation and perform a prospective, randomized, controlled, double-blind, efficacy/safety study of oxcarbazepine ER for the adjunctive the treatment of partial onset seizures in children ages one month to < 2 years. The primary efficacy endpoint during the controlled phase will examine seizure frequency based upon Video/EEG data.

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	March 2017
Trial Completion Date:	March 2021
Final Report Submission Date:	September 2021
Other:	

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

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

This is a PREA requirement. A waiver has been given for children under 1 month due to the impractical nature of studying a population that is very small in number. A deferral has been granted for those patients ages 1 month to < 6 years of age. It is appropriate for a PMR because the drug is about to be approved for children 6 years and older and adults, and the present formulation cannot be safely swallowed by children under 6 years of age. Therefore an age appropriate formulation must be developed and appropriate studies be performed. This study examines patients 1 month to 2 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 Oxcarbazepine ER in the adjunctive the treatment of partial onset seizures in the ages 1 month < 2 years.

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

- **Which regulation?**

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

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

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

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

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

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

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

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

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

Deferred pediatric trial under PREA: A prospective, randomized, controlled, double-blind, efficacy/safety study of oxcarbazepine ER for the adjunctive the treatment of partial onset seizures in children ages one month to < 2 years. The primary efficacy endpoint during the controlled phase will examine seizure frequency based upon Video/EEG data.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

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

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

Agreed upon:

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

☐ Other

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

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

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

_____
(signature line for BLAs)

PMR/PMC Development Template for Oxcarbazepine ER
PMR # 1938-2

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

PMR/PMC Description: The Sponsor is to develop an age appropriate extended release formulation and perform a prospective, randomized, controlled, double-blind, efficacy/safety study of oxcarbazepine ER for the adjunctive the treatment of partial onset seizures in children ages 2 to < 6 years. The primary efficacy endpoint during the controlled phase will examine seizure frequency based upon diary data.

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	March 2017
Study/Clinical trial Completion Date:	March 2021
Final Report Submission Date:	September 2021
Other:	

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

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

This is a PREA requirement. A waiver has been given for children under 1 month due to the impractical nature of studying a population that is very small in number. A deferral has been granted for those patients ages 1 month to < 6 years of age. It is appropriate for a PMR because the drug is about to be approved for children 6 years and older and adults, and the present formulation cannot be safely swallowed by children under 6 years of age. Therefore an age appropriate formulation must be developed and appropriate studies be performed. This study examines patients 2 to < 6 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 oxcarbazepine ER in the adjunctive the treatment of partial onset seizures in the ages to 2 to < 6 years.

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

- **Which regulation?**

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

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

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

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

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

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

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

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

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

Deferred pediatric trial under PREA: A prospective, randomized, controlled, double-blind, efficacy/safety study of oxcarbazepine ER for the adjunctive the treatment of partial onset seizures in children ages 2 to < 6 years. The primary efficacy endpoint during the controlled phase will examine seizure frequency based upon diary data.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

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

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

Agreed upon:

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

☐ Other

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

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

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

_____
(signature line for BLAs)

PMR/PMC Development Template for Oxtellar XR
PMR # 1938-4

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

PMR/PMC Description: A clinical trial to examine pharmacokinetics and tolerability in children ages 1 month to 6 months using an age appropriate extended release oxcarbazepine formulation.

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	June 2015
Study/Clinical trial Completion Date:	June 2016
Final Report Submission Date:	December 2016
Other:	

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

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

This is a PREA study. The new formulation (extended-release oxcarbazepine), is unsuitable for pediatric patients less than 4 years of age. Therefore, an age appropriate extended release formulation is being developed for evaluation in children ages 1 month to 6 months.

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 characterize the pharmacokinetics and tolerability of an age appropriate extended release formulation of oxcarbazepine in children ages 1 month to 6 months. This information will inform dosing for the pivotal efficacy/safety trial in the specific age groups.

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 clinical trial to examine pharmacokinetics and tolerability in children, ages 1 month to 6 months, using an age appropriate extended release oxcarbazepine formulation.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

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

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

Agreed upon:

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

☐ Other

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

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

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

_____
(signature line for BLAs)

PMR/PMC Development Template for Oxtellar XR
PMR # 1938-3

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

PMR/PMC Description: A clinical trial to examine pharmacokinetics and tolerability in children ages 6 months to 4 years, using an age appropriate extended release oxcarbazepine formulation.

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	June 2015
Study/Clinical trial Completion Date:	June 2016
Final Report Submission Date:	December 2016
Other:	

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

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

This is a PREA study. The new formulation (extended-release oxcarbazepine), is unsuitable for pediatric patients less than 4 years of age. Therefore, an age appropriate extended release formulation is being developed for evaluation in children 6 months to 4 years of age.

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 characterize the pharmacokinetics and tolerability of an age appropriate extended release formulation of oxcarbazepine in children age 6 months to 4 years. This acquired information will inform dosing for the pivotal efficacy/safety trial in the specific age groups.

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 clinical trial to examine pharmacokinetics and tolerability in children ages 6 months to 4 years, using an age appropriate extended release oxcarbazepine formulation.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

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

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

Agreed upon:

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

☐ Other

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

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

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

_____
(signature line for BLAs)

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

/s/

SALLY U YASUDA
10/19/2012

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

Product Title	**OXTELLAR XR (oxcarbazepine) extended-release tablets, for oral use**
Applicant	Supernus
Application/Supplement Number	NDA 202810-S-1
Type of Application	Original NDA
Indication	Adjunctive therapy of partial seizures in adults and children 6 to 17 years old
Established Pharmacologic Class[1]	Antiepileptic drug (AED)
Office/Division	ODEI/DNP
Division Project Manager	Stephanie Parncutt
Date FDA Received Application	December 19, 2011
Goal Date	October 19, 2012
Date PI Received by SEALD	October 18, 2012
SEALD Review Date	October 18, 2012
SEALD Labeling Reviewer	Eric Brodsky
SEALD Division Director	Laurie Burke

PI = prescribing information

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

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

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

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

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

Highlights (HL)

GENERAL FORMAT

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

Comment:

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

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

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

Comment:

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

Comment: *Horizontal line should be extended for the headings in HL.*

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

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

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

Comment:

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

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

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: *The proprietary name should be in UPPER-CASE.*

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.

Comment:

Adverse Reactions

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

Comment:

Patient Counseling Information Statement

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

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

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

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

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

Comment:

Revision Date

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

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

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

Comment:

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

Comment:

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

Comment:

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:

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: *Move this statement to end of TOC.*

Full Prescribing Information (FPI)

GENERAL FORMAT

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

Comment:

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

Comment:

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

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

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

Comment:

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

Comment:

NO 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: *One cross-reference in Section 8.4 and one in Section 17 are not correct.*

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:

"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:

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

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

Comment:

Patient Counseling Information

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

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

Comment:

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/s/

ERIC R BRODSKY
10/18/2012

LAURIE B BURKE
10/18/2012

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

Label and Labeling Memorandum

Date:	October 18, 2012
Reviewer:	Loretta Holmes, BSN, PharmD Division of Medication Error Prevention and Analysis
Team Leader:	Irene Z. Chan, PharmD, BCPS Division of Medication Error Prevention and Analysis
Drug Name:	Oxtellar XR (Oxcarbazepine) Extended-release Tablets 150 mg, 300 mg, and 600 mg
Application Type/Number:	NDA 202810
Applicant:	Supernus Pharmaceuticals, Inc.
OSE RCM #:	2012-80

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

Contents

1 INTRODUCTION

This memorandum evaluates the revised container labels and professional sample blister card labeling for Oxtellar Extended-release Tablets submitted on October 17, 2012 (see Appendix A). The Division of Medication Error Prevention and Analysis (DMEPA) previously reviewed the revised container labels and professional sample blister card labeling under OSE Review 2012-80, dated October 10, 2012.

2 MATERIALS REVIEWED

DMEPA evaluated the following labels and labeling.

- Revised container labels submitted on October 17, 2012
- Revised professional sample blister card labeling submitted on October 17, 2012

Additionally, our recommendations in OSE Review 2012-80, dated October 10, 2012 were reviewed to assess whether the revised labels and labeling adequately address our concerns from a medication error perspective.

3 CONCLUSION AND RECOMMENDATIONS

Review of the revised documents show that the Applicant has implemented all of DMEPA's recommendations under OSE Review 2012-80, dated October 10, 2012 and we find them acceptable. Therefore, we have no further recommendations.

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

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/s/

LORETTA HOLMES
10/18/2012

IRENE Z CHAN
10/18/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

M E M O R A N D U M

Date:	October 17, 2012
From:	Nadia Hejazi, M.D., Medical Officer Pediatric and Maternal Health Staff
Through:	Hari Cheryl Sachs, M.D., Team Leader Lynne Yao, MD, OND Acting Associate Director Pediatric and Maternal Health Staff Office of New Drugs
Document ID Number:	NDA 202819
Sponsor:	Supernus Pharmaceuticals, Inc.
Drug:	Oxtellar XR, formerly (b) (4) (oxcarbazepine extended-release tablets)
Proposed Indication:	Adjunctive therapy for adults and pediatric patients ages 6 to 16 yrs with partial onset seizures
Dosage form and route of administration:	Extended-release (ER) oral tablets 150, 300, (b) (4) and 600 mg
Dosing regimen:	Once daily
PeRC Date:	August 29, 2012
Consult Question:	The Division of Neurology is requesting PMHS assistance with PeRC review preparation.

PMHS worked with DNP in preparing paperwork for the review of the pediatric plan by the Pediatric Review Committee (PeRC) which took place on August 29, 2012. DNP asked for input on the appropriate age group for which an age-appropriate formulation would be required. PeRC recommended that an age-appropriate formulation be developed for patients less than 6 years of age who would be unable to swallow a tablet. (See Appendix 1 for agreed upon PREA PMR's as of October 16, 2012).

The PeRC agreed with the Division's plan to waive the required studies under PREA in pediatric patients less than 1 month because studies are impossible or highly impractical. Studies will be deferred in patients 2 to < 6 years for the development of an age appropriate formulation. If the age-appropriate formulation is not bioequivalent then the sponsor will need to conduct safety and efficacy studies in this age group.

This extended-release product will be labeled for use in pediatric patients 6 years and older based on extrapolation of efficacy from adults. Extrapolation is supported by PK studies in pediatric patients for the extended and immediate release formulations, in addition to pediatric efficacy data from the immediate release formulation. PeRC agreed with the plan.

PMHS also participated in labeling meetings for oxcarbazepine extended release and the input provided is reflected in the approved labeling, including Section 8.4 Pediatric Use. Please refer to final labeling negotiated with the sponsor for specific details.

Appendix 1: PREA PMR's

1. A clinical trial to examine pharmacokinetics and tolerability in children ages 1 month to 6 months using an [redacted] (b) (4) oxcarbazepine.

Final Protocol Submission: June 30, 2015
Study/Trial Completion: June 30, 2016
Final Report Submission: December 31, 2016

2. A clinical trial to examine pharmacokinetics and tolerability in children ages 6 months to 4 years using an oxcarbazepine [redacted] (b) (4) formulation.

Final Protocol Submission: June 30, 2015
Study/Trial Completion: June 30, 2016
Final Report Submission: December 31, 2016

3. Deferred pediatric trial under PREA: A prospective, randomized, controlled, double-blind, efficacy/safety study of oxcarbazepine ER for the adjunctive treatment of partial onset seizures in children ages 2 to <6 years. The primary efficacy endpoint during the controlled phase will examine seizure frequency based upon diary data.

Final Protocol Submission: March 31, 2017
Study/Trial Completion: March 31, 2021
Final Report Submission: September 30, 2021

4. Deferred pediatric trial under PREA: A prospective, randomized, controlled, double-blind, efficacy/safety study of Oxcarbazepine ER for the adjunctive the treatment of partial onset seizures in children ages 1 month to < 2 years. The primary efficacy endpoint during the controlled phase will examine seizure frequency based upon Video/EEG data.

Final Protocol Submission: March 31, 2017
Study/Trial Completion: March 31, 2021
Final Report Submission: September 30, 2021

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/s/

HARI C SACHS
10/19/2012

LYNNE P YAO
10/22/2012

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

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

Memorandum

Date: October 16, 2012

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

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

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

Mathilda Fienkeng, PharmD
Acting Team Leader
DPDP

Subject: OPDP's comment for NDA 202810
Tradename® (oxcarbazepine) extended release tablets

Background

Thank you for the opportunity to review the proposed Prescribing Information (PI) for Tradename® (oxcarbazepine) extended release tablets (FDA dated version 10/15/2012). Please see attached PI with our comments incorporated therein. If you have any questions, please contact Quynh-Van Tran at (301) 796-0185 or Quynh-Van.Tran@fda.hhs.gov.

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/s/

QUYNH-VAN TRAN
10/16/2012

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

Memorandum

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

Date: October 11, 2012

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

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

Subject: NDA 202810
DCDP Comments for draft MG for TRADENAME (oxcarbazepine) extended-release tablets for oral administration

DCDP has reviewed the proposed Medication Guide (MG) for TRADENAME (oxcarbazepine) extended-release tablets. We have reviewed DMPP's comments from 10/04/12 and agree with those changes. We have no additional comments at this time.

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

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

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/s/

MEETA N PATEL
10/18/2012

505(b)(2) ASSESSMENT

Application Information		
NDA # 202810	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: [redacted] (b) (4) (both proposed names are under review) Established/Proper Name: oxcarbazepine Dosage Form: extended-release tablets Strengths: 150, 300 and 600mg		
Applicant: Supernus Pharmaceuticals, Inc.		
Date of Receipt: December 19, 2011		
PDUFA Goal Date: October 19, 2012	Action Goal Date (if different): May try to take Action by September 19, 2012	
Proposed Indication(s): adjunctive therapy for partial seizures in adults and in children ages [redacted] (b) (4) 17.		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

[redacted]

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Trileptal tablets; NDA 021014	Safety and Efficacy Data
Perucca, et al, 2010	**Highlights** and **Section 2. Dosage and Administration** sections of Labeling

*each source of information should be listed on separate rows

(Note for 505(b)(2) Committee: Upon review, the clinical reviewer determined that reliance on Trileptal oral suspension (NDA 21285) was not necessary for approval.

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The principal bridging study for the present application includes a crossover study that examines the similarity in bioavailability (Cmax and AUC), of the Sponsor's ER product administered once daily as compared to the RLD (Trileptal) administered twice daily, during steady state.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☒ NO ☐

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☒ NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

Trileptal tablets; NDA 021014

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☒ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Trileptal tablets	NDA 021014	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").
This application provides for a new formulation.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☐ NO ☐

*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☒ NO ☐
*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES ☒ NO ☐

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):

Trileptal (oxcarbazepine) Tablets, NDA 21-014, referenced in application.
Trileptal (oxcarbazepine) Oral Suspension, NDA 21-285, referenced in application
Multiple generic equivalents to the above products

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): **7037525**

No patents listed ☐ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☒ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☒ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s): ***7037525***

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☒ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☒ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): *March 19, 2012*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☒ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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/s/

STEPHANIE N PARNCUTT
10/10/2012

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

Label, Labeling and Packaging Memorandum

Date:	October 10, 2012
Reviewer:	Loretta Holmes, BSN, PharmD Division of Medication Error Prevention and Analysis
Team Leader:	Irene Z. Chan, PharmD, BCPS Division of Medication Error Prevention and Analysis
Drug Name:	Oxcarbazepine Extended-release Tablets 150 mg, 300 mg, and 600 mg
Application Type/Number:	NDA 202810
Applicant:	Supernus Pharmaceuticals, Inc.
OSE RCM #:	2012-80-1

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

Contents

1 INTRODUCTION

This memorandum evaluates the revised container labels and professional sample blister card labeling for Oxcarbazepine Extended-release Tablets submitted on September 6, 2012 (see Appendix A). The Division of Medication Error Prevention and Analysis (DMEPA) previously reviewed the proposed container labels and professional sample blister card labeling under OSE Review 2012-80, dated July 3, 2012.

2 MATERIALS REVIEWED

DMEPA evaluated the following:

- Revised container labels submitted on September 6, 2012
- Revised professional sample blister card labeling submitted on September 6, 2012

Additionally, our recommendations in OSE Review 2012-80 were reviewed to assess whether the revised labels and labeling adequately address our concerns from a medication error perspective.

3 CONCLUSIONS AND RECOMMENDATIONS

Review of the revised documents show that the Applicant has not adequately implemented all of DMEPA's recommendations under OSE Review 2012-80. Therefore, we have the following recommendations which should be conveyed to the Applicant and implemented prior to approval.

3.1 COMMENTS TO THE APPLICANT

A. Container Labels and Professional Sample Blister Card Labeling

1. The 150 mg statement of strength as well as other statements are in (b) (4) font on a yellow background and are difficult to read due to the lack of sufficient contrast between the two colors. We recommend replacing the (b) (4) font with a black font, outlining the (b) (4) font with black, or using other means to improve contrast.

2. Although we recognize you have attempted to better differentiate your strengths within your product line, we still believe the strengths lack sufficient differentiation. The dark yellow utilized for 150 mg looks similar to the brown color utilized for 600 mg. Additionally, the pinkish-brown utilized for 300 mg also looks similar to the brown color utilized for 600 mg. Although the color used for the 600 mg strength is darker we believe they continue to look too similar. Consider the use of alternate colors for strength differentiation to minimize the risk of selection error.

3. Per the Office of New Drug Quality Assessment, revise the storage statement to read: "Store at 25°C (77°F); excursions 15°C to 30°C (59°F to 86°F) [See

USP controlled room temperature]. Protect from light and moisture." We recommend dashes not be used in order to provide clarity and prevent the potential for misinterpretation of the "-" symbol.

B. Container Labels

1. The Medication Guide (MG) statement is located on a side panel. Relocate this statement to the principal display panel (PDP) and place it under the "Once daily. Swallow whole. Do not cut, crush..." statements. Additionally, use a bold font for the MG statement [see 21 CFR 208.24(d)]. In order to make more space on the PDP to accommodate this revision, consider removing the graphic located above the tradename.

2. Use a bold font for the statement "Once Daily".

C. Professional Sample Blister Card Labeling

1. The statement "Sample Pack" is redundant since the statement "Professional Sample—Not for Sale" is already present on the PDP. Therefore, we recommend you delete the statement "Sample Pack". Additionally, deleting the statement will make room for the statement of strength to be revised as recommended in C.2, below.

2. Remove the asterisk (*) from the statement of strength. Revise the statement of strength to read: "600 mg per tablet". The following format is acceptable:

600 mg
per tablet

3. The MG statement lacks prominence. Use a bold font for the statement, [see 21 CFR 208.24(d)].

4. Add the following statement to the right inside panel: "Take as prescribed by your healthcare provider."

If you have further questions or need clarifications, please contact Sandra Griffith, OSE Regulatory Project Manager, at 301-796-2445.

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/s/

LORETTA HOLMES
10/10/2012

IRENE Z CHAN
10/10/2012

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

PATIENT LABELING REVIEW

Date:	**October 2, 2012**
To:	Russell Katz, MD, Director **Division of Neurology Products (DNP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Team Leader, Patient Labeling Team **Division of Medical Policy Programs (DMPP)** Melissa Hulett, RN, BSN, MSBA Team Leader, Patient Labeling Team **Division of Medical Policy Programs**
From:	Sharon W. Williams, MSN, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs**
Subject:	DMPP Review of Patient Labeling (Medication Guide)
Drug Name (established name):	(oxcarbazepine)
Dosage Form and Route:	Extended-Release Tablets
Application Type/Number:	NDA 202810
Applicant:	Supernus Pharmaceuticals

1 INTRODUCTION

On December 19, 2011, Supernus Pharmaceuticals submitted an original New Drug Application indicated for adjunctive therapy in the treatment of partial seizures in adults and children 6 years to 17 years of age.

On January 9, 2012 the Division of Neurology Products (DNP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide for oxcarbazepine.

2 MATERIAL REVIEWED

- Draft oxcarbazepine Medication Guide (MG) received on December 19, 2011, and received by DMPP on September 28, 2012.
- Draft oxcarbazepine Prescribing Information (PI) received December 19, 2011, revised by the Review Division throughout the current review cycle and received by DMPP on September 28, 2012.
- Approved TRILEPTAL comparator labeling dated March 3, 2011.

3 REVIEW METHODS

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

In our review of the MG we have:

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

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

SHARON W WILLIAMS
10/10/2012

MELISSA I HULETT
10/10/2012

LASHAWN M GRIFFITHS
10/10/2012

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: July 30, 2012

TO: Stephanie Parncutt, MHA, Regulatory Health Project Manager
Steven Dinsmore, D.O., Medical Officer
Division of Neurology Products

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

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

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

SUBJECT: Evaluation of Clinical Inspections

NDA: 202-810

APPLICANT: Supernus Pharmaceuticals, Inc.

DRUG: Oxcarbazepine (b) (4)

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review
INDICATION: Adjunctive therapy in subjects with refractory partial seizures due to epilepsy.
CONSULTATION REQUEST DATE: February 16, 2012
DIVISION ACTION GOAL DATE: October 19, 2012
PDUFA DATE: Not listed (see Action Goal Date)

I. BACKGROUND:

The sponsor, Supernus Pharmaceuticals Inc., submitted a New Drug Application for the use of oral oxcarbazepine (OXC) an antiepileptic drug (AED) as an adjunctive therapy for the treatment of partial seizures in adults. A partial seizure is an episode of abnormal electrical activity that is the product of a lesion in some part of the cerebral cortex. These lesions may have been present since birth or earlier, or they may develop following head trauma, infections, stroke, and certain other conditions. Oxcarbazepine is approved in the U.S. as Trileptal®, an antiepileptic drug indicated in monotherapy or adjunctive therapy for the treatment of partial seizures in adults, as monotherapy in the treatment of partial seizures in children aged 4 years and above, and as adjunctive therapy in children aged 2 years and above. The recommended initial dosage is 600 mg/day, given in divided doses.

The sponsor has developed a once daily (QD) OXC extended-release (XR) product to be equivalent to OXC administered twice daily. The Applicant proposes that reducing the frequency of dosing may increase compliance and providing the drug in an extended-release formulation may alleviate some of the side effects observed with Trileptal®.

The sponsor submitted a new formulation for approval of OXC extended–release as adjunctive therapy at 1200 and 2400 mg QD tablet in subjects with a diagnosis of simple partial seizures and complex partial seizures with or without secondarily generalized seizures. The sponsor is seeking approval of the new formulation by submitting data from a pivotal study Protocol SPN 804 P301 to support approval of the pending application.

Protocol 804P301 entitled "A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Three-Arm, Parallel Group Study to Evaluate the Efficacy and Safety of Oxcarbazepine Extended-Release (OXC XR) (1200 and 2400 mg/day) as Adjunctive Therapy in Subjects with Refractory Partial Seizures due to Epilepsy on up to Three Concomitant Medications" was a multicenter, multiple-dose, randomized (1:1:1 ratio), double-blind, placebo-controlled, three arm, parallel group study in male and female subjects (18 to 65 years of age, inclusive) with refractory partial epilepsy on at least one and up to three concomitant AEDs. The treatment phase was compromised of three periods: Titration, maintenance, and either conversion or tapering.

The primary objective of Study 804P301 was to evaluate the efficacy of adjunctive OXC XR in the treatment of partial seizures in subjects with refractory epilepsy on at least one and up to three other AEDs in adults.

The secondary objectives were: 1) to assess safety and tolerability of adjunctive OXC XR in the treatment of partial seizures of partial origin in subjects with refractory epilepsy on at least one and up to three other AEDs, 2) to assess the effect of OXC XR on the subject's global impression of change in his/her epilepsy status and to assess the effect of OXC XR on quality of life as assessed by the Quality of Life in Epilepsy Inventory-31 (QOLIE-31), and 3) to assess secondarily generalized seizures for each treatment group.

The review division requested inspection of three foreign clinical investigators for the pivotal protocol Study 804P301 because data from the protocol are considered essential to the

approval process. These sites were targeted for inspection due to: 1) enrollment of a relatively large number of subjects, 2) domestic and foreign data show conflicting results pertinent to decision-making, and 3) the need to determine if sites conducted the trial ethically and were in compliance with GCP and local regulations.

II. RESULTS (by protocol/site):

Name of CI, site # and location	Protocol and # of subjects	Inspection Dates	Final Classification
Penko M. Shotekov, M.D. Department of Neurology University Hospital "Alexagrovska" Medical University-Sofia, 1 St Georgi Sofliski Str. 1431 Sofia, Bulgaria Site #701	Protocol 804P301 Number of subjects: 11	5/28-31/ 2012	VAI
Piotr Czapinski, M.D. Niepubliczny Zaklad Opieki Zdrowtnei Centrum Leczenia Padaczki 1 Migreny 25 Kielecka UI Karkov, Poland 31-523 Site# 406	Protocol 804P301 Number of subjects: 11	5/21-25/2012	VAI
Silvio Basic, M.D., Ph.D. Clinical Hospital Neurology Department 6 Gojka Suska Ave Zagreb, Croatia 10001 Site# 510	Protocol 804P301 Number of subjects: 9	5/21-24/2012	NAI

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

Protocol Study 804P301

1. **Penko M. Shotekov, M.D.**
   Sofia, Bulgaria

   a. What Was Inspected: This inspection was performed as a data audit for NDA 202810. At this site, 11 subjects were screened, and 11 subjects were randomized into the study. Six subjects completed the study. Review of the Informed Consent

documents, for all subjects reviewed, verified that subjects signed consent forms prior to enrollment.

An audit of 11 subjects' records was conducted. The medical records reviewed included drug accountability, IRB files, vital signs, patient diaries, Quality of Life Questionnaire, laboratory reports, ECG, inclusion/exclusion criteria, and the use of concomitant medications. There were no deaths at this site. There were no limitations to the inspection.

b. **General observations/commentary:** Comparison of the source documents, case report forms, and data listings noted that these were in agreement. At the conclusion of the inspection, a one item Form FDA 483 was issued to the clinical investigator for failing to report an adverse event. Subject #7 experienced dizziness and nausea, and this adverse event was not reported to the sponsor.

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

c. Assessment of Data Integrity: Although a single regulatory violation was noted at Dr. Shotekov's site, the finding is not likely to significantly affect overall data integrity or subject safety. The data from Dr. Shotekov's site are considered reliable in support of the application.

2. **Piotr Czapinski, M.D.**
Krakow, Poland

a. What Was Inspected: At this site, a total of 11 subjects were screened and 11 subjects were randomized into the study. Eight subjects completed the study, and three subjects were discontinued due to adverse events. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed consent forms prior to enrollment.

The medical records/source data for all subjects were reviewed including drug accountability records, vital signs, laboratory results, IRB records, patient diaries, financial disclosures, laboratory reports, the use of prior and concomitant medications, and inclusion/exclusion criteria. Source documents were compared to CRFs and data listings for primary efficacy endpoints and adverse events listing.

b. General Observations/Commentary: At the conclusion of the inspection, a one item Form FDA 483 was issued to Dr. Czapinski. Our investigation found two transcription errors in the e-CRF entries for the Quality of Life in Epilepsy (QOLIE). For Subject 406001, the source document showed for Visit 2, question 10, "Did you feel tired?" subject answered 3, "A good bit of time", and for Visit 7, question 30, "Mental effects of antiepileptic medication" subject answered 3, "Not very worried". The CRF reported a score of 2, "somewhat worried".

The medical records reviewed were verifiable based on the information available at the site. There were no known limitations to the inspection. There were no deaths and no evidence of under-reporting of adverse events.

c. Assessment of Data Integrity: Although regulatory deviations were noted, the minor discrepancies are not likely to critically impact primary efficacy and safety analyses; therefore, OSI does not consider the effect on overall data integrity to be significant. In general, the data in support of clinical efficacy and safety at Dr. Czapinski's site are considered reliable and appear acceptable in support of the pending application.

3. Silvio Basic, M.D., Ph.D.
Zagreb, Croatia

a. What Was Inspected: At this site, a total 9 subjects were screened, and 9 subjects were randomized into the study. Three subjects were discontinued due to adverse events. Six subjects completed the study and one subject continued on the open label phase of the study. Review of the Informed Consent Documents, for all subjects records reviewed, verified that all subjects signed consent forms prior to enrollment.

The medical records/source documents for 9 subjects were reviewed including drug accountability records, vital signs, IRB files, laboratory test results, patient diaries, Quality of Life Questionnaire, ECG reports, inclusion/exclusion criteria, and use of concomitant medications. Source documents for subjects were compared to case report forms and data listings, to include primary efficacy endpoints and adverse events

b. General Observations/Commentary: At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Basic. The medical records reviewed were found to be in order, organized and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were no known limitations to the inspection.

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

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Three clinical investigator sites were inspected in support of this application. The inspections of Dr. Basic revealed no regulatory violations and the final classification for this inspection is No Action Indicated (NAI). While regulatory violations were identified during the inspections of Drs. Shotekov and Czapinski, the findings are not likely to critically impact primary efficacy and safety analyses; therefore, OSI does not consider the effect on overall data integrity to be significant. The final classification for the inspection of Dr. Shotekov is Voluntary Action Indicated (VAI) and for Dr. Czapinski is also VAI. Overall, the data submitted from these sites are considered acceptable in support of the pending application.

{*See appended electronic signature page}*

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

CONCURRENCE:

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Susan Leibenhaut, M.D.
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/s/

ANTOINE N EL HAGE
08/02/2012

SUSAN LEIBENHAUT
08/02/2012

SUSAN D THOMPSON
08/02/2012

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

Label, Labeling and Packaging Review

Date:	July 3, 2012
Reviewer:	Loretta Holmes, BSN, PharmD Division of Medication Error Prevention and Analysis (DMEPA)
Team Leader:	Irene Z. Chan, PharmD, BCPS Division of Medication Error Prevention and Analysis (DMEPA)
Division Director:	Carol A. Holquist, RPh Division of Medication Error Prevention and Analysis (DMEPA)
Drug Name:	Oxcarbazepine Extended-release Tablets 150 mg, 300 mg, and 600 mg
Application Type/Number:	NDA 202810
Applicant:	Supernus Pharmaceuticals, Inc.
OSE RCM #:	2012-80

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Contents

1 INTRODUCTION

This review evaluates the proposed container labels, blister card labeling, Medication Guide and package insert labeling for Oxcarbazepine Extended-release Tablets (NDA 202810) for areas of vulnerability that could lead to medication errors. If approved, this product will be the first extended-release oxcarbazepine product on the market.

1.1 REGULATORY HISTORY

NDA 202810 for Oxcarbazepine Extended-release Tablets is a 505(b)(2) application. The reference listed drugs are Trileptal tablets (NDA 021014) and Trileptal oral suspension (NDA 021285).

The proposed proprietary name, (b) (4), was reviewed under separate cover (OSE Review # 2012-373).

1.2 PRODUCT INFORMATION

The following product information was provided in the December 19, 2011 submission.

- **Active Ingredient:** Oxcarbazepine
- **Indication of Use:**
  Adults: Adjunctive therapy in the treatment of partial seizures
  Children: Adjunctive therapy in the treatment of partial seizures in children (b) (4) to 17 years of age
- **Route of Administration:** Oral
- **Dosage Form:** Extended-release Tablets
- **Strength:** 150 mg, 300 mg and 600 mg
- **Dose and Frequency of Administration:** See Appendix A
- **How Supplied:** 150 mg, 300 mg and 600 mg strengths in the following packaging configurations: 5-count professional sample blister card and 100-count bottle for commercial distribution
- **Storage:** Store at 25ºC (77ºF); excursions permitted between 15ºC and 30ºC (59ºF to 86ºF)
- **Container and Closure Systems:** The 100-count bottles have (b) (4) closures

2 METHODS AND MATERIALS REVIEWED

This product will be the first marketed extended-release oxcarbazepine, if approved. Using the principals of human factors and Failure Mode and Effects Analysis,[1] along

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

with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted December 19, 2011 (Appendix B)
- Professional Sample Blister Card Labeling submitted December 19, 2011 (Appendix C)
- Professional Sample Blister Card Mockup mailed to the Agency on February 23, 2012 (no image)
- Insert Labeling submitted April 10, 2012 (no image)
- Medication Guide submitted April 10, 2012 (no image)

Additionally, we compared the [redacted] (b) (4) proposed labels and labeling against the currently marketed Trileptal labels (Appendix D) to identify any potential safety issues.

3 MEDICATION ERROR RISK ASSESSMENT

The following section describes the results of our risk assessment of the product design, labels and labeling.

3.1 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

The strengths and dosage form proposed for Oxcarbazepine Extended-release Tablets are reasonable for adults given the proposed indication, dosage and administration of this product. However, the available strengths and dosage form may not adequately meet the needs of the younger pediatric population who may not be able to swallow the extended-release tablets whole or who may require doses that fall in-between the proposed tablet strengths.

DMEPA identified the following deficiencies in the container labels, professional sample blister card, and the insert labeling:

A. Packaging Design of the Professional Sample Blister Card Labeling

The Applicant is proposing a 5-count professional sample blister pack. The number of tablets provided in the 5-count professional sample blister card is inconsistent with the Dosage and Administration section of the Full Prescribing Information, which provides for dose adjustments after one week. [redacted] (b) (4)

An information request was sent to the Applicant regarding their rationale for having a 5-count professional sample for that product instead of a 7-count professional sample, given the recommended increases in dose at weekly intervals during the titration period. In a cover letter received on March 28, 2012, the Applicant clarified that the 5-count professional sample is not intended for titration, but rather as a sample until patients can fill their full prescription at the pharmacy. We find their rationale for having a 5-count blister card reasonable.

B. Container Labels and Professional Sample Blister Card Labeling

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

C. Insert Labeling

- Error-prone symbols are used in the Dosage and Administration section of the insert labeling

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

4 CONCLUSIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase the readability and prominence of important information on the labels to promote the safe use of the product, to mitigate any confusion, and to clarify information. (b) (4)

[redacted]

5 RECOMMENDATIONS

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

A. General Comments for all labels and labeling (150 mg, 300 mg, and 600 mg)

1. The strengths lack sufficient differentiation. All of the labels have a green color block with a blue border on the bottom third of the principal display panel, which increases the look-alike similarity between the different strengths. Delete the green color block and the blue border in order to improve strength differentiation.
2. Ensure the established name has a prominence commensurate with the proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features [21 CFR 201.10(g)(2)].

3. The numerical strength is above its corresponding unit of measure. Relocate the unit of measure so that it is beside the numerical strength (i.e., 150 mg, 300 mg, and 600 mg).

4. The net quantity and "Rx only" statements are too prominent due to the bold font. Debold the font for these statements.

5. The "EXTENDED-RELEASE" in the dosage form is in all uppercase letters, which decreases the readability of the statement. Revise the presentation from upper case to title case (i.e., Extended-release).

6. The 300 mg strength is printed on a (b) (4) background with a brownish font. The 600 mg strength appears to reverse the presentation of the 300 mg strength, leading to the 300 mg and 600 mg strengths having similar colors that are not well differentiated from one another. Additionally, the yellow background color of the 150 mg strength and the (b) (4) background of the 300 mg strength are not sufficiently distinct due to minimal contrast. We recommend choosing different colors for strength differentiation that are distinct within the product line and ensure that they do not overlap with the colors already utilized for strength differentiation within the Trileptal product line.

7. The extended-release tablets overlap in strength with the currently marketed immediate-release strengths. In order to help differentiate the two formulations, place the statement "Once-a-day" or a similar statement on the principle display panel. Additionally, add the statement "Swallow whole, do not cut, crush or chew" to the principle display panel as well.

8. The NDC numbers only contain the first five numbers (i.e., 17772-XXX-XX) and are, therefore, not complete. Include the entire NDC number on all container labels and blister card labeling.

9. The Supernus logo is too prominent as compared to the proprietary name, established name and product strength. Decrease the size of the logo.

10. The storage and handling information states "Store in well-closed container" at XX temperature and "Protect from moisture". These two statements are not in the insert labeling. Ensure the storage statements are consistent between all labels and labeling.

B. Container Labels

1. The side panel contains an oval text box that contains a text description of the tablets contained inside the bottle. This appears to be of limited help in identifying the tablets. Additionally, it is not clear what the word "modified" in the description means. Consider placing an actual photograph of the tablet on the principal display panel in order to help with differentiation. Otherwise, delete these text boxes and text descriptions.

2. There is no Medication Guide statement on the container labels [see 21 CFR 208.24(d)]. We recommend the following language

dependent upon whether the Medication Guide accompanies the product: "Attention Pharmacist: Dispense the accompanying Medication Guide to each patient." Additionally, use a bold font for the statement.

C. Professional Sample Blister Card Labeling

1. There is no Medication Guide statement on the blister card labeling. To the principle display panel, we recommend adding a statement to the physician that each patient is required to receive the medication guide and ensure that one is provided with each sample.
2. Revise the statement of strength to read "Each tablet contains XX mg". This statement may help to prevent patients from confusing all five tablets in the blister card as containing a single dose.
3. There are no instructions on how to remove the tablets from the blister card. Provide brief instructions on the inside panel for how to remove the tablets from the blister card.
4. The panel containing the tablets does not have the proprietary name, and established name. Place this information on the inside right panel.
5. Revise the statement [redacted] (b) (4) to read "Professional Sample Not for Sale".
6. The statement [redacted] (b) (4)

D. Insert Labeling

1. Section 2: Dosage and Administration
   a. The dangerous symbol "/" is used when expressing the daily dose (e.g., 300 mg/day or 600 mg/day). Replace the symbol "/" with the word "per" when referring to the total daily dose (e.g., 600 mg per day). Additionally, remove the symbol "-" and insert the intended meaning. For example, revise "1200-2400 mg/day" to read 1200 mg to 2400 mg per day".
   b. In the section *Patients with Renal Impairment*, the symbol "<" is used (i.e., "<30 mL/min"). Remove the symbol "<" and revise the statement to read "less than 30 mL/min".
   c. The dosage information states "Tradename is administered as a single daily dose taken before food." This statement is confusing and should be clarified because is it not clear whether the product should be taken with meals or on an empty stomach.
2. Section 16: How Supplied/Storage and Handling

   The professional sample blister cards are listed in this section. Professional samples are not for commercial distribution and, therefore,

should not be listed. Delete the professional sample blister card information.

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

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

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/s/

LORETTA HOLMES
07/03/2012

IRENE Z CHAN
07/03/2012

CAROL A HOLQUIST
07/05/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # 202810 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: (b) (4) Established/Proper Name: oxcarbazepine Dosage Form: tablets Strengths: 150mg, 300mg, and 600 mg.		
Applicant: Supernus Pharmaceuticals, Inc. Agent for Applicant (if applicable): Tami Martin, RN, Esq.		
Date of Application: December 19, 2011 Date of Receipt: December 19, 2011 Date clock started after UN:		
PDUFA Goal Date: October 19, 2012	Action Goal Date (if different):	
Filing Date: February 17, 2012	Date of Filing Meeting: February 9, 2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 5		
Proposed indication(s)/Proposed change(s): Adjunctive therapy for partial seizures in adults and in children ages 4-17.		

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

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

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

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): **077417**	

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

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

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		X		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**		X		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs***		X		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:		X		**There is no unexpired exclusivity for this product.** (NDA 021014 and NDA 021285)

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

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

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug***		X		

Designations and Approvals list at: *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm*				

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 3 ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	X			Module 1.3.5.3 Exclusivity Request
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		Confirmed by Martha Heimann on 3/14/12.
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			X	Confirmed by Martha Heimann on 3/14/12.

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

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

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

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

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

Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X			Confirmed by Courtney Suggs on 3/13/12

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

If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?		**The Sponsor has requested a waiver for birth to** (b) (4) **years of age.**		Confirmed by Courtney Suggs on 3/13/12
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***		**No. It will be requested.**		Confirmed by Courtney Suggs on 3/13/12
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***		**No. This will be requested.**		Confirmed by Courtney Suggs on 3/13/12
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		X		Confirmed by Courtney Suggs on 3/13/12
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	X			
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the DCRMSRMP mailbox***		X		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☐ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**

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

Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	X			
Is the PI submitted in PLR format?[4]	X			

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**

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

Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:*** ***PEDS (1/5/12)*** ***PLT (1/9/12*** ***DDMAC (1/9/12)*** ***DSI Clinical (3/1/12)***	X			
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** preIND meeting (6/29/07) EOP2 (5/2/11) ***If yes, distribute minutes before filing meeting***	X			

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** preNDA Preliminary responses (5/18/11) ***If yes, distribute minutes before filing meeting***	X			
Any Special Protocol Assessments (SPAs)? **Date(s):** SPA Meeting (11/23/09) SPA Response (5/6/08) ***If yes, distribute letter and/or relevant minutes before filing meeting***	X			

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 9, 2012

BLA/NDA/Supp #: 202810

PROPRIETARY NAME: (b) (4)

ESTABLISHED/PROPER NAME: oxcarbazepine

DOSAGE FORM/STRENGTH: tablets 105mg, 300mg, and 600mg.

APPLICANT: Supernus Pharmaceuticals, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Adjunctive therapy for partial seizures in adults and in children ages (b) (4) 17.

BACKGROUND:

Supernus Pharmaceuticals, Inc., ("Supernus") is providing an original 505(b)(2) New Drug Application for oxcarbazepine extended-release tablets (NDA 202810). This 505(b)(2) New Drug Application references the Trileptal® New Drug Application 021014 [oxcarbazepine oral tablet (Novartis)] and Trileptal® New Drug Application 021285 [oxcarbazepine oral suspension (Novartis)]. New Drug Application 021014 was approved in January, 2000; NDA 021285 was approved May, 2001. Supernus expects NDA 202810 for oxcarbazepine extended-release tablets to be subjected to a standard regulatory review.

In a Pre-NDA meeting held May 23, 2011, Supernus and the Division of Neurology Products discussed the planned content for this New Drug Application. The key pivotal study for this New Drug Application is Protocol 804P301, titled "*Multicenter, Double-Blind, Randomized, Placebo-Controlled, Three-Arm, Parallel Group Study to Evaluate the Efficacy and Safety of Oxcarbazepine Extended-Release (SPN-804O) (1200 and 2400mg/d) as Adjunctive Therapy in Subjects with Refractory Partial Seizures due to Epilepsy on up to Three Concomitant Antiepileptic Medications.*"

REVIEW TEAM:

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

Clinical	Reviewer:	Steven Dinsmore	Y
	TL:	See CDTL	

Clinical Pharmacology	Reviewer:	Veneeta Tandon	Y
	TL:	Angela Men	Y
Biostatistics	Reviewer:	Ohidul Siddiqui	Y
	TL:	Kun Jin	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Ed Fisher	Y
	TL:	Lois Freed	N
Product Quality (CMC)	Reviewer:	Prafull Shiromani	Y
	TL:	Martha Heimann	Y
Facility Review/Inspection	Reviewer:	Antoine El-Hage	Y
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Loretta Holmes	Y
	TL:	Irene Chan	Y
OSE/DRISK (REMS)	Reviewer:		
	TL:	Kendra Worthy	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:	Yanyan (Jenny) Qin	Y
	TL:		

ONDQA Biopharm	Sandra Suarez	Y
Patient Labeling Team	Sharon Williams, Melissa Hulett	Y
PEDS	Courtney Suggs, Nadia Hejazi	Y
DDMAC	Quynh-Van Tran and Meeta Patel	Y

FILING MEETING DISCUSSION:

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

• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Russell Katz, M.D.

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional):

	Review Classification: ☒ Standard Review ☐ Priority Review
	ACTIONS ITEMS
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	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.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
☐	Other

Stephanie N. Parncutt	March 13, 2012
Regulatory Project Manager	Date
Chief, Project Management Staff	Date

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.

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/s/

STEPHANIE N PARNCUTT
05/17/2012

REGULATORY PROJECT MANAGER
PLR FORMAT LABELING REVIEW

Application: NDA 202810

Name of Drug: (b) (4) (oxcarbazepine) Extended Release tablets

Type of Application: Original NDA: 505(b)(2)

Applicant: Supernus Pharmaceuticals, Inc.

Labeling Reviewed

Submission Date: December 19, 2011

Receipt Date: December 19, 2011

Background and Summary Description

Supernus Pharmaceuticals, Inc. (Supernus) submitted NDA 202810 for oxcarbazepine extended-release tablets (SPN-804O) and proposes the following indication: as adjunctive therapy for partial seizures in patients with epilepsy. NDA 202810 is a 505(b)(2) New Drug Application referencing the Trileptal® New Drug Applications. Supernus wishes to cross reference NDA 21014 for the oral tablet as the primary reference and NDA 21285 for the oral solution, as necessary.

Review

The submitted labeling was reviewed in accordance with the labeling requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" section of this review. Labeling deficiencies are identified in this section with an "X" in the checkbox next to the labeling requirement.

In addition, the following labeling issues were identified:

1. The Patient Counseling Information does not have command language. Instead of "patients should be advised", one can state "Advise patients."

Conclusions/Recommendations

All labeling deficiencies identified in the SRPI section of this review and identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to resubmit

labeling that addresses all identified labeling deficiencies by March 23, 2012. The resubmitted labeling will be used for further labeling discussions.

Stephanie N. Parncutt	2/15/2012
Regulatory Project Manager	Date
Robbin Nighswander	3/6/2012
Chief, Project Management Staff	Date

Selected Requirements for Prescribing Information (SRPI)

This document is a checklist that identifies critical issues during the labeling review. Only identified deficiencies are checked (if nothing is checked then there are no SRPI deficiencies).

Highlights (HL)

- **General comments**

☒ HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.

Comment: HL does not have ½ inch margins on all size and is not in 8 point font.

☒ HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.

Comment: It is difficult to determine if the HL meets the ½ page requirement because it is not in the correct format.

☐ There is no redundancy of information.

☐ If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)

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

☐ All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.

☐ Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.

☐ Section headings are presented in the following order:

• **Highlights Limitation Statement** (required statement)
• **Drug names, dosage form, route of administration, and controlled substance symbol, if applicable** (required information)
• **Initial U.S. Approval** (required information)
• **Boxed Warning** (if applicable)
• **Recent Major Changes** (for a supplement)
• **Indications and Usage** (required information)
• **Dosage and Administration** (required information)
• **Dosage Forms and Strengths** (required information)
• **Contraindications** (required heading – if no contraindications are known, it must state "None")
• **Warnings and Precautions** (required information)
• **Adverse Reactions** (required AR contact reporting statement)
• **Drug Interactions** (optional heading)
• **Use in Specific Populations** (optional heading)
• **Patient Counseling Information Statement** (required statement)

- **Revision Date** (required information)

- **Highlights Limitation Statement**

  ☒ Must be placed at the beginning of HL, **bolded,** and read as follows: "**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: Needs to be bolded.

- **Product Title**

  ☒ Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol

  Comment: Need to include ROA.

- **Initial U.S. Approval**

  ☒ The verbatim statement "Initial U.S. Approval" followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

  Comment: Should not include the month; "January" should be removed.

- **Boxed Warning**

  ☐ All text in the boxed warning is **bolded**.

  ☐ Summary of the warning must not exceed a length of 20 lines.

  ☐ Requires a heading in UPPER-CASE, **bolded** letters containing the word "**WARNING**" and other words to identify the subject of the warning (e.g.,"**WARNING: LIFE-THREATENING ADVERSE REACTIONS**").

  ☐ Must have the verbatim statement "***See full prescribing information for complete boxed warning.***" If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**

  ☒ Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

  Comment: Remove RMC header.

  ☐ The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, "Dosage and Administration, Coronary Stenting (2.2) – 2/2010."

  ☐ For each RMC listed, the corresponding new or modified text in the FPI must be marked

with a vertical line ("margin mark") on the left edge.

☐ A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.

☐ Removal of a section or subsection should be noted. For example, "Dosage and Administration, Coronary Stenting (2.2) ~~ removal 2/2010."

- **Indications and Usage**

☐ If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)]." Identify the established pharmacologic class for the drug at:

http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm.

- **Contraindications**

☐ This section must be included in HL and cannot be omitted. If there are no contraindications, state "None."

☐ All contraindications listed in the FPI must also be listed in HL.

☐ List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.

☐ For drugs with a pregnancy Category X, state "Pregnancy" and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

☒ Only "adverse reactions" as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as "adverse events" or "treatment-emergent adverse events," should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).

Comment: Instead of "adverse experiences" insert "adverse reactions."

☐ For drug products other than vaccines, the verbatim **bolded** statement, "**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**" must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

☒ Must include the verbatim statement: "**See 17 for Patient Counseling Information**" or if the product has FDA-approved patient labeling: "**See 17 for Patient Counseling Information and (insert either "FDA-approved patient labeling" or "Medication Guide")**.

Comment: Remove "FDA-Approved."

- **Revision Date**

  ☐ A placeholder for the revision date, presented as "Revised: MM/YYYY or Month Year," must appear at the end of HL. The revision date is the month/year of application or supplement approval.

Contents: Table of Contents (TOC)

☐ The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.

☐ The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.

☒ All section headings must be in **bold** type, and subsection headings must be indented and not bolded.

Comment: The subsections in the TOC are not indented.

☐ When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:

8.1 Pregnancy

8.3 Nursing Mothers (not 8.2)

8.4 Pediatric Use (not 8.3)

8.5 Geriatric Use (not 8.4)

☐ If a section or subsection 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."

Full Prescribing Information (FPI)

- **General Format**

  ☒ A horizontal line must separate the TOC and FPI.

  Comment: No horizontal line is present between these two parts.

  ☒ The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.

Comment: This needs to be added.

☒ The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

Comments: All section and subsection numbers should not have a trailing period.

- **Boxed Warning**

  ☐ Must have a heading, in UPPER CASE, **bold** type, containing the word "**WARNING**" and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.

  ☐ Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**

  ☐ For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

  ☒ Only "adverse reactions" as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as "adverse events" or "treatment-emergent adverse events," should be avoided.

  Comments: Multiple places do not use the term adverse reaction.

  ☒ For the "Clinical Trials Experience" subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

  Comment: This statement should be in 6.1; not after 6.

  ☒ For the "Postmarketing Experience" subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

  "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: This statement should be in 6.2. Note, it was slightly modified because to be consistent with the reactions listed in this section. Use in Specific Populations**

  ☐ Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**
  - ☐ This section is required and cannot be omitted.
  - ☒ Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement "See FDA-approved patient labeling (insert type of patient labeling)." should appear at the beginning of Section 17 for prominence. For example:
    - "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: The identical words are not in the sponsor's proposed label.

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/s/

STEPHANIE N PARNCUTT
04/10/2012

DSI CONSULT: Request for Clinical Inspections

Date: February 16, 2012

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Antoine El Hage
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: *Steven Dinsmore, D.O., Medical Officer, DNP*
Norman Hershkowitz, M.D., Neurology Team Leader, DNP
Russell Katz, M.D., Director, DNP

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

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA-202810
Applicant/ Applicant contact information (to include phone/email): Supernus Pharmaceuticals, Inc.
Contact: Tami Martin, RN, Esq.; Tel: 301-838-2607; Email: tmartin@supernus.com
Drug Proprietary Name: (b) (4) (oxcarbazepine) tablets
NME or Original BLA (Yes/No): NO
Review Priority (Standard or Priority): Standard

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

Proposed New Indication(s): all proposed indications overlap with indications of reference product

PDUFA:
Action Goal Date: October 19, 2012
Inspection Summary Goal Date: August 19, 2012

II. Protocol/Site Identification

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

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site #: 701 **Name:** Penko Minkov Shotekov MD, DSc; **Address**: Department of Neurology, University Hospital "Alexandrovska", Medical Univesity-Sofia, 1 St. Georgi Sofiiski Str., 1431 Sofia, Bulgaria **Phone**: general university number: (092) 660 156, source: internet search	804P301	11	1. site is greater than 90th percentile of enrollment, represents 3% of randomized subjects 2. One of top 7 sites driving efficacy outcome. 3. site had 18 non-serious adverse events, 10th most frequent of all sites 4. 10 protocol deviations, 4th most frequent of all sites 5. 45% subject discontinuation
Site #: 406 **Name:** Piotr Czapinski, MD **Address**: Niepubliczny Zaklad Opieki Zdrowotnej Centrum Leczenia Padaczki i Migreny 25 Kielecka Ul. Krakow, Poland 31-523 **Phone**: no phone number from any source, none in PAREXEL CV	804P301	11	1. Large enrollment, 11 subjects is greater than the 90th percentile of enrollment, represents 3% of randomized subjects. 2. Unusually large placebo effect, 72 percent reduction in median seizure frequency with a maximum treatment effect of 75.4% reduction. 3. site had 75 non-serious adverse events, 2nd most frequent of all sites.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site #:510 **Name:** Silvio Basic, MD PhD **Address**: Clinical Hospital Neurology Department 6 Gojka Suska Ave. Zagreb, Croatia 10001 **Source of phone & email:** Safety & Efficacy study of Ladostigil in Mild to moderate probable Alzheimers-ClinicalTrials.gov **Phone**: 385 98 30 99 52 **Email:** silvio.basic@kbd.hr No contact information except address in the PAREXEL CV contained in the submission	804P301	9	1. Enrollment greater than 3rd quartile. 2. 44% subject discontinuations

III. Site Selection/Rationale

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

Rationale for DSI Audits
A multifactorial analysis of study sites was conducted with examination of 5 parameters to rank sites for inspection. These 5 parameters in order of importance were recruitment, contribution to primary efficacy results, frequency of non-serious adverse events, number of protocol deviations, and proportion of subject discontinuations.

Domestic Inspections: none, no site had enrollment greater than 3rd quartile

Reasons for inspections (please check all that apply):

____ Enrollment of large numbers of study subjects
____ High treatment responders (specify):
____ Significant primary efficacy results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
____ Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

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

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

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

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

Should you require any additional information, please contact *Stephanie N. Parncutt, RPM,* at *301-796-4098 or Steven Dinsmore, D.O.,* at 301-796-4155.

Concurrence: (as needed)

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

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/s/

STEPHANIE N PARNCUTT
03/01/2012

STEVEN T DINSMORE
03/01/2012

NORMAN HERSHKOWITZ
03/01/2012

RUSSELL G KATZ
03/01/2012