

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205836Orig1s000

205837Orig1s000

205838Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

PMR 3042-1

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

NDA/BLA # 205,836 (0000)
Product Name: 205,837 (0000)
205,838 (0000)
BRIVIACT (brivaracetam) (tablets, oral solution and intravenous solution)

PMR/PMC Description: Deferred pediatric study under PREA: A pharmacokinetic analysis to determine a dosing regimen in children from 4 years to less than 16 years of age that provides drug exposure that is similar to the exposure that is effective in adult patients with partial onset seizures. This analysis will require pharmacokinetic data from studies of both adult and pediatric patients. These studies have already been performed.

PMR/PMC Schedule Milestones:

Final Analysis Plan Submission:	<u>10/2016</u>
Final Report Submission:	<u>6/2020</u>
Other:	<u>MM/DD/YYYY</u>

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

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

This is a PREA requirement. A waiver has been granted for children less than 1 month due to the impractical nature of studying a population that is very small in number. A deferral has been granted for those ages 1 month to < 16 years of age. A PMR is required based upon PREA and the fact that the drug is about to be approved for adults and a pediatric a study has not been completed.

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

This study is required by PREA. As the present drug is approved for [REDACTED] (b) (4), this PMR [REDACTED] (b) (4)

3. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

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

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

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

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

A pharmacokinetic analysis to determine a dosing regimen in children from 4 years to less than 16 years of age that provides drug exposure that is similar to the exposure that is effective in adult patients with partial onset seizures. This analysis will require pharmacokinetic data from studies of both adult and pediatric patients. These studies have already been performed.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- 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

Continuation of Question 4

- 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)

What is requested is an analysis of data from studies, which have already been performed, ^{(b) (4)}

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?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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

PMR 3042-2

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

NDA/BLA # 205,837 (000)
Product Name: BRIVIACT (brivaracetam); (intravenous solution)

PMR/PMC Description: Deferred pediatric study under PREA: A pharmacokinetic and safety analysis in children from 1 month to less than 16 years of age to determine whether the bioavailability of the intravenous and oral formulations is similar and to determine an acceptable safety margin of the intravenous formulation when administered at doses that are found acceptable for oral administration. The study should include routine safety monitoring including careful cardiac monitoring before, during, and after infusion. Subjects should be balanced among age cohorts.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>08/2016</u>
	Study/Trial Completion:	<u>01/2020</u>
	Final Report Submission:	<u>06/2020</u>
	Other:	<u>MM/DD/YYYY</u>

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 granted for children less than 1 month due to the impractical nature of studying a population that is very small in number. A deferral has been granted for those ages 1 month to < 16 years of age. A PMR is required based upon PREA and the fact that the drug is about to be approved for adults and a pediatric study has not been completed.

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.”

This study is required by PREA. A pharmacokinetic/safety analysis to determine whether there is similar bioavailability and acceptable safety margin of this intravenous formulation when administered at doses that are found acceptable for oral administration.

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?

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

A pharmacokinetic and safety analysis in children from 1 month to less than 16 years of age to determine whether the bioavailability of the intravenous and oral formulations is similar and to determine an acceptable safety margin of the intravenous formulation when administered at doses that are found acceptable for oral administration. The study should include routine safety monitoring including careful cardiac monitoring before, during, and after infusion. Subjects should be balanced among age cohorts.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- 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

Continuation of Question 4

- 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
-

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?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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

PMR # 3042-3

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

NDA/BLA # 205,836 (0000)
Product Name: 205,837 (0000)
205,838 (0000)
BRIVIACT (brivaracetam) (tablets, oral solution and intravenous solution)

PMR/PMC Description: Deferred pediatric study under PREA: A prospective, randomized, controlled, double-blinded, efficacy and safety study of brivaracetam for the adjunctive treatment of partial onset seizures in children from 1 month to less than 4 years of age. The primary efficacy endpoint during the controlled phase will examine seizure frequency based upon video/electroencephalographic data. The placebo and drug treatment groups will be compared by inferential statistical methods to identify a treatment effect. Routine safety endpoints should be monitored. Behavioral and cognitive endpoints should be included. Subjects should be balanced among age cohorts.

PMR/PMC Schedule Milestones: Final Protocol Submission: 05/2017
Study/Trial Completion: 02/2022
Final Report Submission: 08/2022
Other: _____ MM/DD/YYYY

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

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

This is a PREA requirement. A waiver has been granted for children less than 1 month due to the impractical nature of studying a population that is very small in number. A deferral has been granted for those ages 1 month to < 16 years of age. A PMR is required based upon PREA and the fact that the drug is about to be approved for adults and a pediatric a study has not been completed.

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

This study is required by PREA. The goal of this study is to evaluate the efficacy and short term safety of brivaracetam in the adjunctive treatment of partial onset seizures in the ages 1 month < 4 years. Efficacy and short term safety will be studied.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

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

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

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

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

A prospective, randomized, controlled, double-blinded, efficacy and safety study of brivaracetam for the adjunctive treatment of partial onset seizures in children from 1 month to less than 4 years of age. The primary efficacy endpoint during the controlled phase will examine seizure frequency based upon video/electroencephalographic data. The placebo and drug treatment groups will be compared by inferential statistical methods to identify a treatment effect. Routine safety endpoints should be monitored. Behavioral and cognitive endpoints should be included. Subjects should be balanced among age cohorts.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- 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

Continuation of Question 4

- 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?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
 - There is not enough existing information to assess these risks
 - Information cannot be gained through a different kind of investigation
 - The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
 - The trial will emphasize risk minimization for participants as the protocol is developed
-

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

PMR # 3042-4

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

NDA/BLA # 205,836 (0000)
Product Name: 205,837 (0000)
205,838 (0000)
BRIVIACT (brivaracetam) (tablets, oral solution and intravenous solution)

PMR/PMC Description: Deferred pediatric study under PREA: Long-term safety study of brivaracetam in the adjunctive treatment of partial onset seizures in children from 1 month to less than 16 years of age. Routine safety measures should be monitored. Behavioral and cognitive endpoints should be included. A total of at least 200 patients must be enrolled. Subjects should be balanced among age cohorts.

PMR/PMC Schedule Milestones (based on the Sponsors iPSP):	Final Protocol Submission:	3/2011 <u>(completed)</u>
	Study/Trial Completion:	<u>08/2022</u>
	Final Report Submission:	<u>12/2020</u>
	Other:	<u>MM/DD/YYYY</u>

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

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

This is a PREA requirement. A waiver has been granted for children less than 1 month due to the impractical nature of studying a population that is very small in number. A deferral has been granted for those ages 1 month to < 16 years of age. A PMR is required based upon PREA and the fact that the drug is about to be approved for adults and a pediatric study has not been completed.

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

Long-term safety study of brivaracetam in the adjunctive treatment of partial onset seizures in children from 1 month to less than 16 years of age. Routine safety measures should be monitored. Behavioral and cognitive endpoints should be included. A total of at least 200 patients must be enrolled. Subjects should be balanced among age cohorts.

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:**

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Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

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

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

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

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

Long-term safety study of brivaracetam in the adjunctive treatment of partial onset seizures in children from 1 month to less than 16 years of age. Routine safety measures should be monitored. Behavioral and cognitive endpoints should be included. A total of at least 200 patients must be enrolled. Subjects should be balanced among age cohorts.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- 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

Continuation of Question 4

- 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?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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
02/18/2016



MEMORANDUM

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

Date: February 17, 2016

To: Billy Dunn, M.D., Director
Division of Neurology Products

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

From: Martin S. Rusinowitz, M.D.
Controlled Substance Staff

Subject: Product name: Brivaracetam, NDAs 205836, 205837, 205838
Trade Name: Briviact:
Oral Tablets 10 mg, 25 mg, 50 mg and 100 mg
Intravenous 10 mg/mL
Oral Solution 10 mg/mL
Indication: Adjunctive Therapy in the Treatment of Partial Onset Seizures in
Patients 16 Years of Age and Older with Epilepsy
Sponsor: UCB, Inc.
PDUFA Goal Date: November 20, 2015

Materials Reviewed:

Sponsor's Drug Abuse Liability Evaluation; October 27, 2014
Sponsor's Clinical Study Report NO1296; October 6, 2009
Sponsor's Clinical Overview; October 30, 2014
Sponsor's Summary of Clinical Safety; October 29, 2014
Sponsor's Synopsis of Individual Studies; October 6, 2014

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I. Summary

1. Background

This memorandum responds to a consult request by the Division of Neurology Products (DNP) to evaluate the abuse potential of Brivaracetam (BRV) in the submissions for NDAs 205836 (10mg, 25mg, 50mg, 75mg and 100mg oral tablets), 205837 (10mg/mL intravenous) and 205838 (10mg/mL oral solution). BRV is a new molecular entity (NME) anticonvulsant proposed for

use as adjunctive therapy in the treatment of partial onset seizures (POS) in patients 16 years of age and older with epilepsy. BRV is not marketed anywhere in the world.

BRV is pharmacologically similar to levetiracetam (LEV), an anti-epileptic drug (AED) which also has a selective and high affinity for a brain-specific binding site synaptic vesicle protein 2A (SV2A). Additionally it produces reverse inhibition induced by negative modulators of GABA and glycine, and inhibits sodium (Na⁺) channels. The Sponsor claims that binding to the SV2A site appears to be the primary target for both drug's pharmacological activity.

The Sponsor asserts, with the submission of its clinical trial results being reviewed by DNP, that BRV is efficacious in the treatment of POS with minimal side effects. Studies supporting the intravenous (IV) and oral solution formulations are claimed to demonstrate similar pharmacokinetics (PK) properties to the oral tablet formulation. Effective daily dosages studied range from 5mg/day up to 200mg/day, while the Sponsor's proposed daily dosage is from 100mg/day to 200mg/day.

This review is primarily based on the Sponsor's Drug Abuse Liability Evaluation. It includes studies that evaluate the non-clinical chemical, mechanistic, pharmacological, pharmacokinetic, clinical and epidemiological properties of BRV. It also details a Human Abuse Potential Study along with clinical trial adverse events (AEs) related to abuse potential and the drug's dependence potential after withdrawal. The Sponsor has requested that BRV be placed in to a (b) (4) of the Controlled Substances Act (CSA).

2. Conclusions

After review of all abuse-related data submitted with NDAs 205836, 205837 and 205838, CSS concludes that BRV has abuse potential most similar to drugs in Schedule V of the CSA, such as lacosamide, ezogabine and pregabalin. This conclusion is based on the similarity in abuse potential of the above three AEDs recently placed into Schedule V. Much like BRV, in separately-conducted human abuse potential studies, ezogabine, pregabalin and lacosamide each produced positive subjective effects that are statistically similar to those produced by a Schedule IV benzodiazepine, such as diazepam or alprazolam (ALP), positive control. Benzodiazepine abuse is characteristically associated with the drug's intoxicating effects along with sedation and significant withdrawal symptoms.

BRV, again similar to ezogabine, pregabalin and lacosamide, differed from diazepam and ALP in terms of their negative subjective response profile on sedation measures, and withdrawal syndromes following drug discontinuation. Additionally, in more than 2,000 epileptic patients included in the BRV phase 3 clinical trials there were very few Treatment Emergent Adverse Effects (TEAEs) which were abuse-related.

The Sponsor also included LEV as an unscheduled comparator because it is pharmacologically related to BRV and has a similar mechanism of action and AE profile. Unfortunately, justification for the use of LEV as an "unscheduled" control is not scientifically valid because it has not undergone a formal abuse potential assessment by FDA.

Thus, despite some similarities between BRV and the Schedule IV drugs, BRV is most similar to Schedule V AEDs (ezogabine, pregabalin and lacosamide) in terms of its overall abuse potential.

3. Recommendations

1. Based on the profile of effects in animal and human studies following BRV administration and withdrawal, CSS recommends that BRV be placed by the Drug Enforcement Administration (DEA) into Schedule V of the CSA. (b) (4)

2. Upon review of the label text proposed by the Sponsor, CSS recommends the following track change revisions based on our evaluation of the abuse potential data submitted in the NDAs.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Briviact (b) (4)

9.2 Abuse

In a human abuse potential study (b) (4), single doses of Briviact (b) (4) were compared to alprazolam (C-IV) (1.5 mg and 3 mg). Briviact (b) (4) fewer sedative, euphoric, (b) (4) effects (b) (4) alprazolam; however, Briviact (b) (4)

(b) (4)

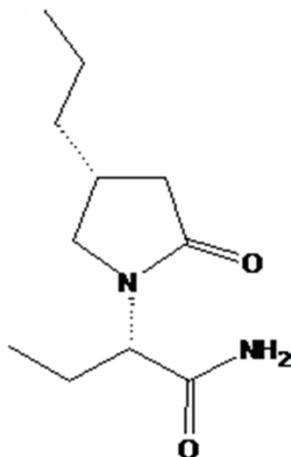
9.3 Dependence

There was no evidence of physical dependence potential or a withdrawal syndrome with Briviact in a pooled review of placebo-controlled adjunctive therapy studies.

II. Discussion

1. Chemistry

The chemical structure of BRV ((2S)-2-[(4R)-2-oxo-4-propyltetrahydro-1Hpyrrol-1-yl]butanamide) is shown in Figure 1.

Figure 1: Chemical Structure of BRV

1.1 Substance Information

Table 1 outlines the physicochemical properties of BRV.

Table 1: Physicochemical Properties of BRV

Property	Description
Appearance	white to off-white crystalline powder
Partial Coefficient	the partition coefficient (D) in n-octanol/water at pH 7.4, expressed as log D, equals 1.04, implying that the molecule is amphiphilic (possessing hydrophilic and lipophilic properties)
Ionization	not ionizable in water at any pH
Polymorphism	(b) (4)
Hydrosolubility	freely soluble in water
Solubility	very soluble in ethanol, freely soluble in acetonitrile and very slightly soluble in n-hexane

1.2 Potential Drug Isomers

The BRV molecule has two chiral centers and is the diastereoisomer of four stereoisomers.

1.3 In Vitro Manipulation and Abuse via I.V. Injection, Snorting and Smoking

1.3.1 Solubility of the Tablet Formulation in Aqueous and Organic Solvents

Brivaracetam is very soluble in water, ethanol and many organic solvents

1.3.2 Intranasal Insufflation

Since BRV is very soluble, it is likely to be easily absorbed by mucous membranes when taken intranasally. As described in Section 1.3.4, it is not likely to be crushed or chewed to increase absorption for the purposes of abuse.

The quantity of drug required to achieve subjective effects may be a limiting factor since BRV will be commercially available only in dosage strengths up to 100mg. Therefore 10 tablets would be required to achieve a 1,000 mg dose, which produced euphoria in the Human Abuse Potential Study (HAPS). With a tablet weight of 540mg this would represent 5.4 grams of drug product. The Sponsor asserts that other outside studies have suggested that the maximum that most abusers could insufflate at one time is 1 to 2 grams.

1.3.3 Smoking

No data is available. Since temperatures commonly used for smoking inhalation are greater than 200° and BRV melts at 76°, this route of abuse would seem unlikely to be relevant without a vaporizer.

1.3.4 Extraction and Manipulation

BRV has been designated as a Biopharmaceutics Classification System (BCS) Class 1 because of its high permeability and solubility. Although in vitro crushing and chewing studies have not been done, these manipulations would seem unnecessary to increase absorption given the tablet's high solubility. It would be relatively easy to extract the active drug from tablets using room temperature water as the solvent. This solution, at a reasonably low volume, could be easily injected intravenously. The oral abuse of a solubilized BRV tablet is possible but might be limited because of its strong bitter taste. The consumption of the oral solution (NDA 208838) in high doses for abuse purposes would also seem unlikely since sorbitol, an excipient, may cause diarrhea because of its laxative effect. Similarly, the I.V. formulation (NDA 208837) could obviously be abused intravenously. Extraction of the BRV drug substance from the oral solution would be very difficult for an abuser.

It is not likely that BRV substance would be synthesized by a "street chemist" as a potential drug of abuse.

Expertise in organic synthesis would be necessary as the synthesis of BRV is (b) (4)

2. Nonclinical Pharmacology

BRV is a 2-pyrrolidone derivative which is structurally related to LEV. Pharmacological studies indicate that BRV shows potent and complete seizure suppression in animal models mimicking partial epilepsy and elevates the focal seizure threshold as well as inhibits secondary generalization of seizure activity. BRV also shows suppression of primary generalized seizures and demonstrates protection against acute seizures induced by maximal electroshock and maximal doses of various chemoconvulsants. These findings suggest a broad spectrum activity profile of BRV in animal models of epilepsy

2.1 Receptor Binding and Functional Assays

The pharmacological properties of BRV appear to be primarily from a selective interaction with SV2A, similar but more potent than that of LEV. (b) (4)

BRV did not significantly bind to any of the common abuse-related molecular targets or to any other CNS target. The molecular pharmacology of BRV demonstrates selective binding to SV2A, and no other potentially abuse-related molecular targets. Other binding sites included sites known to be associated with abuse potential (GABA/benzodiazepine, dopamine [D1 and D2]), serotonin (1A, 1B, 2A, 3, 5A, 6, and 7), cannabinoid (CB1, CB2), NMDA/glutamate, channels (calcium, potassium, sodium, chloride), transporters (dopamine, norepinephrine) and sites that are not typically associated with abuse potential (acetylcholine (muscarinic and nicotinic), adenosine, norepinephrine (alpha and beta), histamine, and neurokinin).

LEV is the only other compound known to bind to this receptor. Besides LEV, BRV is not structurally related to any other AED or any of the major classes of abused sedative euphoric drugs, including barbiturates, benzodiazepines, cannabinoids, opiates (and opioid-like compounds), or dissociative anesthetics.

2.2 Safety Pharmacology/Metabolites

Single dose pharmacokinetic studies, as well as toxicokinetic evaluations, were performed in mice, rats, dogs and monkeys. The Sponsor's data indicates that BRV is rapidly and totally absorbed after oral administration. BRV distributes rapidly to the brain, has a low plasma protein binding, and does not show clinically relevant tissue accumulation. BRV does not impair cytochrome P-450 isoforms, epoxide hydrolase or drug transporters in a clinically significant manner.

2.3 Findings from Safety Pharmacology and Toxicology Studies

Safety pharmacology and toxicology studies were performed with BRV in mice, rats and dogs. Central nervous system effects were observed and consisted mainly of decreased reactivity and activity, motor incoordination and ataxia. There was a significant decrease in spontaneous

locomotor activity only at very high doses which would be equivalent to a dose of 19mg/kg in humans, about 6 times the maximum daily clinical dose of 200mg.

The Irwin Test in rats elicited dose-related CNS depression at high doses with changes in autonomic, sensorimotor and neuromuscular functions. Dose-related clinical signs occurred at varying degrees of intensity suggesting mild to moderate CNS depression (passivity, decreased alertness and decreased grooming), with changes in neuromuscular (decreased grip strength), sensorimotor functions (decreased startle and touch responses) and ataxia.

2.4 Animal Behavioral Studies

A drug discrimination study and a self-administration study were completed in order to evaluate the abuse potential of BRV. A benzodiazepine, chlordiazepoxide (CDP), was selected as a positive control in both studies.

Although not pharmacologically similar to benzodiazepines, BRV's adverse events (AEs) of somnolence, dizziness, and decreased alertness were observed in humans. These findings, as well as ataxia observed at higher doses in animal toxicology studies, indicate that BRV has some CNS depressant like effects, most evident at higher doses. Therefore, CDP was chosen as a C-IV CNS depressant with anticonvulsant, anti-anxiety and mild myorelaxant properties, as well as abuse potential.

BRV demonstrated only partial generalization to the training drug cue across a broad range of test doses that escalated upward to overtly behaviorally toxic test doses of 320 mg/kg. The highest dose of BRV (320mg/kg) produced approximately 62% drug-appropriate responding in 3 out of the 8 animals tested across a broad range of test doses. The partial generalization to the CDP discriminative stimulus was observed only at very high doses of BRV that were also associated with behavioral toxicity, possibly indicating that the discriminative stimulus effects of BRV in rats are different than those of CDP, across a wide range of doses.

The Sponsor speculates that the CDP discriminative stimulus appears to be based on 2 distinct features of benzodiazepines: direct motor sedative activity and anxiolysis. The partial generalization between BRV and CDP seems to be most likely related to direct drug-induced changes in motor function or muscle relaxant properties in these rats. Signs of behavioral toxicity induced by BRV (e.g., ataxia) at the highest test doses that produced the greatest number of lever press responses on the CDP appropriate lever would appear to support this conclusion.

Neither CDP nor BRV were avidly self-administered by rats. Both consistently engendered very low numbers of injections per test session when compared to cocaine. Each tested dose of BRV showed a significant drop in total number of self-injections on Day 2 of substitution, whereas CDP tended to maintain similar Day 1 to Day 2. Both CDP and BRV consistently engendered very low numbers of injections per test session when compared to cocaine. When compared, CDP appeared to maintain Day 1 patterns of responding on Day 2 of testing to a greater extent than BRV. Each tested dose of BRV showed a significant drop in total number of self-injections on Day 2 of substitution, whereas CDP tended to maintain similar Day 1 to Day 2 patterns at both 0.32 and 0.56mg/kg/infusions. The pattern of rates-of-responding over the 3-day

substitution period following access to the low dose of BRV (0.32mg/kg/injection) was consistently low and similar to vehicle conditions.

Therefore, under limited access conditions (1 hour per day) IV CDP injections failed to be avidly self-administered in rats. Brivaracetam at doses of 0.32 to 10mg/kg/infusion did not have positive reinforcing effects in rats conditioned to self-administer cocaine.

2.5 Tolerance and Physical Dependence Studies in Animals

A chronic dosing study was performed to evaluate the physical dependence potential of BRV in male rats. The potential of BRV to induce a classic withdrawal syndrome following abrupt cessation during chronic administration was compared to that of CDP in a 30-day chronic administration study in rats. (As a C-IV benzodiazepine with significant physical dependence, CDP appears to be an appropriate positive control.) Observations for morbidity, mortality, injury, and the availability of food and water were conducted twice daily for all animals. Clinical observations were conducted once prior to each first daily dose and at approximately 6 hours following the first dose each day of chronic exposure and withdrawal phases. No specific BRV-related clinical findings were noted during either 65 or 175 mg/kg bid administration in these rats. CDP-treated rats showed signs of respiratory distress, weight loss, poor or unkempt appearance, as well as gastroparesis during the 30 days of CDP 225 mg/kg bid administration. CDP-treated rats demonstrated limited growth over the course of 30 days of treatment. There was an approximate 100 gram weight difference between CDP, vehicle or BRV treated rats in the final days of this study. These findings suggest that BRV does not have physical dependence potential consistent with or similar to CDP in rats.

These animal studies are consistent with the clinical findings in the Phase 2 Study NO1162, a cohort of patients (without epilepsy) who were evaluated after abrupt discontinuation of BRV without a taper period. Four weeks of treatment with BRV 200 mg/day (the maximally recommended daily dose) did not cause any relevant signs or symptoms of withdrawal following abrupt discontinuation.

3. Clinical Pharmacology

3.1 Absorption, Distribution, Metabolism, Elimination (ADME)

BRV is rapidly and completely absorbed orally with a Tmax of about 1 hour after dosing in fasting subjects. The plasma half-life is 9 hours in healthy adults but decreases to 6 hours following repeated administration at high doses (800 mg/day). Protein binding is 17.5%. PK is dose-proportional for Cmax (dose range 10 mg to 1400 mg) and AUC (dose range 10 mg to 600 mg), and slightly more than dose-proportional for AUCs at 1000 mg and 1400 mg doses. The oral bioavailability is not affected by food, but under fed conditions the absorption rate is slowed and the Tmax is delayed by 3 hours.

Renal clearance of BRV represents 5 to 10% of the total clearance. Only 3 to 7% of the dose is excreted as parent compound in urine. The three main metabolites are found in urine and do not

appear to have significant activity. One active metabolite, with potency 20-times less than the parent, represents less than 3% of the dose in urine and was not found in human plasma.

3.2 Drug/Product Interaction

The potential for other drugs to interact on the absorption, distribution, and renal excretion of BRV appears to be low. BRV is not inhibited by gemfibrozil, a known inhibitor of cytochrome P450 CYP 2C8 and CYP 2C9. The clearance of BRV was increased by approximately 30% in subjects taking hepatic enzyme inducing AEDs (carbamazepine, phenytoin, phenobarbital, and primidone), and was doubled by rifampicin. BRV has the potential to interact with compounds that are substrates of epoxide hydrolase. The potential of BRV to interact with compounds that are substrates of CYP2C19 and CYP3A4 appears to be low at therapeutic doses.

BRV does not impair the efficacy of oral contraceptives containing levonorgestrel and ethinylestradiol. It did not interact with midazolam, a CYP3A4 probe, nor did it modify the plasma concentrations of carbamazepine, lamotrigine, LEV, oxcarbazepine metabolite, phenobarbital, phenytoin, topiramate, valproic acid, and zonisamide. The epoxide metabolite of carbamazepine was significantly increased. It appears that BRV may enhance the effects of alcohol.

4. Clinical Studies

4.1 Study NO1295 Design

The Sponsor's Human Abuse Potential Study NO1295 was a randomized, double-blind, triple-dummy, placebo, unscheduled and scheduled comparator-controlled, single-dose crossover Phase 1 clinical pharmacology study to assess the abuse potential of BRV. The details are shown in Table 2.

Table 2: Human Abuse Potential Study NO1295

Design	Primary Endpoints	Treatments	Number of Subjects
R, DB, AC, PC, MD, seven-arms crossover to evaluate the abuse potential of single dose intact oral BRV	VAS Emax for Drug Liking, Overall Drug Liking, High, and ARCI PCAG scale	ALP 1.5 mg ALP 3.0 mg BRV 50 mg BRV 200 mg BRV 1000 mg LEV 4000 mg Placebo	44 randomized and 36 subjects completed all treatment periods

Abbreviations: DB = double blind; PC = placebo-controlled; AC = active-controlled; R = randomized; MD=multidose; ARCI PCAG scale= Addiction Research Center Inventory (ARCI) Pentobarbital Chlorpromazine Alcohol Group (PCAG) scale

Healthy male and female subjects who were recreational CNS depressant users (defined as a minimum of 10 lifetime recreational experiences with CNS depressants and at least 1

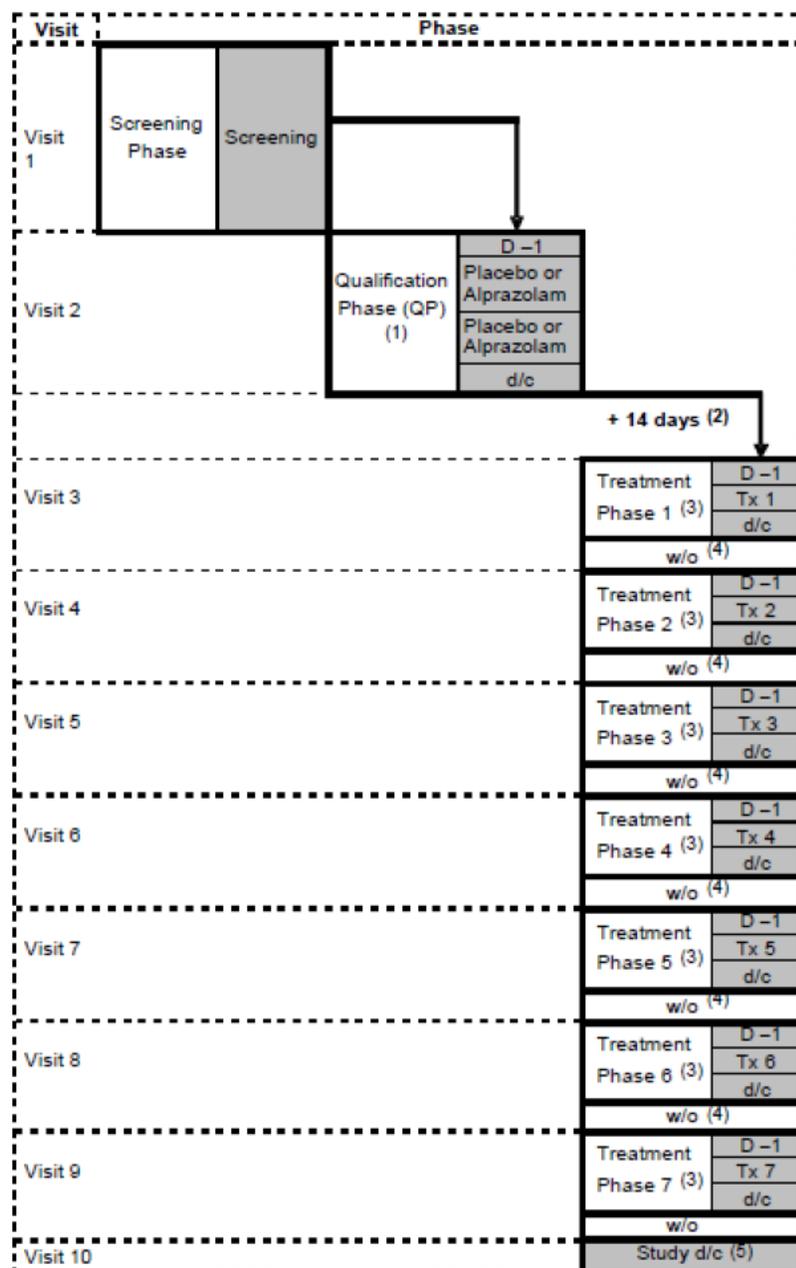
recreational use of a CNS depressant in the 3 months prior to the screening) between 18 and 55 years were eligible for this trial. Most subjects were cannabis users, although 16 subjects used other CNS depressants. The other CNS depressants used were primarily benzodiazepines (ALP, diazepam, lorazepam, temazepam, and clonazepam). A few subjects had previously used gammahydroxybutyrate, and methaqualone (no longer marketed). The demographic data of the ITT population is shown in Table 3.

Table 3: Study NO1295 ITT Population Demographics

Characteristic	N / %
Female	10 (22.7)
Male	34 (77.3)
White	29 (65.9)
African American	12 (27.3)
Asian	3 (6.8)
Age (yrs.), mean (SD)	35.4 (9.35)
Weight (kg), mean (SD)	76.1 (11.88)
Height (cm), mean (SD)	172.7 (9.01)
BMI (kg/m ²), mean (SD)	25.4 (2.46)
BSA (m ²), mean (SD)	1.9 (0.19)

During an initial Qualification Phase, subjects received placebo and ALP 2mg on 2 consecutive days. Those able to sufficiently distinguish placebo from ALP received single doses of BRV 50mg, 200mg, and 1000mg as well as LEV 4,000mg, ALP 1.5mg and 3mg, along with placebo administered orally in a randomized double-blind, triple-dummy order over 7 Treatment Periods. The treatments were separated by wash-out intervals of 7 to 10 days. The study ended with a Discharge Visit examination approximately 7 days after the last administration of the study medication. The total duration of the study for each subject was about 15 weeks. Forty-two male and female subjects were planned to be enrolled in this trial. Five subjects were allocated to each of 7 treatment sequences in order to have at least 35 completers. PK samples were collected at predose, 1, 2, 3, 6, 8, 12, and 24 hours post-dose. Pharmacodynamic (PD) assessments were completed over 24 hours postdose. All 44 subjects who were randomized to the Treatment Phase were included in the Intent-to-Treat (ITT) population and per-protocol populations. Thirty-six subjects completed the study and 8 subjects discontinued early. The subjects were primarily Caucasian males and ranged in age from 20.5 to 55.1 years old. Fifteen subjects who had protocol deviations affecting the PD variables were partially excluded from the per-protocol population (only the missing or affected period(s) were excluded from the analysis). The Sponsor's Study Schematic is reproduced below in Figure 2.

Figure 2: Study NO1295 Schematic



The following PD variables were the primary dependent variables in this trial, while Take Drug Again VAS was a secondary variable.

- Bipolar Drug Liking VAS**; Assesses the response to the question “At this moment, my liking for this drug is.” Values for this scale range from 0 (strong disliking) to 100 (strong liking), with 50 representing a “neutral” value

- **Bipolar Overall Drug Liking VAS;** Assesses the response to the question “Overall, my liking for this drug is,” asked at the end of the day (12 hours) and the next day (24 hours postdose). Values range from 0 (strong disliking) to 100 (strong liking), with 50 representing a “neutral” value.
- **Unipolar High VAS;** Assesses the response to the question “I am feeling high”. Values range from 0 (definitely not) to 100 (definitely so).
- **ARCI Pentobarbital Chlorpromazine Alcohol Group (PCAG);** Assesses sedation. For the ARCI scale assessments, subjects answer a list of 49 questions that contribute to 1 or more of the 5 ARCI scales used in this study (other scales included Amphetamine, Morphine Benzedrine Group [MBG], Benzedrine Group [BG], and Lysergic Acid Diethylamide [LSD]). For all ARCI scales, one point is given for each response that agrees with the scoring direction on the scale (i.e., “True” or “False”) and no points are given when the answer is opposite to the scoring direction. Example of questions on the ARCI PCAG scale include “My speech is slurred” (True), and “I am full of energy” (False). Values for the ARCI PCAG range from 0 (no sedation) to 15 (strong sedation).
- **Take Drug Again VAS;** Assesses the response to the question “I would take this drug Again,” asked at 12 and 24 hours postdose. Values for this scale can range from 0 (definitely not) to 100 (definitely so).

The other secondary pharmacodynamic variables included the Subjective Effects VAS, Any Drug Effects VAS, Good Drug Effects VAS, and Bad Drug Effects VAS), ARCI Morphine Benzedrine Group (MBG), and ARCI Lysergic Acid Diethylamide (LSD). The ARCI Benzedrine Group (BG) and Dizziness VAS were also included.

The investigative doses of BRV explored in the efficacy studies were between 2.5 mg and 100 mg BID. The highest incidence of euphoric mood occurred at the 200 mg dose range. The maximum tolerated dose (MTD) for BRV in healthy subjects is 1000 mg as a single dose and more than 800 mg per day as repeated doses. The selected doses for Study NO1295 included 50 mg, 200 mg and a high maximally tolerated dose of 1000 mg that is 10-fold higher than the highest dose per intake evaluated therapeutically or 5-fold higher than the total daily dose.

Although BRV is a CNS depressant, it does not belong to any established molecular pharmacologic class associated with abuse. The Sponsor chose ALP as a positive control because it has sedative and anticonvulsant properties and a CNS depressant profile somewhat similar to BRV. Because LEV is pharmacologically related to BRV and has a similar mechanism of action and AE profile, it was chosen by the Sponsor as an unscheduled comparator. The 4000 mg LEV dose represents 2.66 times the maximal recommended single dose of 1500 mg.

4.1.2 Study NO1295 Results

Abuse potential analysis: Comparison between BRV and Positive Control

This study was considered statistically valid if on at least 3 of 6 endpoints at the 95% confidence intervals (CIs) of differences of the Emax of either dose of ALP and placebo did not include zero, and a non-descending dose-response was observed. On all 6 endpoints, ALP had a statistically larger mean response than placebo, and the 95% CIs of differences in Emax of both ALP doses and placebo did not include zero. An ascending dose-response was observed for all primary endpoints, other than Drug Liking VAS, which was slightly lower for ALP 3 mg compared to 1.5 mg. The study was therefore considered valid and sensitive for detecting the abuse-related subjective effects of sedative drugs. (See Dr. Wei Liu's Statistical Review and Evaluation for details; DARRTS 3/12/15)

Mean Drug Liking VAS Scores over Time

All active treatments showed higher Emax values compared to placebo, while Emin values showed relatively little difference between placebo and the active treatments. Median Emax was lower than the mean value for placebo; however, median values tended to be higher than mean values for the active treatments (other than BRV 50 mg). AUC showed a pattern of results similar to Emax. Both doses of ALP were significantly different from placebo. In addition, all BRV doses and LEV 4000 mg were also significantly different from placebo. BRV 50 mg and LEV 4000 mg were not significantly different from placebo, while BRV 200 mg and 1000 mg were significantly higher. Compared to ALP 1.5 mg and 3 mg, BRV 50 mg showed significantly less Drug Liking. The BRV 200 mg dose was not significantly different from both doses of ALP, while BRV 1000 mg was slightly higher than ALP 3 mg, but not significantly different from 1.5 mg. The LEV 4000 mg treatment showed significantly less Drug Liking compared to both ALP doses. The 2 lower doses of BRV (50 mg and 200 mg) were not significantly different from LEV 4000 mg. BRV 1000 mg showed significantly higher Drug Liking in comparison to LEV 4000 mg.

Table 4: Descriptive Statistics for Drug Liking VAS by Treatment

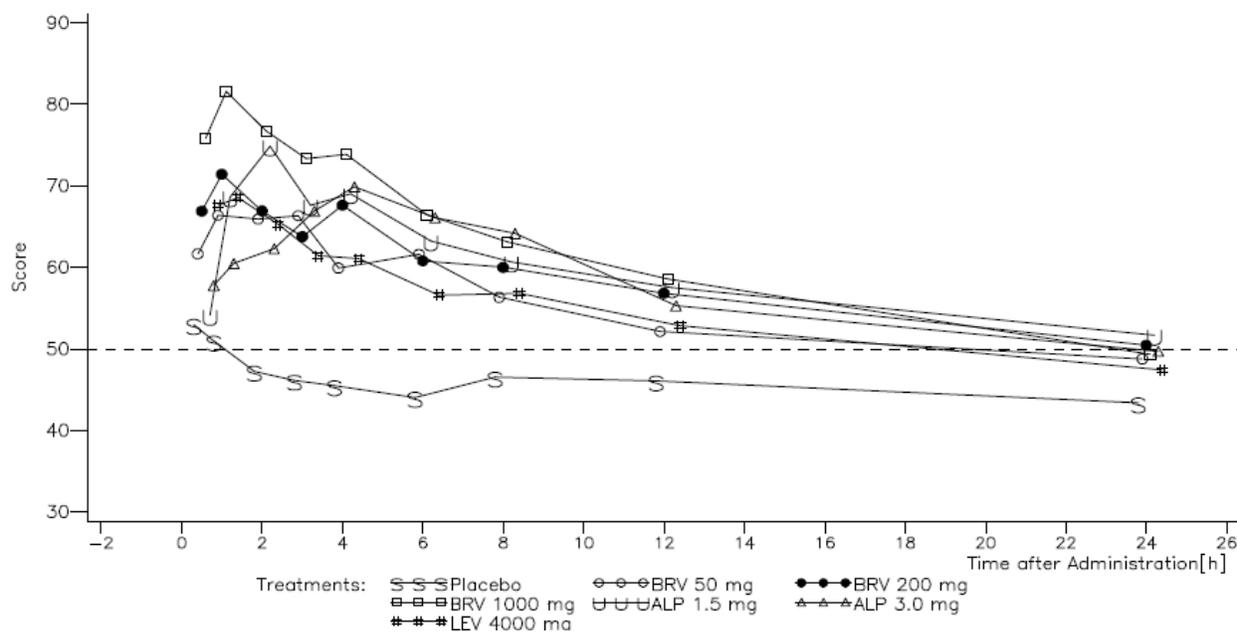
Treatment	Mean Emax (SD)	Mean Emin (SD)	Mean AUE (SD)	N
Placebo	57.9 (24.9)	38.2 (21.1)	533 (236)	39
BRV 50 mg	79.3 (18.0)	41.8 (22.3)	684 (255)	41
BRV 200 mg	82.6 (17.8)	43.1 (21.9)	718 (252)	40
BRV 1000 mg	89.0 (15.5)	44.3 (18.7)	780 (209)	41
ALP 1.5 mg	87.3 (14.2)	36.1 (19.9)	734 (222)	41
ALP 3 mg	83.7 (17.5)	31.7 (24.5)	728 (241)	40
LEV 4000 mg	76.8 (22.0)	41.0 (22.9)	676 (271)	43

AUE=area under the time effect curve; Emax=maximum effect; Emin=minimum effect; SD=standard deviation; VAS=visual analog scale

As demonstrated in Figure 3, reproduced from the Sponsor's Clinical Study Report N01295, p.74, placebo scores decreased from the neutral point (50) responses for the active treatments showed scores that increased into the liking range of the scale, peaking at approximately 1 hour postdose for BRV and LEV and 2 hours for ALP 1.5 mg. The onset of liking effects was more gradual with ALP 3 mg, reaching a peak at approximately 4 hours postdose. The active

treatments remained in the liking range of the scale until about 8 hours (LEV and BRV 50 mg) to 12 hours (BRV 200 mg and 1000 mg and ALP 1.5 mg and 3 mg) postdose. Since the faster the onset of liking effects generally indicates a greater abuse potential, these data may suggest that BRV has a greater potential for abuse than ALP.

Figure 3: Mean Drug Liking VAS Scores over Time



Mean Overall Drug Liking VAS Scores at 12 and 24 hours

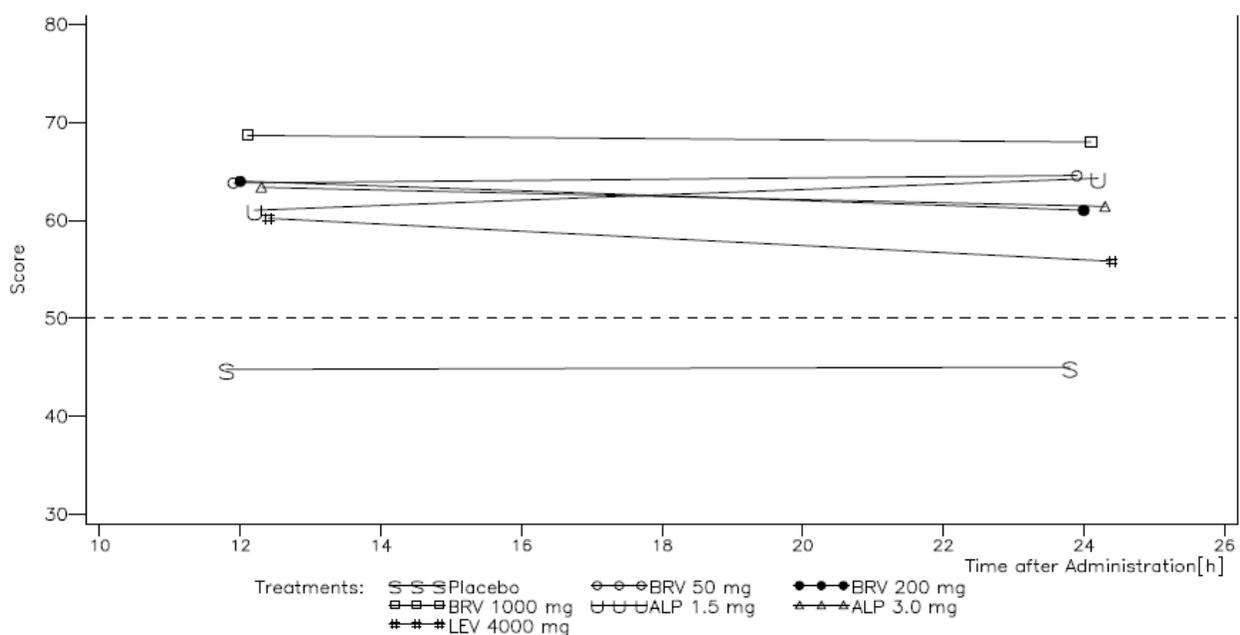
Descriptive statistics for Overall Drug Liking VAS parameters are summarized by treatment in Table 5 for Emax, Emin, and mean effect (mean of 12 and 24 hours postdose), respectively. Consistent with the time course, while Emax, Emin, and mean values were slightly lower than the neutral point (50) with placebo, all active treatments had Emax, Emin, and mean values that were higher than placebo and in the Drug Liking range of the scale. In most cases, median values were similar or slightly higher than the mean values.

Table 5: Descriptive statistics for Overall Drug Liking VAS by Treatment

Treatment	Mean Emax (SD)	Mean Emin (SD)	Mean Effect (SD)	N
Placebo	46.7 (27.8)	43.1 (26.6)	44.9 (26.78)	39
BRV 50 mg	67.1 (27.4)	61.3 (26.2)	64.2 (26.56)	41
BRV 200 mg	66.7 (27.3)	58.3 (28.1)	62.5 (26.88)	40
BRV 1000 mg	74.9 (21.6)	61.9 (26.0)	68.4 (22.26)	41
ALP 1.5 mg	67.7 (26.1)	57.7 (27.7)	62.7 (25.74)	41
ALP 3 mg	69.3 (29.0)	55.5 (30.0)	62.4 (28.27)	40
LEV 4000 mg	62.8 (29.7)	53.6 (28.9)	58.2 (28.56)	43

E_{max}=maximum effect; E_{min}=minimum effect; mean effect = mean of 12 and 24 hours; SD=standard deviation; VAS=visual analog scale

As demonstrated in Figure 4, reproduced from the Sponsor's Clinical Study Report N01295, p.78, scores for placebo were slightly less than neutral, while scores for all active treatments were similar and in the liking range at both 12 and 24 hours post-dose. Emax, Emin, and mean values were slightly lower than the neutral point (50) with placebo, while all active treatments had Emax, Emin, and mean values that were higher than placebo and in the liking range of the scale. Overall Drug Liking Emax values for all active treatments were greater than that of placebo. None of the active treatments significantly differed from one another in Overall Drug Liking, other than BRV 1000 mg, which was significantly greater compared to ALP 1.5 mg.

Figure 4: Mean Overall Drug Liking VAS Scores at 12 and 24 hours

Mean High VAS Scores over Time

The mean Emax, AUE (0-12), and AUE (0-24) values of the active treatments were higher than those observed for placebo. For the active treatments, most median Emax and AUE (0-12) values were higher than the mean values. The placebo median values for AUE (0-12) and AUE (0-24) were lower than the mean values. The High VAS Emax values for ALP, BRV, and LEV were all significantly greater than placebo. BRV 50 mg, 200 mg BRV, and LEV 4000 mg were not significantly different from twice placebo, while BRV 1000 mg was significantly greater than 2-times placebo.

The 50 mg dose of BRV had a significantly lower High VAS Emax compared to ALP 1.5 mg and 3 mg, while BRV 200 mg was significantly lower than ALP 3 mg, but not significantly different from ALP 1.5 mg. The high dose of BRV (1000mg) was not significantly different from either dose of ALP. LEV 4000 mg showed significantly lower High Emax compared to both ALP doses. Compared to LEV 4000 mg, BRV 1000 mg had a significantly higher High VAS Emax value, while BRV 50 mg and 200 mg were not significantly different from LEV.

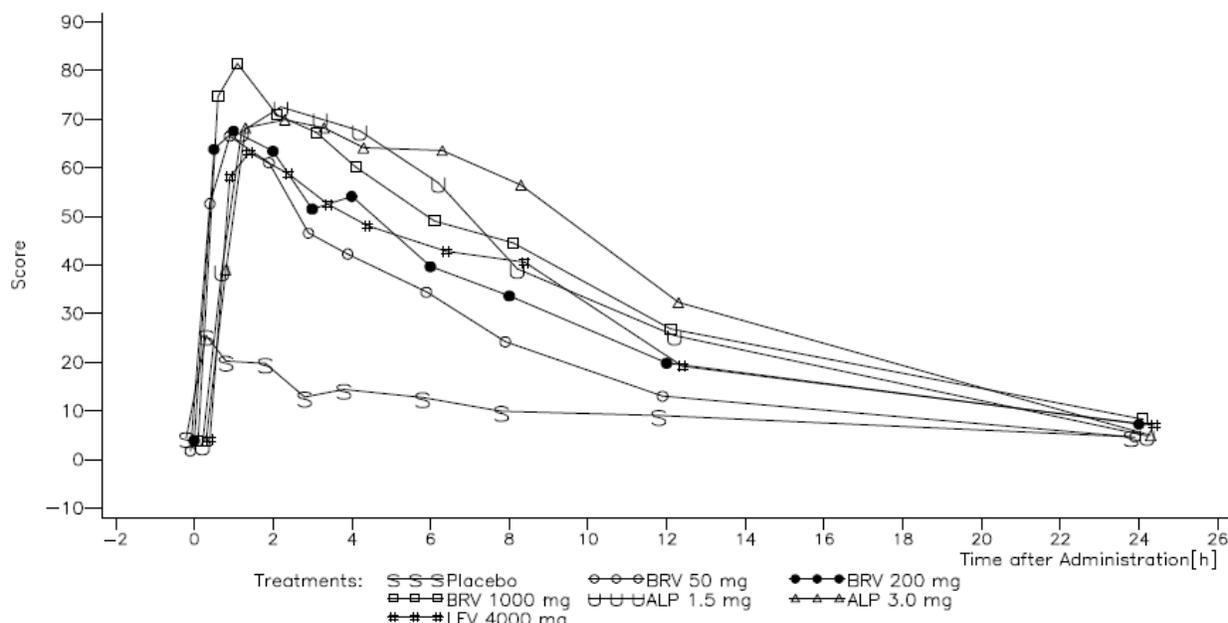
Table 6: Descriptive statistics for High VAS by Treatment

Treatment	Mean Emax (SD)	Mean AUE,0-12 (SD)	Mean AUE,0-24 (SD)	N
Placebo	32.1 (33.7)	157 (246)	240 (389)	39
BRV 50 mg	75.5 (23.7)	416 (283)	522 (446)	41
BRV 200 mg	80.7 (18.0)	500 (289)	663 (469)	40
BRV 1000 mg	88.1 (19.9)	614 (272)	825 (500)	41
ALP 1.5 mg	87.0 (18.5)	598 (274)	780 (472)	41
ALP 3 mg	88.3 (13.0)	667 (254)	890 (448)	40
LEV 4000 mg	76.1 (26.9)	507 (328)	667 (510)	43

AUE=area under the time effect curve; E_{max}=maximum effect; SD=standard deviation; VAS=visual analog scale

As demonstrated in Figure 5, reproduced from the Sponsor's Clinical Study Report N01295, p.82, the placebo showed a small initial increase in scores that lasted for several hours and remained slightly above the no effects point (0) for 24 hours postdose. All the active treatments showed effects that were higher than placebo until at least 12 hours post-dose, other than BRV 50 mg, which returned to placebo levels by 12 hours post-dose. Both ALP doses showed similar effects, however, the 3 mg dose showed a slightly longer duration of action compared to the 1.5 mg dose. BRV showed a slightly more rapid onset compared to ALP, but the decline in effects was also more rapid, in particular at the BRV 50 mg dose.

Figure 5: Mean High VAS Scores over Time



Mean ARCI PCAG Scale (Sedative Effect)

The mean Emax, AUE(0-12), and AUE(0-24) values were higher for the active treatments compared to placebo; these appeared to be the highest for ALP 1.5 mg and 3 mg compared to BRV and LEV. The differences between the treatments were less for AUE (0-24) compared to Emax and AUE (0-12). The median Tmax was 0.5 hours for placebo, 1 hour for BRV 50 mg, 2 hours for BRV 200 mg and 1000 mg, ALP 1.5 mg and LEV 4000 mg, and 4 hours postdose for ALP 3 mg.

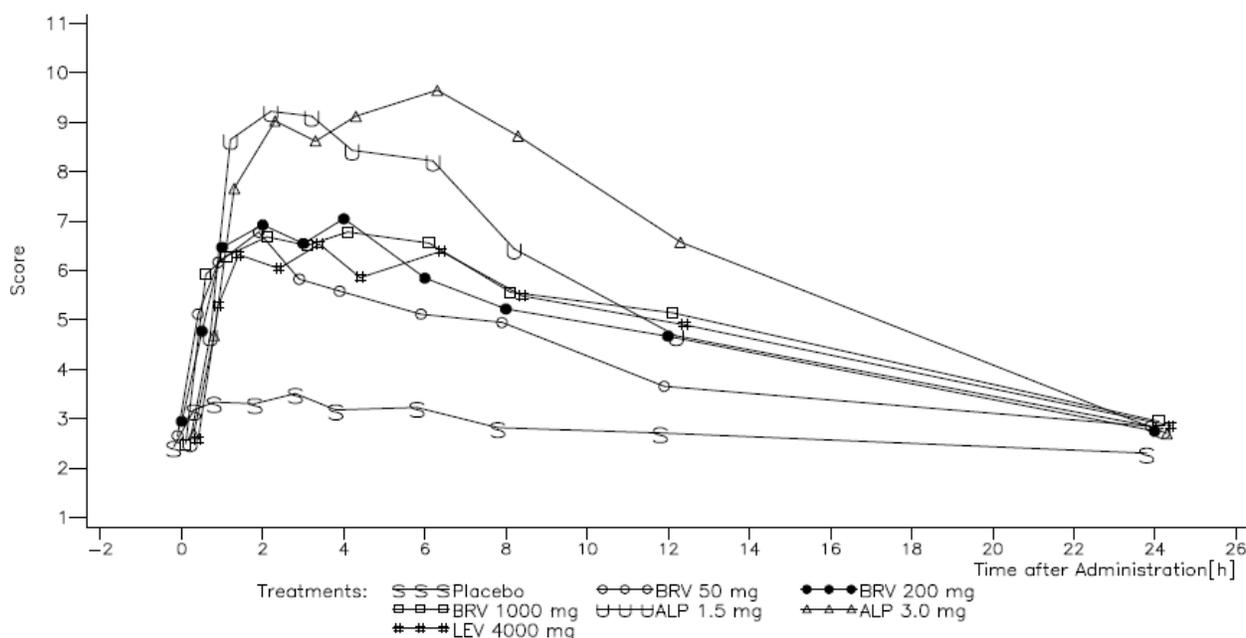
Both doses of ALP, all doses of BRV, and LEV 4000 mg had significantly higher ARCI PCAG Emax values compared to placebo. None of the BRV doses or LEV 4000 mg were significantly different from 2-times placebo on ARCI PCAG Emax values. All doses of BRV had significantly lower ARCI PCAG Emax values compared to both ALP 1.5 mg and 3 mg. LEV also had a significantly lower Emax compared to both ALP doses. ARCI PCAG Emax values for BRV were not significantly different from LEV 4000 mg at any dose.

Table 7: Descriptive statistics for ARCI PCAG by Treatment

Treatment	Mean Emax (SD)	Mean AUE,0-12 (SD)	Mean AUE,0-24 (SD)	
Placebo	4.6 (3.2)	36.6 (20.7)	66.8 (33.5)	39
BRV 50 mg	8.0 (3.3)	61.3 (29.4)	100 (44.4)	41
BRV 200 mg	8.7 (3.4)	68.8 (34.2)	112 (55.8)	40
BRV 1000 mg	8.8 (3.3)	71.8 (33.3)	120 (57.4)	41
ALP 1.5 mg	10.8 (2.4)	85.5 (28.0)	130 (46.2)	41
ALP 3 mg	12.0 (2.1)	98.7 (27.6)	154 (52.5)	40
LEV 4000 mg	8.4 (3.5)	68.5 (34.0)	1150(53.2)	43

ARCI=Addiction Research Center Inventory; AUE=area under the time effect curve; E_{max}=maximum effect; PCAG=Pentobarbital Chlorpromazine Alcohol Group; SD=standard deviation.

As demonstrated in Figure 6, reproduced from the Sponsor's Clinical Study Report N01295, p.86, even though placebo scores increased slightly above Baseline, both ALP doses showed an increase in mean ARCI PCAG scores, which peaked at approximately 2 hours post-dose for the 1.5 mg dose, and 6 hours post-dose for the 3 mg. The increases in ARCI PCAG scores in response to BRV and LEV were lower than those of ALP. The effects of BRV and LEV appeared to be relatively similar in duration and magnitude, other than BRV 50 mg, which showed slightly lower scores, compared to 200 mg and BRV 1000 mg and LEV 4000 mg.

Figure 6: Mean ARCI PCAG Scale (Sedative Effect)

Mean Take Drug Again VAS Scores at 12 and 24 hours

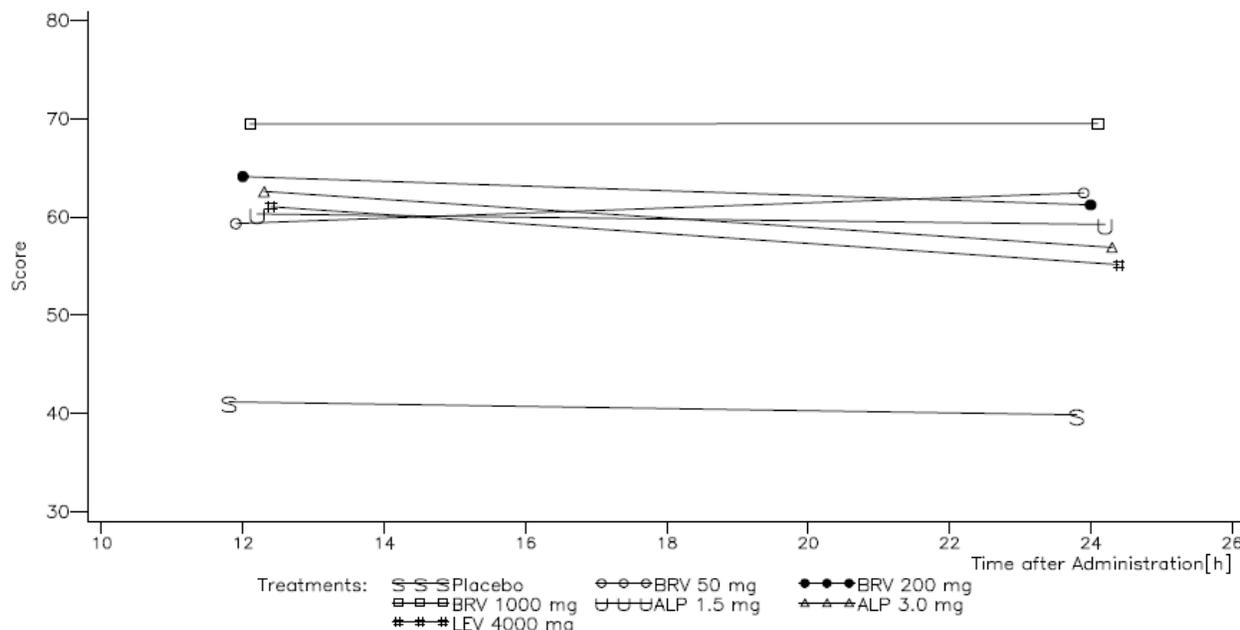
ALP 1.5 mg and 3 mg had significantly higher Take Drug Again Emax values compared to placebo. All BRV doses and LEV 4000 mg were also significantly greater than placebo. Take Drug Again Emax values for BRV 50 mg and 200 mg were not significantly different from ALP 1.5 mg or 3 mg. However, BRV 1000 mg was slightly greater than ALP; this was statistically significant at both ALP doses compared to ALP 1.5 mg and 3 mg. LEV 4000 mg was also not significantly different from either dose of ALP on the Take Drug Again VAS for 1.5 mg and 3 mg. BRV 50 mg and 200 mg were not significantly different from LEV 4000 mg while BRV 1000 mg was slightly higher than LEV 4000 mg.

Table 8: Descriptive statistics for Take Drug Again VAS by Treatment

Treatment	Mean Emax (SD)	Mean Effect (SD)	N
Placebo	44.5 (36.5)	40.5 (33.89)	39
BRV 50 mg	65.0 (34.3)	60.9 (33.01)	41
BRV 200 mg	66.4 (33.9)	62.7 (33.85)	40
BRV 1000 mg	76.8 (28.7)	69.5 (28.78)	41
ALP 1.5 mg	64.0 (32.8)	59.8 (31.58)	41
ALP 3 mg	66.6 (34.3)	59.8 (34.54)	40
LEV 4000 mg	63.7 (35.2)	58.3 (34.02)	43

As demonstrated in Figure 7, reproduced from the Sponsor's Clinical Study Report N01295, p.80, the placebo scores were slightly less than neutral at both timepoints, while scores for the active treatments were similar and in the positive range of the scale at both time points. The scores for BRV 1000 mg were slightly higher than the other treatments. The mean Emax values for active treatments were greater than placebo; these were the lowest for LEV 4000 mg and highest for BRV 1000 mg.

Figure 7: Mean Take Drug Again VAS Scores at 12 and 24 hours



4.1.3 Abuse Potential Analysis: Comparison between BRV and Positive Control

BRV 50 mg showed significantly lower Emax values compared to both ALP doses on 3 of 4 primary endpoints; only the Overall Drug Liking VAS was not significantly different between BRV 50 mg and ALP 1.5 mg and 3 mg. For BRV 200 mg, Emax values of the ARCI PCAG scale were significantly lower compared to ALP 1.5 mg and 3 mg, and lower for the High VAS compared to ALP 3 mg. No significant differences were observed in Drug Liking and Overall Drug Liking VASs.

The highest dose of BRV (1000mg) showed significantly lower ARCI PCAG Emax values compared to ALP 1.5 mg and 3 mg. On the Drug Liking VAS, BRV 1000mg was not significantly different from ALP 1.5 mg, but had a significantly higher effect compared to 3 mg; however, on this scale the 1.5 mg dose showed a higher effect than the 3 mg dose of ALP. On the Overall Drug Liking VAS, BRV 1000 mg had a significantly higher effect compared to ALP 1.5 mg, but was not significantly different from 3 mg. No significant differences were observed between BRV 1000 mg and either dose of ALP on the High VAS.

BRV showed differences from ALP on some positive effects measures; most notably, it was associated with less euphoria at all doses (ARCI MBG). On Good Drug Effects VAS and High VAS, BRV 50 mg had significantly lower effects compared to both ALP doses. In addition, all BRV doses showed significantly fewer sedative effects compared to ALP and fewer stimulant-like effects, in particular, as compared to the 3 mg dose. Any Drug Effects were lower

for 50 mg BRV, but not different between 200 mg and 1000 mg BRV compared to ALP. A pairwise comparison between BRV and ALP is summarized for the primary variables in Table 9.

Table 9: ANOVA/ANCOVA Results for BRV vs ALP (Emax of Primary Variables)

Estimate of Difference (95% CI)						
	ALP 1.5 mg			ALP 3 mg		
	BRV 50 mg	BRV 200 mg	BRV 1000 mg	BRV 50 mg	BRV 200 mg	BRV 1000 mg
Drug Liking VAS	-8.9 (-14.1, -3.6)	-4.7 (-10.3, 1.0)	1.5 (-2.7, 5.7)	-5.5 (-10.8, -0.1)	-1.2 (-7.0, 4.6)	4.9 (0.5, 9.3)
Overall Drug Liking VAS	-2.0 (-9.2, 5.3)	-1.1 (-8.8, 6.6)	7.1 (0.1, 14.2)	-4.2 (-12.5, 4.2)	-3.3 (-12.1, 5.5)	4.9 (-3.3, 13.1)
High VAS	-12.0 (-19.0, -4.9)	-6.2 (-12.7, 0.2)	1.0 (-5.8, 7.8)	-13.0 (-19.1, -7.0)	-7.3 (-12.6, -2.0)	-0.03 (-5.7, 5.7)
ARCI PCAG	-3.0 (-4.0, -1.9)	-2.1 (-3.2, -1.1)	-2.0 (-3.1, -1.0)	-4.1 (-5.1, -3.1)	-3.2 (-4.3, -2.2)	-3.2 (-4.2, -2.1)

4.1.4 Assessment of Study NO1295 Data, Confirmed by Dr. Liu's Statistical Conclusions (DARRTS 3/12/15)

- The assay sensitivity showed a significant difference between the placebo and both doses of ALP.
- There were significant differences at all doses of BRV compared with placebo in all primary endpoints, suggesting the drug-abuse potential of BRV.
- There were no significant differences of all BRV testing doses from the positive control ALP in drug-liking (at the moment) VAS. These results support the potential for BRV abuse.
- High doses of LEV (4,000mg) demonstrated drug liking similar to BRV and ALP on most primary endpoints.

4.2 Adverse Event Profile through All Phases of Development

All TEAEs that occurred after the start of study drug were searched for by the Sponsor using a list of potentially abuse-related adverse events (AEs) shown in their table, reproduced in Table 10. Adverse events were coded using the Medical Dictionary of Regulatory Activities (MedDRA) version 15.0, and presented by system organ class and preferred term.

Table 10: Potentially Abuse-Related Adverse Events

ABNORMAL BEHAVIOUR*	DRUG SCREEN POSITIVE	MOOD SWINGS
ABNORMAL DREAMS*	DRUG TOLERANCE	MULTIPLE DRUG OVERDOSE
ACCIDENTAL OVERDOSE	DRUG TOLERANCE DECREASED	MULTIPLE DRUG OVERDOSE ACCIDENTAL
ACCIDENTAL POISONING	DRUG TOLERANCE INCREASED	MULTIPLE DRUG OVERDOSE INTENTIONAL
ACUTE PSYCHOSIS*	DRUG WITHDRAWAL CONVULSIONS	MUSCLE RIGIDITY
AFFECT LABILITY*	DRUG WITHDRAWAL HEADACHE	NEEDLE TRACK MARKS
AFFECTIVE DISORDER*	DRUG WITHDRAWAL MAINTENANCE THERAPY	NEONATAL COMPLICATIONS OF SUBSTANCE ABUSE*
AGGRESSION*	DRUG WITHDRAWAL SYNDROME	NERVOUSNESS
AGITATION*	DRUG WITHDRAWAL SYNDROME NEONATAL	NIGHTMARE
AGITATION POSTOPERATIVE	DYSARTHRIA	OVERDOSE
AMNESIA	ELEVATED MOOD*	PARAESTHESIA
ANGER	EMOTIONAL DISORDER*	PARANOIA*
ANXIETY*	EMOTIONAL DISTRESS*	PERSONALITY CHANGE*
ASTHENIA	ENERGY INCREASED	POLYSUBSTANCE DEPENDENCE*
COGNITIVE DISORDER	EUPHORIC MOOD	PSYCHOMOTOR HYPERACTIVITY
COMMUNICATION DISORDER	FATIGUE	PSYCHOMOTOR SKILLS IMPAIRED
CONFUSIONAL STATE	FEELING ABNORMAL	PSYCHOTIC DISORDER*
DELIRIUM*	FEELING DRUNK	REBOUND EFFECT
DELUSION*	FEELING JITTERY	RESTLESSNESS
DEPENDENCE*	FEELING OF RELAXATION	SEDATION
DEPERSONALISATION*	FLASHBACK*	SENSORY DISTURBANCE
DEPRESSED MOOD	HALLUCINATION	SKIN NECROSIS
DEPRESSION	HALLUCINATION, AUDITORY	SLUGGISHNESS
DEREALISATION*	HALLUCINATION, OLFATORY	SOMATIC DELUSION*
DISORIENTATION*	HALLUCINATION, SYNAESTHETIC	SOMATIC HALLUCINATION*
DISSOCIATION*	HALLUCINATION, TACTILE	SOMNOLENCE
DISSOCIATIVE DISORDER	HALLUCINATION, VISUAL	STEROID WITHDRAWAL SYNDROME
DISTURBANCE IN ATTENTION	HALLUCINATIONS, MIXED	STUPOR
DISTURBANCE IN SOCIAL BEHAVIOUR*	HOSTILITY*	SUBSTANCE ABUSE*
DIZZINESS	HYPERVIGILANCE*	SUBSTANCE ABUSER
DRUG ABUSE*	HYPOAESTHESIA	SUBSTANCE USE
DRUG ABUSER	ILLUSION*	SUBSTANCE-INDUCED MOOD DISORDER*
DRUG ADMINISTERED AT INAPPROPRIATE SITE	IMPATIENCE	SUBSTANCE-INDUCED PSYCHOTIC DISORDER*
DRUG DEPENDENCE*	INAPPROPRIATE AFFECT*	THINKING ABNORMAL*

Table 10: (cont'd)

DRUG DEPENDENCE, ANTEPARTUM*	INDIFFERENCE	THOUGHT BLOCKING*
DRUG DEPENDENCE, POSTPARTUM*	INTENTIONAL DRUG MISUSE*	TOXICITY TO VARIOUS AGENTS
DRUG DETOXIFICATION	INTENTIONAL OVERDOSE	TRANSIENT PSYCHOSIS*
DRUG DIVERSION	LETHARGY	WITHDRAWAL ARRHYTHMIA
DRUG LEVEL ABOVE THERAPEUTIC	MATERNAL USE OF ILLICIT DRUGS	WITHDRAWAL SYNDROME
DRUG LEVEL INCREASED	MEMORY IMPAIRMENT	
DRUG REHABILITATION	MENTAL IMPAIRMENT	
DRUG SCREEN	MOOD ALTERED	

* Terms found on the proposed list by Love & Sun, 2013.

The primary pool for evaluation of abuse potential used in this Review was the Phase 3 double-blinded, placebo-controlled pool (the largest pool) for the primary indication of POS. Most of these AEs were further assessed and substantiated by reviewing the accompanying patient case report form narratives. The remaining patient pools consisted of Phase 1 studies (including the Human Abuse Potential Study NO1295) along with studies of special populations including elderly subjects, those with renal and hepatic insufficiency as well as pediatric populations. All together, these included many fewer subjects than the primary pool and did not reveal any AEs not seen in that pool.

The most common TEAE in the category of euphoria-related events and hallucinations was dizziness, which occurred in a higher incidence with BRV compared to placebo. All other events of this nature occurred in less than 1.0% of subjects. Feeling drunk was reported in 5 BRV-treated subjects and none in the placebo-treated subjects. Euphoric mood was reported in 3 subjects (0.2%), which was similar to placebo (0.3%). All other events occurred only in 1 or 2 subjects, including in some cases only placebo-treated subjects. Overall, 1000mg BRV was associated with the highest incidence of euphoric mood, followed by the other BRV doses (200mg and 50mg) and LEV (4000mg), while the incidence of euphoric mood following ALP (1.5mg and 3mg) was lower.

Sedative-related TEAEs were the most common type of event overall, with somnolence occurring in 11.9% of BRV-treated subjects compared to 6.4% with placebo. Fatigue was also more common in BRV-treated subjects (7.4%) vs. placebo-treated subjects (3.4%).

The incidence of stimulant-related or dissociative/psychotic events was very low (<1.0% of subjects). The most common event in the stimulant category was nervousness (0.8% with BRV vs. 0.4% with placebo), and the most common event in the dissociative/psychotic category were paresthesia (0.9% in both groups) and aggression (0.8% with BRV vs 0.7% with placebo). Other CNS events, including mood disorders and motor/cognitive impairment events also occurred with a low incidence. The most common events of these types were depression (1.7% with BRV vs. 0.6% with placebo) and anxiety (1.6% with BRV vs. 0.7%with placebo) in the mood

disorders category, and memory impairment (1.0% with BRV vs. 0.7% with placebo) in the motor/cognitive impairment category.

Table 11: Potentially Abuse-Related AEs in Pooled Phase 3 Studies

Preferred Term	Placebo N=686 n (%)	Overall BRV N=1717 n (%)
Lethargy	1 (0.1)	3 (0.2)
Nervousness	3 (0.4)	13 (0.8)
Restlessness	2 (0.3)	7 (0.4)
Psychomotor hyperactivity	0	4 (0.2)
Energy increased	0	1 (<0.1)
Feeling jittery	1 (0.1)	0
Paresthesia	6 (0.9)	15 (0.9)
Aggression	5 (0.7)	13 (0.8)
Hypoesthesia	3 (0.4)	9 (0.5)
Agitation	0	9 (0.5)
Confusional state	1 (0.1)	6 (0.3)
Abnormal behavior	1 (0.1)	3 (0.2)
Nightmare	1 (0.1)	3 (0.2)
Anger	1 (0.1)	3 (0.2)
Abnormal dreams	2 (0.3)	2 (0.1)
Psychotic disorder	2 (0.3)	2 (0.1)
Disorientation	0	1 (<0.1)
Sensory disturbance	1 (0.1)	1 (<0.1)

4.3 Safety Profile

Seven subjects (0.4%) in the BRV group experienced treatment-emergent serious adverse events (SAEs) potentially related to abuse potential compared with 1 placebo-treated subject (0.1%). In the BRV group, treatment-emergent SAEs of fatigue, amnesia, dizziness, agitation and depression were each reported in 1 subject, while an SAE of psychotic disorder was reported in 2 subjects. One placebo-treated subject had a SAE of depression. There were no reports of abuse, misuse, dependence or withdrawal with BRV. A few TEAEs related to outcomes possibly associated with substance abuse were associated with other AEDs administered during BRV studies (e.g., some other AED drug levels increased, with associated toxicity to various agents).

None of the AEs of ‘overdose’ reported during clinical development were related to overdose of BRV alone. BRV did not cause acute or chronic intoxication in humans after oral intake of multiples of the pharmacologically active doses. There are no data on single intakes exceeding 1400mg, but at that dose somnolence and dizziness were the most frequently reported AEs. In humans, the maximum tolerated dose of BRV was 1000mg after single intake and 800mg/day after repeated dosing during 2 weeks.

4.4 Evidence of Abuse, Misuse and Diversion in Clinical Trial

Eleven placebo-treated subjects (1.6%) had potentially abuse-related TEAEs associated with permanent discontinuation of the study drug compared with 43 BRV-treated subjects (2.5%). The most common of these were dizziness (0.6% with BRV vs. 0.1% with placebo), depression (0.5% with BRV vs. 0.3% with placebo), fatigue (0.3% with both treatments), and somnolence (0.3% with BRV vs. 0.1% with placebo).

There were no reports of diversion in any of the TEAE analysis sets for BRV (preferred term: drug diversion), additionally the Sponsor reports no cases of diversion during clinical development of BRV.

4.5 Tolerance and Physical Dependence Studies in Humans

Physical dependence potential might be suspected if there was an increase in incidence of adverse events from on-treatment to down-titration to post-treatment and/or if there was a change in a pattern of events across these periods. Convulsions were the only adverse event which occurred with significance and increased with down-titration in 3 patients. This is most likely due to the subjects POS history and not a withdrawal event from BRV. No epileptic subjects in Phase 3 studies had abrupt discontinuation of BRV without a down-titration as this might exacerbate the patient's underlying seizure disorder.

A cohort of patients, without epilepsy, in Phase 2 Study NO1162 was evaluated after discontinuation of BRV without a taper period. Four weeks of treatment with BRV 200 mg/day (intended maximally recommended daily dose) did not cause any relevant signs of withdrawal symptoms following abrupt discontinuation. Overall, there appeared to be a much higher incidence of AEs during treatment than occurred following abrupt discontinuation of BRV.

Tolerance to BRV was difficult to assess in these clinical trials. The efficacy of treating POS appeared to remain stable at any given dosage and it was not possible to determine if a breakthrough seizure was secondary to tolerance or the patient's underlying epileptic disorder. Since BRV treatment was maintained over time for subjects completing each time point there appeared to be limited potential for tolerance to develop to the effects of BRV on seizure reduction.

5. Regulatory Issues and Assessment

None

6. Other Relevant Information

None

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/s/

MARTIN S RUSINOWITZ
02/16/2016

MICHAEL KLEIN
02/17/2016

**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: December 30, 2015

To: Billy Dunn, MD
Director
Division of Neurology Products (DNP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

Shawna Hutchins, MPH, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Mathilda Fienkeng, PharmD
Team Leader
Office of Prescription Drug Promotion (OPDP)

From: Nyedra W. Booker, PharmD, MPH
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Dhara Shah, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

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

Drug Name (established name), Dosage Form and Route, Application Type/Number: BRIVIACT (brivaracetam) tablets for oral use, NDA 205836
BRIVIACT (brivaracetam) injection for intravenous use, NDA 205837
BRIVIACT (brivaracetam) oral solution, NDA 205838

Applicant: UCB, Inc.

1 INTRODUCTION

On November 19, 2014 UCB, Inc. submitted for the Agency's review, an original New Drug Application (NDA) for BRIVIACT (brivaracetam) tablets for oral use, BRIVIACT (brivaracetam) injection for intravenous use, and BRIVIACT (brivaracetam) oral solution. The proposed indication for BRIVIACT (brivaracetam) is for adjunctive therapy in the treatment of partial onset seizures in patients 16 years of age and older with epilepsy.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology Products (DNP) on January 6, 2015 and January 9, 2015, respectively for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for BRIVIACT (brivaracetam) tablets for oral use, BRIVIACT (brivaracetam) injection for intravenous use, and BRIVIACT (brivaracetam) oral solution.

2 MATERIAL REVIEWED

- Draft BRIVIACT (brivaracetam) tablets for oral use, BRIVIACT (brivaracetam) injection for intravenous use, and BRIVIACT (brivaracetam) oral solution MG received on November 19, 2014 and received by DMPP on December 16, 2015.
- Draft BRIVIACT (brivaracetam) tablets for oral use, BRIVIACT (brivaracetam) injection for intravenous use, and BRIVIACT (brivaracetam) oral solution MG received on November 19, 2014, and received by OPDP on December 22, 2015.
- Draft BRIVIACT (brivaracetam) tablets for oral use, BRIVIACT (brivaracetam) injection for intravenous use, and BRIVIACT (brivaracetam) oral solution Prescribing Information (PI) received on November 19, 2014 and received by DMPP on December 16, 2015.
- Draft BRIVIACT (brivaracetam) tablets for oral use, BRIVIACT (brivaracetam) injection for intravenous use, and BRIVIACT (brivaracetam) oral solution Prescribing Information (PI) received on November 19, 2014, revised by the Review Division throughout the review cycle, and received by OPDP on December 22, 2015.

3 REVIEW METHODS

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

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more

accessible for patients with vision loss. We have reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

SHAWNA L HUTCHINS
12/30/2015

DHARA P SHAH
12/30/2015

LASHAWN M GRIFFITHS
12/30/2015

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

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

Memorandum

Date: December 23, 2015

To: Eric Bastings, M.D., Deputy Director,
Division of Neurology Products (DNP)

Norman Hershkowitz, M.D., Lead Medical Officer, DNP

Steven Dinsmore, M.D., Medical Officer, DNP

Cathleen Michaloski, BSN, MPH, RAC
Sr. Regulatory Project Manager, DNP

From: Dhara Shah, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Mathilda Fienkeng, PharmD, Team Leader OPDP

Subject: OPDP draft full Prescribing Information (PI), Medication Guide, and carton and container labeling comments for BRIVIACT (brivaracetam) Tablets for Oral Use, Oral Solution and Injection, for Intravenous Use

NDA: 205836, 205837, 205838

On January 9, 2015, DNP consulted OPDP to review the proposed package insert (PI), Medication Guide, and carton and container labeling for BRIVIACT (brivaracetam) Tablets for Oral Use, Oral Solution and Injection, for Intravenous Use (Briviact).

PI

OPDP reviewed the version of the draft PI titled "Briviact PI MG 12.16 DNP clean 205836, 7, 8" obtained through the DNP Sharepoint on December 22, 2015, and our comments are provided below.

Medication Guide

A combined OPDP and Division of Medical Policy Programs (DMPP) patient labeling review is being conducted and comments on the Medication Guide will be sent under separate cover.

Carton and Container Labeling

OPDP reviewed the draft carton and container labeling accessed on December 22, 2015, through the following eCTD links:

- [Application 205836 - Sequence 0041 - 1.14.1.1 Draft Carton and Container Labels -](#)
- [Application 205837 - Sequence 0037 - 1.14.1.1 Draft Carton and Container Labels -](#)
- [Application 205838 - Sequence 0038 - 1.14.1.1 Draft Carton and Container Labels -](#)

OPDP has the following comments:

OPDP is concerned that the prominence and disparate font styles of the established name and proprietary name in the presentations on the carton and container labeling do not meet the regulatory requirements. Therefore, OPDP recommends revising the established name on the proposed carton and container labeling to be in accordance with 21CFR 201.10(g)(2) which states that, “[t]he established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.”

The draft carton and container labeling includes presentations marked “FPO” (for placement only). Please note that that OPDP is unable to comment on the acceptability of presentations labeled FPO.

Thank you for your consult. If you have any questions, please contact Dhara Shah (240) 402-2859 or Dhara.Shah@fda.hhs.gov.

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/s/

DHARA P SHAH
12/23/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM TO FILE

From: Hari Cheryl Sachs, M.D.
Team Leader, Pediatrics Team
Division of Pediatric and Maternal Health

Through: Lynne P. Yao, M.D., Division Director,
Division of Pediatric and Maternal Health

To: The Division of Neurology Products (DNP)

Drug: BRIVIACT (brivaracetam) tablets, solution, injection

NDAs: 205836, 205837, 205838

Applicant: UCB

Drug Class: Antiepileptic

Indication(s) partial onset seizures (POS)

Subject: Review of Pediatric Review Committee (PeRC) paperwork

Materials Reviewed:

- September 30, 2014, agreed upon initial Pediatric Study Plan (iPSP)
- PeRC paperwork

BACKGROUND

DPMH was consulted by DNP to review the PeRC paperwork for Briviact [brivaracetam (BRV) tablets, solution and intravenous], a New Molecular Entity (NME) submitted for the treatment of partial onset seizures (POS) in patients 16 years and older with epilepsy.

We refer to the September 30, 2014, agreed initial pediatric study plan (iPSP) to study brivaracetam in pediatric patients (≥ 1 month to < 16 years of age) as adjunctive treatment for POS summarized below.

Pediatric Plan Summary

The applicant requested a partial waiver for the neonatal age group (birth to < 1 month of age) based on the exclusion of the neonatal age group from the International League Against Epilepsy (ILAE) definition of epilepsy associated with POS and because studies are impossible or highly impracticable in neonates because there are too few children with confirmed epilepsy in this age group.

The applicant has completed an open-label, PK study of adjunctive administration of BRV in pediatric epilepsy patients 1 mo and older and requested a deferral of the following pediatric studies with POS in ages 1 month to < 16 years on the basis that pediatric studies have not yet been completed and BRV is ready for approval in adults:

Study	Description	Protocol submission	Study Initiation	Estimated Final Report Submission
N1266	Long term open-label safety study (1 mo to < 17 y)	Mar 2011	(b) (4)	(b) (4)
(b) (4)	Double-blind, efficacy and safety study (1 mo to 4 years)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	Intravenous PK and safety study (1 mo to (b) (4) years)	(b) (4)	(b) (4)	Jun 2020

Information abstracted from agreed upon iPSP Tables 5-1 and 10-1.

This partial waiver and studies in the deferral request matches the agreed-upon iPSP.



(b) (4)

DPMH Recommendations and Conclusion

DPMH provided input into preparation of the PeRC documents. DPMH advised that, depending on the timing of communications regarding the division's decision (b) (4)

(b) (4) he timing of the studies may also require adjustment.

On Nov 18, 2015, DNP presented the pediatric program to PeRC and revised the pediatric plan (b) (4) The plan will now include the following POS studies:

- PK and safety study (4 years and older)
- Efficacy study (1 mo to 4 years of age)
- Long-term safety (1 mo and older)

PeRC agrees with the modifications in the plan (see PeRC minutes, pending).

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/s/

HARI C SACHS
11/24/2015

LYNNE P YAO
11/28/2015

M E M O R A N D U M

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

DATE: November 16, 2015

TO: William H. Dunn M.D.
Director (Acting)
Division of Neurology Products
Office of Drug Evaluation I
Office of New Drugs

FROM: Xiaohan Cai, Ph.D. and Sripal R. Mada, Ph.D.
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Director (Acting)
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

SUBJECT: Review of EIR covering NDA 205837 and NDA 205838
inspection conducted at PRA, Zuidlaren, The
Netherlands

At the request of Division of Neurology Products, Office of Drug Evaluation I, Office of New Drugs, the Office of Study Integrity and Surveillance (OSIS), Office of Translational Sciences (OTS) arranged an inspection of the following clinical studies at PRA, Zuidlaren, The Netherlands.

Studies:

EP0007: "A Randomized, Single-Center, Open-Label, 5-Way Crossover, Single-Dose Bioavailability/Bioequivalence Comparison of Brivaracetam Oral Tablets (10 mg, 50 mg, 75 mg, and 100 mg) and Brivaracetam Intravenous Bolus Injection (100 mg) in Healthy Volunteers"

N01296: "Randomized, Monocenter, Open-Label, Two-Way Cross-Over, Single-Dose Bioequivalence Study of Two Different Formulations of Brivaracetam in Healthy Fasting Subjects"

ORA Inspector Sandra S. Saniga conducted inspection of clinical portions of studies EP0007 and N01296 at PRA from September 07-11, 2015. The audit included a thorough review and examination of facilities, personnel records, electronic records and signatures, protocols, subject records, subject consent forms, IRB documentation, test article accountability, and interviews and discussions with PRA's management and staff. Reserve samples were collected for study N01296 only. Following the inspection of clinical portions, Form FDA 483 was issued to PRA (Attachment 1). The firm responded to Form FDA 483 on October 1, 2015 (Attachment 2). The Form FDA 483, the firm's response to Form FDA 483, and our evaluation follow.

OBSERVATION 1:

The informed consent document lacked a description of reasonably foreseeable risks or discomforts to the subject.

Specifically, the UCB Investigator's Brochure for Brivaracetam (or BRV), dated 08 Nov 2012, states that the Predicted AEs that are common with the class of drugs to which BRV belongs, and/or AEs that may be predicted to occur based on the pharmacological properties of BRV, even if not yet observed with BRV, include elevated liver enzymes, weight change, osteoporosis, dysarthria, disturbance in attention, emotional lability/mood swings, hostility, rash/Stevens Johnson Syndrome, and vomiting.

The informed consent document for Study EP0007 that used the investigational drug Brivaracetam failed to include this information.

Firm's Response: The firm acknowledged that not all of the predicted adverse events (AEs) for both healthy volunteers and patients that were listed in the Investigator's Brochure for BRV were included in the informed consent form (ICF). The AEs in the ICF only included AEs that occurred in healthy volunteers. As corrective action, PRA will include within the ICF any predicted AEs that are included in the Investigator's Brochure. In addition, PRA will change their SOPs to add a formal and documented risk review on all of the potential AEs to be added to the ICF.

OSIS Evaluation:

Because study EP0007 enrolled healthy subjects and no aforementioned AEs in the 483 observation were reported as drug related, there is no evidence that the safety of the subjects was compromised. In the opinion of this reviewer, the proposed corrective actions are acceptable and this observation is not likely to affect the study outcome.

Conclusion:

Following review of the inspectional findings, this reviewer concludes that the data from the audited studies are reliable. Therefore, this reviewer recommends that the clinical portion of the following studies be accepted for further Agency review:

Application	Studies	Drug Product	Sponsor	Recommend
NDA 205837	EP0007	Brivaracetam Intravenous Bolus Injection	UCB Pharma SA, Brussels, Belgium	Acceptable
NDA 205838	N01296	Brivaracetam Oral Solution 10 mg/mL (1%)	UCB Pharma SA, Brussels, Belgium	Acceptable

Xiaohan Cai, Ph.D.
OSIS, DGDBE

Sripal R. Mada, Ph.D.
OSIS, DGDBE

Final Site Classification:

VAI - PRA, Zuidlaren, The Netherlands
FEI: 3005991010

CC:

OSIS/Kassim/Taylor/Miller/Nkah/Fenty-Stewart/Kadavil
OSIS/DGDBE/Haidar/Skelly/Choi/Cai
OSIS/DNDBE/Bonapace/Dasgupta/Cho
OND/ODE-I/ONP/Dunn

ORAHQ/OMPTO/DMPTI/BIMO/Arline/Turner/Alexis/Braswell/Johnson
/Colon/Saniga

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical
Sites/PRA, Zuidlaren, The Netherlands

Draft: XC 11/03/2015

Edit: YMC 11/13/2015; SRM 11/16/2015; SHH 11/16/2015

NDA 205837; OSI file# BE6895; Study# EP007

NDA 205838; OSI file# BE6895; Study# N01296

FACTS: **11537383**

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/s/

XIAOHAN CAI
11/16/2015

SRIPAL R MADA
11/17/2015

SAM H HAIDAR
11/17/2015

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: November 9, 2015

Requesting Office or Division: Division of Neurology Products (DNP)

Application Type and Number: NDA 205836, NDA 205838, NDA 205837

Product Name and Strength: Briviact (brivaracetam)
Tablets, 10 mg, 25 mg, 50 mg, 75mg, and 100 mg
Oral Solution 10 mg /mL
Injection 10 mg/mL

Submission Date: August 28, 2015

Applicant/Sponsor Name: UCB Inc.

OSE RCM #: 2014-2544-1, 2014- 2545-1, 2014-2546-1

DMEPA Primary Reviewer: Justine S. Harris, BS, RPh

DMEPA Team Leader: Danielle Harris, PharmD, BCPS

1 PURPOSE OF MEMO

The Division of Neurology Products (DNP) requested that we review the revised container label and carton labeling for Briviact (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSION

¹ Harris J. Label and Labeling Review for Briviact (NDAs 205836, 205838, and 205837). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 JUN 25. 26 p. OSE RCM No.: 2014-2544, 2014-2545, 2014-2546.

The revised container label and carton labeling for Briviact is acceptable from a medication error perspective. We have no further recommendations at this time.

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/s/

JUSTINE HARRIS
11/10/2015

DANIELLE M HARRIS
11/10/2015

M E M O R A N D U M

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

DATE: October 8, 2015

TO: William H. Dunn M.D.
Director (Acting)
Division of Neurology Products
Office of Drug Evaluation I
Office of New Drugs

FROM: Hasan A. Irier, Ph.D. and Xikui Chen, Ph.D.
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Director (Acting)
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

SUBJECT: Review of EIR covering NDA 205838 routine inspection
conducted at **UCB Inc., Chemin de Foriest, B-1420
Briane-1' Alleud, Belgium.**

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1. Summary

At the request of Division of Neurology Products, Office of Drug Evaluation I, Office of New Drugs, Xikui Chen, Ph.D. and Hasan Irier, Ph.D. (from the Office of Study Integrity and Surveillance at the Office of Translational Sciences) audited analytical portions of the following two studies utilizing a bioequivalence surveillance inspection approach at **UCB, Chemin de Foriest, B-1420 Briane-1' Alleud, Belgium**, between **September 20 and 26, 2015.**

Review Div.	Appl.	Study	Facility	Drug Product	Sponsor	Recommend
ODE-I, OND	NDA 205837	N01296	Analytical	Brivaracetam(BRV ,ucb 34714) 1%(10 mg/mL)oral Solution	UCB Inc.	Acceptable
Surveillance Inspection	NDA 205836	N01287	Analytical	Brivaracetam(BRV ,ucb 34714) Capsule	UCB Inc.	Acceptable

N01296 (NDA 205838 and NDA 205836): "Randomized, monocenter, open-label, two-way cross-over, singledose bioequivalence study of two different formulations of brivaracetam in healthy fasting subjects"

Date First Sample Analyzed: February 21, 2008

Date Last Sample Analyzed: March 12, 2008

N01287 (NDA 205836): "Monocenter, open-label, randomized, five-way cross-over relative bioavailability/bioequivalence study of BRV solid oral formulations (capsule and tablet) using as reference BRV oral solution with assessment of food effect on BRV oral tablet formulation."

Date First Sample Analyzed: August 9 2007

Date Last Sample Analyzed: September 4, 2007

2. Recommendation

NDA 205837 and NDA 205836:

In the opinion of OSIS reviewers, the firm provided adequate responses to inspectors' queries relevant to the studies N1296 (NDA 205838)and N01287(NDA 205838). the OSIS reviewers concluded that the data from these studies are acceptable for further agency review.

3. Inspectional Findings

The audit included a thorough review of method validation and study records, examination of facility, equipment, interviews and discussions with the firm's management and staff.

Following the inspection of analytical studies N01296 and N01287 at **UCB, Chemin de Foriest, B-1420 Briane-l' Alleud, Belgium, during September 20-26, 2015**, OSIS inspectors, Xikui Chen, Ph.D. and Hasan Irier, Ph.D., concluded that the firm's bioanalytical aspects (method development, validation and sample analysis etc.) are sound and data generated from the two studies audited during this inspection are acceptable. At the conclusion of the inspection, Form FDA-483 was not issued. OSIS inspectors discussed the following item with the firm at the end of the inspection:

1. **During the LC/MS/MS data analyses, the firm manually integrated chromatographic peaks for few of the blanks and pre-dose samples during the study sample runs.** OSIS investigators verified that no quality control and calibrator chromatographic peaks were manually integrated. Upon request by the OSIS investigators, the firm further provided re-analysis of study sample runs without any manual integration of the chromatographic peaks as a comparison to demonstrate that the manual integration did not impact the outcome of the study (**Attachment 1**). The firm also provided documentation stating that since 2009 the firm has not practiced manual integration of the chromatographic peaks. The firm updated their SOPs and trained their staff/analysts regarding automated peak integration of chromatographic peaks accordingly. (**Attachment 2**)

4. Final Site Classification

NAI - UCB, Chemin de Foriest, B-1420 Briane-l' Alleud, Belgium
FEI:3003909356

Xikui Chen -A

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DN: c=US, o=U.S. Government, ou=FDA, ou=People,
cn=Xikui Chen -A, 0.9.2342.19200300.100.1.1=1300181501
Date: 2015.10.08 16:51:38 -04'00'

Xikui Chen, Ph.D.

Hasan Irier -S

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cn=Hasan Irier -S, 0.9.2342.19200300.100.1.1=2001568214
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Hasan Irier, Ph.D.

Sam H. Haidar -S

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Sam H. Haidar, Ph.D., R.Ph.

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OSIS/Kassim/Taylor/Dejernett/Nkah/Fenty-Stewart
OSIS/DGDBE/Chen/Irier/Choi/Skelly/Haidar
OND/ODE-I/ONP/Dunn

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/ANALYTICAL
SITES/UCB-Pharma-Inc-Briane-l' Alleud, Belgium/NDA 205838_Brivaracetam

Draft: HAI 10/02/2015

Edit: SHH 10/08/2015

OSI: BE6895; O:\Bioequiv\EIRCover\205838.ucb.bri
FACTS: 11579403

5. Attachments

Attachment-1. Manual Integration Investigation Report

Attachment-2. SOP 010233-Update and Staff Training records on Manual
Integration Practice.

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/s/

HASAN A IRIER
10/09/2015

XIKUI CHEN
10/09/2015

SAM H HAIDAR
10/10/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: June 25, 2015

Requesting Office or Division: Division of Neurology Products (DNP)

Application Type and Number: NDA 205836, NDA 205838, NDA 205837

Product Name and Strength: Briviact (brivaracetam)
Tablets 10 mg, 25 mg, 50 mg, 75mg, and 100 mg
Oral Solution 10 mg/mL
Injection 10 mg/mL

Product Type: Single Ingredient

Rx or OTC: Rx

Applicant/Sponsor Name: UCB Inc.

Submission Date: November 19, 2014

OSE RCM #: 2014-2544, 2014-2545, 2014-2546

DMEPA Primary Reviewer: Justine S. Harris, BS, RPh

DMEPA Team Leader: Danielle Harris, PharmD, BCPS

1 REASON FOR REVIEW

The Division of Neurology Products asked the Division of Medication Error Prevention and Analysis (DMEPA) to review the proposed labels and labeling for Briviact (brivaracetam) tablets, oral solution, and injection (NDAs 205836, 205838, 205837) to determine if they are at risk for confusion that can result in medication errors

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B-N/A
Previous DMEPA Reviews	C
Human Factors Study	D-N/A
ISMP Newsletters	E- N/A
Other	F –N/A
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

UCB Inc. submitted NDA 205836, pursuant to Section 505(b), for the approval to market brivaracetam tablets (10 mg, 25 mg, 50 mg, 75 mg, and 100 mg) as adjunctive therapy in the treatment of partial onset seizures in patients 16 years of age and older with epilepsy. Also submitted, in parallel, are NDAs for the approval to market brivaracetam injection (10 mg/mL) and an oral solution (10 mg/mL) for the same indication. We reviewed the carton and container labeling, Prescribing Information (PI) and Medication Guide submitted by UCB Inc. to determine if they are at risk for confusion that can result in medication errors. We identified the following areas of vulnerability to medication errors in the container labels, carton labeling, and prescribing information labeling:

- The numeric doses provided in Section 2.1 are not all followed by a corresponding unit of measure. To avoid confusion, we recommend addition of the unit of measure to all doses.
- Section 2.2 presents diluents in terms that are not recognized by healthcare providers (i. [REDACTED] (b) (4)) and should be revised to use familiar terms.
- [REDACTED] (b) (4)
[REDACTED] We recommend these dosage

adjustments appear in the *Dosage and Administration* Section of Highlights to prevent them from being overlooked.

- The oral solution is to be discarded 5 months after opening the container, and a place to record (b) (4) is present on the container and carton labeling. To avoid use beyond 5 months of first opening the bottle, we recommend replacing the words “(b) (4) _____” with “Discard after ____.” In addition, we note that there is a statement in Section 16.2 Storage “Discard any unused TRADENAME oral solution remaining after 5 months of first opening the bottle.” To prevent this information from being overlooked, we recommend that this information also be included in Section 2.2 Administration Instructions.
- Prior to discontinuing the product, a gradual dose reduction is recommended, however, there is no instruction in the PI for how this is to be accomplished.
- The prescription samples, which are available as 14-count blister packs, do not include the milligram per tablet strength, which may lead patients to misinterpret dosage, i.e. entire package vs. tablet. Additionally, the critical information (medication name, strength, lot number, expiration date, (b) (4) and manufacturer) only appear once on the blister packaging. This information should appear over each individual blister so that the critical information remains available to the end user up to the point at which the last dose is removed.
- The NDC numbers for the single vial and carton of 10 vials are the same, which may cause confusion for healthcare providers.
- UCB, Inc. proposes that a Medication Guide be dispensed to each patient; however, this reminder is not consistently displayed on container labels.
- The route of administration is not prominently displayed on the carton labeling for the injection, which may lead to errors in route of administration.
- The net quantity for the hospital unit dose carton can be revised to increase clarity of the packaging configuration.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase clarity, readability, and the prominence of important information to promote the safe use of this product. We provide recommendations in Sections 4.1 and 4.2.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. Revise all labeling to reflect the approved proprietary name, Briviact.
2. Ensure all doses are followed by the appropriate unit of measure throughout the labeling. For example, in Section 2.1 revise “50, 100, and 200 mg” to read “50 mg, 100 mg, and 200 mg.”

3. In Section 2.2, we note that diluents are presented in terms, which are not currently recognized by healthcare providers. To avoid misinterpretation of approved diluents, we recommend revision of “ (b) (4) ” to “5% Dextrose injection, USP” and (b) (4) ” to “0.9% Sodium Chloride injection, USP.” In addition, we recommend removal of the apostrophe in Lactated Ringer’s Injection.
4. (b) (4) we note a dose reduction in patients with hepatic impairment and instructions for restricted use in patients with renal impairment . To avoid this important information being overlooked, we recommend including this information in the Dosage and Administration Section of the Highlights of Prescribing Information.
5. We note that in Section 2.5 Discontinuation of TRADENAME, there is a statement (b) (4) however; there is no instruction as to the dose, frequency, or time frame for which the dosage should be gradually reduced prior to discontinuation. We recommend adding information about the safe discontinuation of Briviact to the Dosage and Administration Section, if available.
6. We note that there is a statement in Section 16.2 Storage “Discard any unused TRADENAME oral solution remaining after 5 months of first opening the bottle.” To prevent this information from being overlooked, we recommend that this information be included in Section 2.2 Administration Instructions.

4.2 RECOMMENDATIONS FOR THE UCB INC

We recommend the following be implemented prior to approval of this NDA:

A. Container Labels (retail and professional sample)

1. For the professional sample blisters: We note that the blister card labeling for the 28 tablet professional samples state (b) (4) . However, since the prescription samples are multi-unit blister packs that will be dispensed to the patient, revise the product strength to read “XX mg per tablet” to clarify the strength per unit and minimize the potential for wrong dose errors.
2. For the professional sample blisters: The proprietary and established name, strength, lot number, expiration date, (b) (4) and manufacturer should appear over each blister cell so that this important information remains available to the end user up to the point at which the last dose is removed. Revise the blister cell label to accommodate all critical information on each blister cell. If it is not possible to label

each blister, a random display of the information can appear multiple times across the back of the blister.

3. For the injection: The last two digits of the NDC # on the vial container label should not be the same as the carton labeling of 10 units. Revise the NDC numbers so that the carton labeling and vial label NDC numbers are different for these two package configurations.
4. For the oral solution: We note the statement “Discard any unused (b) (4) remaining after 5 months of first opening the bottle” followed by “(b) (4) _____”. To avoid use beyond 5 months of first opening the bottle we recommend that you replace the term “(b) (4) _____” with “Discard after _____.”
5. We note that you propose a Medication Guide for your product, however, the statement “Dispense accompanying medication guide to each patient” (b) (4) _____
_____ Ensure that this statement is prominently displayed on the label for all strengths of the 60-count bottles. [see 21 CFR 208.24(d)]

B. Carton Labels (retail and professional sample)

1. For professional sample blister cartons: See A.1 above.
2. The injection carton labeling includes the route of administration in the upper right side of the principal display panel of the carton labeling, however, it lacks prominence. To minimize the potential for errors of wrong route of administration, relocate the statement, “ For Intravenous Use Only” away from the net quantity statement and with the statement of strength, in bold font, for example:

BRIVIACT
(brivaracetam) injection
50 mg/ 5 mL
(10 mg/ mL)
For Intravenous Use Only

- We recommend revision of the net quantity for the hospital unit dose carton labeling to represent the packaging configuration, such as '100 tablets (4 X 25-count blister cards)'.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Briviact (brivaracetam) that UCB submitted on May 11, 2015.

Table 2. Relevant Product Information for Briviact	
Initial Approval Date	N/A
Active Ingredient	brivaracetam
Indication	adjunctive therapy in the treatment of partial onset seizures in patients 16 years of age and older with epilepsy; <div style="background-color: #cccccc; width: 300px; height: 15px; margin-left: 100px;">(b) (4)</div>
Route of Administration	oral and intravenous
Dosage Form	tablets, oral solution, injection
Strength	10 mg, 25 mg, 50 mg, 75 mg and 100 mg tablets 10 mg/mL oral solution 50 mg/5 mL single-use vial
Dose and Frequency	The recommended starting dose is 50 mg twice daily. Based on individual patient response, the dose may be adjusted between 25 mg twice daily and 100 mg twice daily. The injection can be administered intravenously without further dilution or may be mixed with diluents and other drugs listed in the PI.
How Supplied	oral tablets: 10 mg, 25 mg, 50 mg, 75 mg and 100 mg film-coated tablets available in bottles of 60 tablets oral solution: 10 mg/mL 300 ml amber glass bottle Injection: 50 mg/5 mL single-use vial
Storage	Store at 25 °C (77 °F); excursions permitted between 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature]. Do not freeze injection or oral solution; Discard any unused oral solution remaining after 5 months of first opening the bottle. The diluted injection should not be stored for more than 4 hours at room temperature and may be stored in polyvinyl chloride (PVC) bags. Discard any unused portion of the

	injection vial contents.
Container Closure	<p>The bulk tablets will be supplied in HDPE bottles with (b) (4) closures and (b) (4) Aluminum blisters.</p> <p>The oral solution will be supplied in a 300 mL type III amber glass bottle with (b) (4) screw closures.</p> <p>The injection solution is packaged in clear, colorless glass vials closed with a rubber stopper and sealed with an aluminum-crimping cap.</p>

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L:Drive on May 14, 2015 using the terms, Briviact to identify reviews previously performed by DMEPA.

C.2 Results

Our search identified two previous reviews¹², which were not related to label and labeling.

¹ Harris, J. Proprietary Name Review for Briviact (NDAs 205836, 205838, 205837). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 FEB 21. 28 p. Panorama No.: 2014-45369, 2014-45371, 2014-45370.

² Winiarski, A. Proprietary Name Review for Briviact (INDs 070205, (b) (4) 103908, 110606). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2012 OCT 11. 33 p. OSE RCM # 2012-963.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,³ along with postmarket medication error data, we reviewed the following Briviact labels and labeling submitted by UCB Inc. on May 11, 2015.

- Container label
- Carton labeling
- Prescribing Information (no image)
- Medication Guide (no image)

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³ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

JUSTINE HARRIS
06/25/2015

DANIELLE M HARRIS
06/25/2015

MEMORANDUM

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

DATE: June 12, 2015

TO: Division of Neurology Products (DNP)

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 205837

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

OSIS recently inspected the site listed below. The inspectional outcome from the inspection was classified as No Action Indicated (NAI).

Requested Site Inspection

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	

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/s/

SHILA S NKAH
06/12/2015

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: June 10, 2015

TO: Cathleen Michaloski, BSN, MPH. Senior Regulatory Project Manager
Steve Dinsmore D.O., Medical Officer
Division of Antiviral Products

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

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

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 205-836

APPLICANT: UCB Biosciences Inc.

DRUG: Briviact (brivaracetam)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard review

INDICATION: (b) (4)

CONSULTATION REQUEST DATE: January 9, 2015

DIVISION ACTION GOAL DATE: November 20, 2015

PDUFA DATE: November 20, 2015

INSPECTION SUMMARY DUE DATE: September 20, 2015

I. BACKGROUND:

The sponsor, UCB Biosciences Inc., submitted NDAs 205836, 205837, and 205838 for brivaracetam (three formulations: single tablet, oral solution and IV) as (b) (4)

Treatment included adults and pediatric patients 16 years of age and older.

The clinical studies supporting this program were conducted under INDs 70205 and (b) (4) for the solid oral dosage form of brivaracetam. Inspection of Studies 1252, 1253, and 1358 in which oral tablets were studied was requested.

Investigational Drug

Brivaracetam (BRV) reportedly displays a high selective interaction with a novel brain-specific binding site, synaptic vesicle protein 2A (SV2A). This binding site appears to be the major target for its pharmacological activity. Since brivaracetam is extensively metabolized, the seizure protection appears to be associated with the parent compound.

The applicant claims that studies conducted in subjects with refractory epilepsy suffering from partial onset seizures in dose range of BRV explored was from 5 mg/day to 150 mg /day provided therapeutic results. The applicant is seeking approval based on three pivotal studies esigned to support a new drug application/marketing authorization.

The sponsor submitted a new formulation for approval of oral tablet, solution, and intravenous administration. The applicant submitted data primarily generated in foreign countries to support approval for (b) (4).

The Applicant sponsored three pivotal studies which were submitted in support of the application. These protocols are essentially the same with the exception of different dosage formulations and different geographic locations; therefore, a description of key design features for the three protocols are presented as follows:

Protocols: Study N0 1252: “A Multicenter, Double-Blind, Parallel-group, Placebo-Controlled, Randomized Study: Evaluation of the Efficacy and Safety of Brivaracetam in Subjects (>16 to 70 Years Old) with Partial-Onset Seizures”

Study N0 1253: “An International, Double-Blind, Parallel-Group, Placebo-Controlled, Randomized Study: Evaluation of the Efficacy and Safety of Brivaracetam in Subjects (> 16 to 70 Years Old) with Partial-Onset Seizures”, and

Study N0 1258: “A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel-Group Study to Evaluate the Safety and Efficacy of Brivaracetam in Subjects (16 to 80 Years Old) with Partial-Onset Seizures”.

Protocol #1252

This study was a 24-week, phase 3, therapeutic confirmatory, double-blind, parallel-group, placebo-controlled, randomized study conducted in 399 randomized subjects to determine efficacy and safety of BRV in subjects (16 to 70 years of age) with partial-onset seizure (POS). Subjects were enrolled and entered an 8-week Baseline Period. At the end of the Baseline Period, subjects were randomized in a 1:1:1:1 ratio to 1 of 4 treatment arms (BRV 20mg/day, 50mg/day, 100mg/day, or placebo (PBO)). Oral tablets of BRV (10mg and 50mg) and matching placebo were used in the study. Subjects were randomized to the full dose without any Titration phase. The treatment lasted 12 weeks with a daily dose given in equal intakes, morning and evening.

The primary objective of the study was to evaluate the efficacy of BRV at doses of 20, 50, and 100 mg/day in reducing seizure frequency in subjects with partial onset seizures not fully controlled despite optimal treatment with one to two concomitant AEDs, compared with placebo.

The secondary objectives were: 1) to confirm the dose/clinical response relationship, and 2) to assess the safety and tolerability of BRV.

Protocol #1253:

This study was an international therapeutic confirmatory, parallel-group, double-blind, randomized, placebo-controlled study with three active doses of BRV and possible conversion to a long-term follow-up (LFTU) study. Subjects were randomized in 1:1:1:1 central randomization (random permitted blocks) stratified for the study regions of North and Latin America, and Australia for the use of Levetiracetam (LEV) (use/no use at study entry). This was done to ensure the balance between the different groups (placebo, 5mg BRV, 20mg BRV, and 50mg BRV). The number of subjects using LEV as concomitant medication was limited to 20% of the total study population. The total duration of the study was up to 23 weeks with a maximum 13-week exposure to BRV as follows:

- Baseline Period 8 weeks
- Treatment Period 12 weeks
- Down titration Period 1 week
- Study Drug Free Period 2 weeks

The study enrolled about 500 subjects with at least 20% screen failure rate recruited from about 80 to 100 sites.

The primary objective of the study was to evaluate the efficacy of BRV at doses of 5, 20, and 50 mg/day in b.i.d administration in reducing seizure frequency in subjects with partial onset seizures not fully controlled despite optimal treatment with one to two concomitant AEDs. The secondary objectives were: 1) to confirm the dose/clinical response relationship, and 2) to assess the effects of BRV on Type1C seizures.

Protocol #1358:

This study was randomized, double-blind, placebo-controlled, multicenter, therapeutic confirmatory study evaluating two active doses of BRV. The subject population was adults (16 to 80 years of age) with refractory POS whether or not secondarily generalized. Subjects under 18 years of age could be included only where legally permitted and ethically accepted. Subjects were enrolled and entered an 8-week Baseline Period. This was followed by a 12-week double-blind Treatment Period, a 4 week Down-Titration Period followed by a 2 week Study Drug Free Period for subjects not entering the LTFU study. The total duration of the study was approximately 26 weeks with a maximum 16-week exposure to BRV. At the end of the Baseline Period, subjects were randomized in a 1:1:1 central randomization with stratification for country, LEV Status (never used LEV vs prior LEV use only), and the number of AEDs previously used but discontinued prior to study entry (<2 vs >2 AEDs) was used to ensure the balance across treatment groups (PBO, BRV 100mg/day, and 200mg/day within each combination of stratification levels. Subjects were randomized to the full dose without any Titration phase.

The primary objective of the study was to evaluate the efficacy of BRV at doses of 100, and 200 mg/day compared to PBO as adjunctive treatment in adult focal epilepsy subjects with POS not fully controlled despite current treatment with 1 or 2 concomitant AEDs. The secondary objective was to assess the safety and tolerability of effects of BRV.

The review division requested inspection of four clinical investigators for the pivotal studies noted above because data from the studies are considered essential to support the approval of NDA 205-836: one domestic site (AR) for Protocol 1253, and two foreign sites (Italy, Spain) for Protocol 1358, and one foreign site (India) for Protocol 1252 which enrolled a large number of subjects in support of this application. These sites were targeted to evaluate the various regimens and the population proposed for inclusion in labeling. It was for these reasons that it was critical that international sites be included in the inspection. This would be the first approval of this new drug and most of the limited experience was with foreign data. In addition, the sponsor was inspected because the product was designated as an NME; the above sites were covered during the sponsor inspection.

II. RESULTS (by protocol/site):

Name of CI, Location, and Site #	Protocol and # of subjects randomized	Inspection Dates	Final Classification
Victor Biton, M.D. Little Rock, AR 72205 Site #350	Protocol 1253 Number of subjects: 21	3/17-20/2015	Pending (preliminary classification NAI)
Pier P. Quarato, M.D. Poziilli (Isernia) Italy Site #383	Protocol 1358 Number of subjects: 26	3/30- 4/3/2015	Pending (preliminary classification NAI)

Name of CI, Location, and Site #	Protocol and # of subjects randomized	Inspection Dates	Final Classification
Xazvier Salas, M.D. Barcelona, Spain Site #528	Protocol 1358 Number of subjects: 26	5/4-8/2015	Pending (preliminary classification NAI)
Sunha Sanjib, M.D. Banglore, India Site #256	Protocol 1252 Number of subjects: 20	4/13-16/2015	Pending (preliminary classification NAI)
UCB, Inc. Smyrna, GA 30080 Site #N/A	Protocol All 3 listed above	3/10-19/2015	NAI

Key to Classifications

NAI = No deviations

VAI = Deviation(s) from regulations

OAI = Significant deviations from regulations. Data found unreliable.

Pending = Preliminary classification based on e-mail communication from the field; the Establishment Inspectional Report (EIR) has not been received from the field and complete review of EIR is pending. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

1. Victor Biton, M.D.
Little Rock, AR 72205

- a. What Was Inspected:** This inspection was performed as a data audit for NDA 205-836 Study Protocol 1253. At this site, a total of 21 subjects were screened, 21 subjects were randomized into the study, one subject was lost to follow-up, and 20 subjects completed the study. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed informed consent forms prior to enrollment.

The medical records/source data for 21 subjects were reviewed and compared to data listings. The review included drug accountability records, inclusion/exclusion criteria, vital signs, IRB records, financial disclosure, sponsor and monitor audit activities, prior and current medications, and adverse events. Source documents for all subjects were compared to case report forms and data listings including for primary efficacy endpoints and adverse events listings. No deficiencies were noted.

- b. General Observations/Commentary:** At the conclusion of the inspection, no FDA Form FDA 483 was issued to Dr. Biton. However, the field investigator discussed two items with clinical investigator regarding transcription/documentation of

investigational product for two subjects, and lack of documentation regarding phone calls made to subjects. In addition, one subject used a benzodiazepine more than once a week. A note to file documented the occurrence and the site notified the sponsor and the IRB. Overall, 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 by this site are considered reliable and acceptable in support of the pending application.

**2. Pier P. Quarato, M.D.
Poziilli (Isernia), Itlay**

- a. **What Was Inspected:** This inspection was performed as a data audit for NDA 205-836 and inspected Study Protocol 1358. At this site, a total of 28 subjects were screened, two subjects were reported as screen failures, 26 subjects were randomized into the study, two subjects withdrew after being randomized, and 24 subjects completed the study. Review of the Informed Consent Documents, for all subjects records reviewed, verified that all subjects signed informed consent forms prior to enrollment.

The medical records/source documents for the majority of subjects were reviewed. The medical records/source documents for enrolled subjects for certain visits were reviewed including drug accountability records, vital signs, IRB files, inclusion/exclusion criteria, prior and concomitant medications, and adverse events reporting. The field investigator compared the source documents/endpoint values to the data listings for primary efficacy endpoints, and no discrepancies were noted.

- b. **General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Quarato. The medical records reviewed were found to be in order and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were no known limitations to the inspection.
- c. **Assessment of Data Integrity:** The data in support of the clinical efficacy and safety at Dr. Quarato's site are considered reliable and may be used in support of the pending applications

**3. Xavier Salas, M.D., Ph.D.
Barcelona 08035, Barcelona**

- a. **What Was Inspected:** This inspection was performed as a data audit for NDA 205-836 and inspected Study Protocol 1358. At this site, a total of 34 subjects were screened, eight subjects were reported as screen failures, 26 subjects were randomized into the study, and 24 subjects completed the study. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed informed consent forms prior to enrollment.

The medical records/source data for 13 subjects were reviewed for primary/secondary endpoints, informed consent including drug accountability records, vital signs, IRB records, financial disclosure, prior and current medications, and inclusion/exclusion criteria. Source documents for 13 subjects were compared to data listings for primary efficacy endpoints and adverse events listing. There was no evidence of under-reporting of adverse events at this site, except one subject exhibited an elevated eosinophil count at one visit that was not reported as an adverse event.

- b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Salas. However, the non-reporting of adverse event as stated above was discussed with the clinical investigator who agreed with the observation and promised correction.

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 at this site.

- c. Assessment of Data Integrity:** Although a minor deviation was noted at this site, the finding appears to be isolated instances, and it is unlikely that these findings would significantly impact the outcome of the study. Overall, the data submitted in support of the clinical efficacy and safety from this site is considered reliable and may be used in support of the pending applications.

4. Sunha Sanjib, M.D. Banglore, India

- a. What Was Inspected:** This inspection was performed as a data audit for NDA 205-836 Study Protocol 1252. At this site, a total of 20 subjects were screened, 20 subjects were randomized into the study, and 19 subjects completed the study. One subject died shortly after enrollment, but before taking study medications. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed informed consent forms prior to enrollment.

The medical records/source data for 10 subjects were reviewed and compared to data listings. The review included consent forms, drug accountability records, inclusion/exclusion criteria, vital signs, IRB records, financial disclosures, sponsor correspondence, prior and current medications, and adverse events. Source documents for all subjects were compared to case report forms and data listings including for primary efficacy endpoints and adverse events listings. There was no evidence of inaccuracy of the data captured.

- b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Sanjib. 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 study appears to have been conducted adequately, and the data generated by this site appear acceptable and may be used in support of the pending application.

5. UCB Biosciences Inc.
Atlanta Georgia

- a. **What was Inspected:** The inspection audited the three protocols and focused on the three clinical investigators (Biton, Salas and Sanjib) listed above during the course of this sponsor/monitor inspection. In addition, the field investigator noted two additional investigators terminated due to noncompliance (not for the same NDA) uncovered during their audit in (b)(4) and (b)(4). Both sites were terminated, and the FDA was notified. (b)(4)

None of the studies used electronic data capture directly into electronic forms. The inspection reviewed the following: Company history and officer responsibilities, training program, manufacturing/design operations, selection of clinical investigators, quality assurance, study monitoring procedures, data review and reports, protocol adherence, participating clinical investigators, and adverse event reporting.

- b. **General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to the Firm. The inspection found that the sponsor adhered to their SOPs regarding proper monitoring of their clinical investigators. The activities included, but were not limited to, trial drug records, subject records, protocol adherence, case report forms/source documents and adverse events reporting. The medical records reviewed were found adequate and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were sufficient and well organized records. Monitoring of clinical investigator sites was thorough and appeared adequate. There was no evidence of under-reporting of adverse events or protocol deviations.
- c. **Assessment of Data Integrity:** The sponsor monitoring procedures for reviewing the progress of the studies appears to have been conducted adequately and the data submitted by the sponsor may be used in support of the respective indication. In general, the data appear acceptable in support of the pending application.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Four clinical investigator sites were inspected in support of this application. The inspection of the four clinical investigators listed above revealed no regulatory violations. The pending classification for Drs. Biton, Quararo, Salas, and Sanjib are No Action Indicated (NAI), and the final classification for the Sponsor, USB, Inc. is No Action Indicated (NAI). For the preliminary/pending classifications, a summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

Overall, the data submitted from these four sites are considered acceptable and may be used in support of any future resubmission.

{See appended electronic signature page}

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

CONCURRENCE:

{See appended electronic signature page}

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

{See appended electronic signature page}

Kassa Ayalew, M.D. M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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/s/

ANTOINE N EL HAGE
06/11/2015

SUSAN D THOMPSON
06/11/2015

KASSA AYALEW
06/11/2015

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Application: NDAs 205836, 205837, 205838

Application Type: 505 (b)(1) NDA NME

Name of Drug/Dosage Form: BRIVIACT (brivaracetam)

NDA 205836: 10 mg, 25 mg, 50 mg, 75 mg, and 100 mg (tablets)

NDA 205837: 50 mg/5 mL single-use vial (IV)

NDA 205838: 10 mg/mL oral solution

Applicant: UCB Pharmaceuticals Company
1950 Lake Park Drive
Smyrna, GA 30080

Receipt Date: November 20, 2014

Goal Date: November 20, 2015

1. Regulatory History and Applicant's Main Proposals

Brivaracetam is a new chemical entity that is structurally related to piracetam and levetiracetam. (b) (4)

On March 12, 2014, UCB requested a Type B Pre-NDA meeting. UCB planned to file three NDAs to support a film-coated tablet, a solution for injection, and an oral solution of brivaracetam for adjunctive therapy in the treatment of partial onset seizures in patients 16 years and older with epilepsy.

Type B pre-NDA meeting – July 29, 2014

Initial PREA iPSP agreed – September 30, 2014

Mid-cycle Meeting – April 27, 2015

Late-cycle Meeting TBD

Primary reviews due – July 20, 2015

PDUFA Goal Date – November 20, 2015

Associated INDs: 70205 and (b) (4) (oral tabs); 103908 (IV) 110606 (oral soln)

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were not identified in the preliminary review of the PI.

Selected Requirements of Prescribing Information

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

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

Comment:

- yes 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- yes 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- yes 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

- yes 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

- yes 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- yes 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required

Selected Requirements of Prescribing Information

• 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*
• 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:

HIGHLIGHTS DETAILS

Highlights Heading

- yes 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

- yes 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**” The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- yes 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- yes 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- n/a 12. All text in the BW must be **bolded**.

Comment:

- n/a 13. The BW 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 and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Selected Requirements of Prescribing Information

Comment:

- n/a 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

- n/a 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

- n/a 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- n/a 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(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, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- n/a 18. The RMC 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 in Highlights

- yes 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

- yes 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

- yes 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Selected Requirements of Prescribing Information

Comment:

Adverse Reactions in Highlights

- yes 22. 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 in Highlights

- yes 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

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 in Highlights

- yes 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- yes** 25. The TOC should be in a two-column format.
Comment:
- yes** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- n/a** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- yes** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- yes** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- yes** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- yes** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. 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:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- yes 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

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 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Comment:

Selected Requirements of Prescribing Information

- n/a 34. 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

FPI Heading

- yes 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- n/a 36. In the BW, all text should be **bolded**.

Comment:

- n/a 37. The BW 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 and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- yes 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- yes 39. When clinical trials adverse reactions data are 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 practice.”

Comment:

- n/a 40. When postmarketing adverse reaction data are 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 Section in the FPI

- yes 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- n/a** 42. 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 FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

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

/s/

CATHLEEN B MICHALOSKI
01/29/2015

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 # 205826 (tabs) NDA # 205837 (IV) NDA # 205938 (oral soln)	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-								
Proprietary Name: BRIVIACT Established/Proper Name: brivaracetam Dosage Form: oral tabs, IV and oral solution Strengths: <ul style="list-style-type: none"> 10, 25, 50, 75, and 100 mg (oral tabs) 50 mg/5 mL single-use vial (IV) 10 mg/mL oral solution EDR Location: \\CDSESUB1\evsprod\NDA205836\205836.enx \\CDSESUB1\evsprod\NDA205837\205837.enx \\CDSESUB1\evsprod\NDA205838\205838.enx										
Applicant: UCB Pharmaceuticals Company 1950 Lake Park Drive Smyrna, GA 30080										
Agent for Applicant (if applicable):										
Date of Application: November 19, 2014 (cover letter date and 356h date for all 3 NDAs) Date of Receipt: 205836 (tabs): November 22, 2014 (submitted) November 24, 2014 (received) 205837 (IV): November 20, 2014 (received and submitted) 205838 (soln): November 20, 2014 (received and submitted) Date clock started after UN:										
PDUFA Goal Date: November 20, 2015	Action Goal Date (if different):									
Filing Date: January 19, 2015	Date of Filing Meeting: January 9, 2015									
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1 (NME)										
Proposed indication: <div style="background-color: #cccccc; height: 15px; width: 100%; margin-top: 5px;"></div> (b) (4)										
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 20px; text-align: center;">X</td> <td>505(b)(1)</td> </tr> <tr> <td></td> <td>505(b)(2)</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>505(b)(1)</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>505(b)(2)</td> </tr> </table>		X	505(b)(1)		505(b)(2)	<input type="checkbox"/>	505(b)(1)	<input type="checkbox"/>	505(b)(2)
X	505(b)(1)									
	505(b)(2)									
<input type="checkbox"/>	505(b)(1)									
<input type="checkbox"/>	505(b)(2)									
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499										
Type of BLA	<table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 20px; text-align: center;"><input type="checkbox"/></td> <td>351(a)</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>351(k)</td> </tr> </table>		<input type="checkbox"/>	351(a)	<input type="checkbox"/>	351(k)				
<input type="checkbox"/>	351(a)									
<input type="checkbox"/>	351(k)									
<i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>										

Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher submitted
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Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
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Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
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<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (if OTC product):

List referenced IND Number(s): 70205, 75898, 103908

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X	<input type="checkbox"/>		2 NDA rec'd 11/20/14; 1 NDA rece'd 11/24/14
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>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.</i>	X	<input type="checkbox"/>		
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)? <i>For NDAs/NDA supplements, check</i>	X (S)	<input type="checkbox"/>	<input type="checkbox"/>	

<p><i>the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</p> <p><i>If no, ask the document room staff to make the appropriate entries.</i></p>					
Application Integrity Policy		YES	NO	NA	Comment
<p>Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</p> <p>If yes, explain in comment column.</p>		<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<p>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</p>		<input type="checkbox"/>	<input type="checkbox"/>		
User Fees		YES	NO	NA	Comment
<p>Is Form 3397 (User Fee Cover Sheet) included with authorized signature?</p>		<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<p><u>User Fee Status</u></p> <p><i>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.</i></p>		<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid</p> <p><input type="checkbox"/> Exempt (orphan, government) Waived (e.g., small business, public health)</p> <p><input type="checkbox"/> Not required</p>			
<p><i>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.</i></p>		<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears</p> <p><input type="checkbox"/> In arrears</p>			
505(b)(2) (NDAs/NDA Efficacy Supplements only)		YES	NO	NA	Comment
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>		<input type="checkbox"/>		<input type="checkbox"/>	
<p>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)].</p>		<input type="checkbox"/>		<input type="checkbox"/>	
<p>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)]?</p> <p><i>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 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>		<input type="checkbox"/>		<input type="checkbox"/>	

<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p>		<input type="checkbox"/>		<input type="checkbox"/>									
<p>If yes, please list below:</p> <table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>						Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration				
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration										
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>													
Exclusivity		YES	NO	NA	Comment								
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</p>		<input type="checkbox"/>	X										
<p>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)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>		<input type="checkbox"/>	X	<input type="checkbox"/>									
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only)</p> <p>If yes, # years requested: 5 (new moiety)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>		X		<input type="checkbox"/>									
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (NDAs only)?</p> <p>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)?</p> <p><i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i></p>		<input type="checkbox"/>	X	<input type="checkbox"/>									
<p>For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?</p> <p><i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i></p> <p><i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a</i></p>		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>									

supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.				
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Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	X	<input type="checkbox"/>	<input type="checkbox"/>	
<p>Index: Does the submission contain an accurate comprehensive index?</p>	X	<input type="checkbox"/>		
<p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p>If no, explain.</p>	X	<input type="checkbox"/>		
<p>BLAs only: Companion application received if a shared or divided manufacturing arrangement?</p> <p>If yes, BLA #</p>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<p>Forms and Certifications</p> <p><i>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</i></p>				

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<i>certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	X	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	X	<input type="checkbox"/>	<input type="checkbox"/>	
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	<input type="checkbox"/>	<input type="checkbox"/>	
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)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	X	<input type="checkbox"/>		
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i> <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	X	<input type="checkbox"/>		
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>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].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>	X	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification	X	<input type="checkbox"/>	<input type="checkbox"/>	

(that it is a true copy of the CMC technical section) included? <i>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)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>				
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)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <i>12.1.14 Martin Rusinowitz at filing meeting</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input type="checkbox"/>	<input type="checkbox"/>	X	Not a controlled substance at this time
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	X	<input type="checkbox"/>		Initial iPSP agreement 12/8/13 Partial waiver DPMH consult sent 1.6.15
If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?	X	<input type="checkbox"/>	<input type="checkbox"/>	
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? <i>If no, request in 74-day letter</i>	X	<input type="checkbox"/>	<input type="checkbox"/>	
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)? <i>If no, request in 74-day letter</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request?	<input type="checkbox"/>	X		

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted?	X	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>				
REMS	YES	NO	NA	Comment
Is a REMS submitted?	<input type="checkbox"/>	<input type="checkbox"/>	X	
<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	X	<input type="checkbox"/>		
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? ⁴	X	<input type="checkbox"/>		
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?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	X Not Applicable			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<p>X Not Applicable</p> <p><input type="checkbox"/> YES NO</p> <p><input type="checkbox"/> YES NO</p> <p>Clin pharm and biopharm protocols submitted for IV and oral solution formulations (as a 505b1 NDA)</p>
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<p>X YES</p> <p><input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<p>X Not Applicable</p>
<p>CLINICAL</p> <p>Comments: no issues at this time</p>	<p><input type="checkbox"/> Not Applicable</p> <p>X FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p>X Review issues for 74-day letter</p>
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<p>X YES Consult sent 1.9.15</p> <p>NO</p>
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments: Product is not first-in-class, not unusual population for epilepsy, endpoints well established and safety profile known.</p> <p>If no, for an NME NDA or original BLA , include the reason. For example:</p> <ul style="list-style-type: none"> ○ this drug/biologic is not the first in its class 	<p><input type="checkbox"/> YES</p> <p>Date if known:</p> <p>X NO</p> <p><input type="checkbox"/> To be determined</p> <p>Reason: see comments</p>

<ul style="list-style-type: none"> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable (at this time) <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • 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? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<p>X Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>PRODUCT QUALITY (CMC)</p> <p>Comments: review issues expected for the 74 day letter</p>	<p><input type="checkbox"/> Not Applicable X FILE <input type="checkbox"/> REFUSE TO FILE</p> <p>X Review issues for 74-day letter</p>
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p>X YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p>X YES pending w/ CMC <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments: see CMC review team</p>	<p>Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p>X YES <input type="checkbox"/> NO</p> <p>X YES pending per CMC <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p>X Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>

<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application’s pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<p>Yes- Program Application</p> <p>YES NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<p>X YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<p>X YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<p>X YES <input type="checkbox"/> NO</p>
<p>REGULATORY PROJECT MANAGEMENT</p>	
<p>Signatory Authority: Cathleen Michaloski, Sr. RPM, DNP 796-1123</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): April 27, 2015. Late cycle TBD</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional): TBD</p>	

Comments: Application in the Program; 10 month standard clock PDUFA November 20, 2015.	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
X	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. X Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> X Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
X	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).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • 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)
X in draft	Send review issues/no review issues by day 74
X	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	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 in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]

NDA 205836, 205837, 205838
FILING MEETING
Summary and Agenda; revised 1.9.15

DATE: January 9, 2015, 2 pm – 3:30 pm room 4201 WO22

NDA#s: 205836 (oral tabs), 205837 (IV), 205838 (oral solution)

Agenda: each discipline allowed 10 minutes for presentations. See reviewer table below.

SUMMARY:

“PROGRAM” Application (NME); 10 month clock starting at filing 1/20/15; PDUFA 11/20/15

PROPRIETARY NAME: BRIVIACT

ESTABLISHED/PROPER NAME: brivaracetam

DOSAGE FORM/STRENGTH:

- 10, 25, 50, 75, and 100 mg (oral tabs) (N205836)
- 50 mg/5 mL single-use vial (N205837)
- 10 mg/mL solution (N205838)

APPLICANT: UCB, Inc.
1950 Lake Park Drive
Smyrna, GA 30080

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):

(b) (4)

BACKGROUND:

Chronological History:

IND 070205 for brivaracetam solid oral dosage formulations was submitted on July 12, 2004, for the treatment of epilepsy.

Brivaracetam is a new chemical entity that is structurally related to piracetam and levetiracetam.

(b) (4)

(b) (4)

On December 11, 2006, an End-of-Phase 2 meeting was held to discuss the Phase 3 development of brivaracetam as adjunctive therapy in the treatment of partial onset seizures (b) (4) in adults with epilepsy.

[REDACTED] (b) (4)

[REDACTED] (b) (4)

IND 103908 for brivaracetam intravenous formulation was submitted on October 30, 2008, [REDACTED] (b) (4)

[REDACTED]

On January 19, 2010, a Type C meeting was held to discuss the results of the brivaracetam Phase 3 studies for adjunctive therapy in partial onset seizures and an additional proposed Phase 3 supportive study.

In the preliminary comments, the Division did not concur [REDACTED] (b) (4)

[REDACTED] The Division stated that the dose/response for such an effect did not appear to be fully explored. For example, the Phase 3 study N01252 was not a positive study based on the pre-specified primary efficacy analysis, with the 50 mg/day dose not reaching significance, but with the 100 mg/day dose nominally significant. Nonetheless, the dose of 50 mg/day was statistically significant in the other Phase 3 study, N01253, which met the pre-specified primary efficacy analysis, and was a positive study.

The 50 mg/day dose failed in one of two Phase 2 studies as well, where the higher dose of 150 mg/day also failed. During the meeting, the proposed study was discussed. [REDACTED] (b) (4)

[REDACTED]

[REDACTED] The Division stated that UCB had not adequately looked at dose response and strongly suggested that a higher dose be studied. In addition, the Division recommended that the study include three arms (50 mg, 100 mg, and 200 mg). [REDACTED] (b) (4)

[REDACTED]

The Division stated that the proposal may be adequate. In the completed Phase 3 trial, patients on levetiracetam fared worse than patients not on levetiracetam. Therefore, the Division recommended that the trial not exclude patients on levetiracetam.

On September 14, 2010, a Special Protocol Assessment (SPA) Agreement letter was sent for IND 070205 protocol "N01358: A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel-Group Study to Evaluate the Efficacy and Safety of Brivaracetam in Subjects (≥ 16 to 80 years old) with Partial Onset Seizures."

IND 110606 for brivaracetam oral solution was submitted on November 19, 2010, [REDACTED] (b) (4)

[REDACTED]

[REDACTED] (b) (4)

On March 8, 2012, a SPA Agreement letter was sent for an IND 070205 stability protocol.

On March 12, 2014, UCB requested a Type B Pre-NDA meeting. UCB intends to file three NDAs to support a film-coated tablet, a solution for injection, and an oral solution of brivaracetam for adjunctive therapy in the treatment of partial onset seizures in patients 16 years and older with epilepsy.

Type B pre-NDA meeting – July 29, 2014

Initial PREA iPSP agreed – September 30, 2014

Mid-cycle Meeting – April 27, 2015

Late-cycle Meeting - TBD

PDUFA Goal Date – November 20, 2015

Associated INDs: 70205 and (b) (4) (oral tabs); 103908 (IV) 110606 (oral soln)

Agenda: 10- 15 minutes per discipline

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Cathleen Michaloski	Y
	CPMS/TL:	Norman Hershkowitz	Y
Clinical Reviewers	Steve Dinsmore (efficacy) Mary Doi (safety)		Y
Controlled Substance	Reviewer: TL:	Martin Rusinowitz Silvia Calderon/Michael Klein	Y
OSI (clinical site audits)	Reviewer:	Tony El Hage	Y
Clinical Pharmacology	Reviewer:	Michael Bewernitz	Y
	TL:	Angela Men	Y
Biostatistics	Reviewer:	Sharon Yan	Y
	TL:	Kun Jin	
Nonclinical (Pharmacology/Toxicology)	Reviewer:	J Edward Fisher	Y
	TL:	Lois Freed	

Statistics (carcinogenicity)	Reviewer:	Atiar Mohammad Rahman	
	TL:	Karl Lin	
Product Quality (CMC)	Reviewer:	Andrei Ponta (DP) Chuck Jewell (DS) Dahlia Woody (PM) Edwin Jao (manuf process - Soln) Bogdan Kurtuka (maunf process- Tabs)	Y Y Y Y
	TL:	Olen Stephens/Wendy Wilson	Y
Product Quality- Biopharmaceutics	Reviewer:	Okpo Eradiri	Y
	TL:	Angelica Dorantes	Y
CMC Labeling Review	Reviewer:	Martha Heimann	Y
	TL:		
Facility Review/Inspection	Reviewer:	Ebern Dobbin	Y
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Justine Harris	Y
	TL:	Danielle Harris Irene Chan	Y
OSE/DRISK (REMS)	Reviewer:	No REMS at this time	
	TL:		

PATIENT LABELING	Reviewers: Twanda Scales (Patient Labeling; DMPP); Melinda Mclawhorn (OPDP)	Y Y
OTHER Pediatric Consult 1.7.15	Reviewer: Carrie Ceresa Millie Wright- PM	

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

/s/

CATHLEEN B MICHALOSKI
01/15/2015