

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**207975Orig1s000**

**OTHER REVIEW(S)**

## PMR/PMC Development Template

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

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## PMR/PMC Development Template

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

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NDA # 207975  
Product Name: Vantrela ER (hydrocodone bitartrate extended-release) tablets

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PMR Description: 2981-4 A multiple ascending dose thorough QT (tQT) clinical trial in healthy adult volunteers designed to determine the maximum tolerated dose of hydrocodone bitartrate without co-administration of naltrexone and characterize the effect of Vantrela ER tablets on cardiac repolarization.

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PMR Schedule Milestones: Final Protocol Submission: 05/2017  
Trial Completion: 08/2018  
Final Report Submission: 08/2019  
Other: N/A

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

No serious AEs have occurred in the safety database that can be obviously attributed to a cardiac arrhythmia. The clinical team has concluded that the information provided in the NDA supports the safety of approving the product with appropriate warnings, while allowing completion of a definitive thorough-QT study as a postmarketing requirement to further characterize the effects on the QT interval.

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

The data from the Phase 3 trials are sufficient to indicate that Vantrela ER, in the proposed dose range, may result in QT prolongation. The goal is to evaluate the effects of Vantrela ER on cardiac repolarization in a thorough QT trial and to provide additional information to assess the safety of Vantrela ER, which may lead to additional labeling.

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 multiple ascending dose clinical trial in adults to determine the maximum tolerated dose of hydrocodone bitartrate without co-administration of naltrexone to inform the dosing for a thorough QT (tQT) trial of hydrocodone bitartrate and conduct of a tQT trial to determine the effect of Vantrela on cardiac repolarization.

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)

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

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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)

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- Other

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

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

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

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**PMR/PMC Development Coordinator:**

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

## PMR/PMC Development Template

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

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NDA # 207975  
Product Name: Vantrela ER (hydrocodone bitartrate extended-release) tablets

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PMR Description: 2981-1 Conduct a pharmacokinetic and safety study of an age-appropriate formulation of Vantrela ER in patients from ages seven to less than 17 years with pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

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PMR Schedule Milestones: Final Protocol Submission: 06/2017  
Study Completion: 06/2022  
Final Report Submission: 01/2023  
Other: N/A

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

We are deferring submission of this pediatric study for ages seven to 17 years for this application because this product is ready for approval for use in adults, and the pediatric study has not been completed.

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

Safety and PK data are needed to support use in pediatric patients 7 years to < 17 years.

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

*If not a PMR, skip to 4.*

– **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
  
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
  
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

This will be (b) (4) PK and safety study.

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)

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Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

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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)

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Other

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

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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

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**PMR/PMC Development Coordinator:**

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

## PMR/PMC Development Template

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

NDA # NDA 207975  
Product Name: Vantrela ER (hydrocodone bitartrate extended-release) tablets

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PMR Description: 3033-1 A prospective, observational study designed to quantify the serious risks of misuse, abuse, and addiction associated with long-term use of opioid analgesics for management of chronic pain among patients prescribed ER/LA opioid analgesics.

This study (b) (4) address at a minimum the following specific (b) (4):

- a. Estimate the incidence of misuse, abuse, and addiction associated with long-term use of opioid analgesics for chronic pain. Examine the effect of product/formulation, dose and duration of opioid use, prescriber specialty, indication, and other clinical factors (e.g., concomitant psychotropic medications, personal or family history of substance abuse, history of psychiatric illness) on the risk of misuse, abuse, and addiction.
- b. Evaluate and quantify other risk factors for misuse, abuse, and addiction associated with long-term use of opioid analgesics for chronic pain, including but not limited to the following: demographic factors, psychosocial/behavioral factors, medical factors, and genetic factors. Identify confounders and effect modifiers of individual risk factor/outcome relationships.

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PMR Schedule Milestones:	Final Protocol Submission:	11/2015
	Interim Report (Cumulative Enrollment of 470 patients)	5/2017
	Interim Report (Cumulative Enrollment of 1,042 patients)	9/2017
	Interim Report (Cumulative Enrollment of 1,609 patients)	1/2018
	Interim Report (Cumulative Enrollment of 2,300 patients)	6/2018
	Study Completion:	10/2019
	Final Report Submission:	3/2020

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

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

In order to estimate the incidence of misuse, abuse, addiction, overdose, and death associated with use long-term use of opioids for chronic pain, we must be able to access data from adequate numbers of patients who were treated long-term with opioids.

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

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of important adverse effects of long-term opioid use, including misuse, abuse, addiction, overdose and death. The goal of the study is to determine those incidences, and identify risk factors for those outcomes.

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.

The initial type of study that would be anticipated would be a prospective epidemiological study to measure the incidences of the adverse outcomes listed above. However, tools to measure both the risk factors and outcomes have not been validated. As such, validation studies are required prior to the epidemiological studies (see other PMRs). It may be determined, if the outcome codes do not validate well, that other types of studies or clinical trials are needed.

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)

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

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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)

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- Other

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

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

## PMR/PMC Development Template

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

NDA # NDA 207975  
Product Name: Vantrela ER (hydrocodone bitartrate extended-release) tablets

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PMR Description: 3033-2 An observational study designed to measure the incidence and predictors of opioid overdose and death (OOD), as well as opioid abuse/addiction, using patient health records, insurance claims, and death records.

a. Estimate the incidence of abuse/addiction, overdose, and death associated with long-term use of opioid analgesics for chronic pain. Stratify overdose by intentionality wherever possible. Examine the effect of product/formulation, dose and duration of opioid use, prescriber specialty, indication, and other clinical factors (e.g., concomitant psychotropic medications, personal or family history of substance abuse, history of psychiatric illness) on the risk of abuse/addiction, overdose, and death.

b. Evaluate and quantify other risk factors for abuse/addiction, overdose, and death associated with long-term use of opioid analgesics for chronic pain, including but not limited to the following: demographic factors, psychosocial/behavioral factors, medical factors, and genetic factors. Identify confounders and effect modifiers of individual risk factor/outcome relationships. Stratify overdose by intentionality wherever possible.

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PMR Schedule Milestones: Final Protocol Submission: 11/2014  
Study Completion: 4/2019  
Final Report Submission: 9/2019

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

In order to estimate the incidence of misuse, abuse, addiction, overdose, and death associated with use long-term use of opioids for chronic pain, we must be able to access data from adequate numbers of patients who were treated long-term with opioids.

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

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of important adverse effects of long-term use of opioids, including misuse, abuse, addiction, overdose and death. The goal of the study is to determine those incidences, and identify risk factors for those outcomes.

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.

The initial type of study that would be anticipated would be an epidemiological study in large databases to measure the incidences of the adverse outcomes listed above. However, neither the codes for many of the risk factors nor those for these outcomes have been validated. As such, validation studies are required prior to the epidemiological studies (see other PMRs). It may be determined, if the outcome codes do not validate well, that other types of studies or clinical trials are needed.

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.*

## PMR/PMC Development Template

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

NDA #	NDA 207975	
Product Name:	Vantrela ER (hydrocodone bitartrate extended-release) tablets	
PMR Description:	3033-3 A prospective observational study designed to assess the content validity and patient interpretation of the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ). Patient understanding of the concepts of misuse and abuse will also be obtained.	
PMR Schedule Milestones:	Final Protocol Submission:	04/2015
	Study Completion:	10/2015
	Final Report Submission:	01/2016

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

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

The data needed to validate measures and outcomes of opioid-related adverse events would optimally be drawn from a source that includes at least some patients who have been taking opioids long-term.

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

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of important adverse effects of long-term opioid use, including misuse, abuse, addiction, overdose and death.

The goal of PMRs 3033-1 and 3033-2 is to determine those incidences, and identify risk factors for those outcomes. In order to conduct such studies, the outcomes need to be validated, including measures of opioid-related adverse events.

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

***If not a PMR, skip to 4.***

– **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

An observational study would likely be conducted that includes identifying patients who have been prescribed opioids for long-term use, administering a specifically designed survey to identify patients that misuse and/or abuse opioids, and conducting an interview, chart review, or a similar activity to determine if the patients understand the survey instrument, and if the instrument measures what is designed to assess.

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)

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Other

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

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

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.*

## PMR/PMC Development Template

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

NDA # NDA 207975  
Product Name: Vantrela ER (hydrocodone bitartrate extended-release) tablets

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PMR Description: 3033-4 An observational study to evaluate the validity and reproducibility of the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ), which will be used to identify opioid abuse and misuse behaviors among participants who have chronic pain which requires long-term opioid analgesic use.

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PMR Schedule Milestones:

Final Protocol Submission:	<u>04/2015</u>
Study Completion:	<u>10/2016</u>
Final Report Submission:	<u>02/2017</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

The data needed to validate measures of opioid-related adverse events would optimally be drawn from a source that includes at least some patients who have been taking opioids long-term.

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

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of important adverse effects of long-term opioid use, including misuse, abuse, addiction, overdose and death.

The goal of PMRs 3033-1 and 3033-2 is to determine those incidences, and identify risk factors for those outcomes. In order to conduct such studies, the outcomes need to be validated, including measures of opioid-related adverse events.

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

***If not a PMR, skip to 4.***

– **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

An observational study would likely be conducted that includes identifying patients who fulfill the criteria of long-term opioid use, administering a specifically designed survey instrument to identify opioid abuse and misuse behaviors, and then conducting a chart review or a similar activity to determine whether the identified patients actually meet the case definition.

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)

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Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

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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)

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Other

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

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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.*

## PMR/PMC Development Template

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

NDA # NDA 207975  
Product Name: Vantrela ER (hydrocodone bitartrate extended-release) tablets

PMR Description: 3033-5 An observational study to validate measures of prescription opioid Substance Use Disorder and addiction in patients who have received or are receiving opioids for chronic pain.

PMR Schedule Milestones:	Final Protocol Submission:	04/2015
	Study Completion:	12/2016
	Final Report Submission:	05/2017

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

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

The data needed to validate measures of opioid-related adverse events would optimally be drawn from a source that includes at least some patients who have been taking opioids long-term.

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

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of important adverse effects of long-term opioid use, including misuse, abuse, addiction, overdose and death.

The goal of PMRs 3033-1 and 3033-2 is to determine those incidences, and identify risk factors for those outcomes. In order to conduct such studies, the outcomes need to be validated, including measures of opioid-related adverse events.

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

***If not a PMR, skip to 4.***

– **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

An observational study would likely be conducted that includes identifying patients who have been prescribed opioids for long-term use, administering a specifically designed survey instrument (PRISM-5-Op) to identify those with prescription opioid Substance Use Disorder and addiction, and then conducting a chart review or a similar activity to determine whether the identified patients actually meet the case definition.

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)

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Other

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

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

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.*

## PMR/PMC Development Template

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

NDA # NDA 207975  
Product Name: Vantrela ER (hydrocodone bitartrate extended-release) tablets

PMR Description: 3033-6 An observational study to develop and validate an algorithm using coded medical terminologies and other electronic healthcare data to identify opioid-related overdose and death.

PMR Schedule Milestones:	Final Protocol Submission:	11/2014
	Study Completion:	09/2016
	Final Report Submission:	12/2016

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

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

The data needed to validate coded medical terminologies (e.g., ICD9, ICD10, SNOMED) used to identify the opioid-related adverse events: misuse, abuse, addiction, overdose, and death would optimally be drawn from a source that includes at least some patients who have been taking opioids long-term.

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

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of important adverse effects of long-term opioid use, including misuse, abuse, addiction, overdose and death.

The goal of PMRs 3033-1 and 3033-2 is to determine those incidences, and identify risk factors for those outcomes. In order to conduct such studies, algorithms must be developed to reliably identify opioid-related adverse events of misuse, abuse, addiction, overdose and death solely using coded medical terminologies (e.g., ICD9, ICD10, SNOMED).

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

***If not a PMR, skip to 4.***

– **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

An observational study would likely be conducted that includes developing a process or algorithm to reliably identify patients using coded medical terminologies (e.g., ICD9, ICD10, SNOMED) for the opioid-related adverse events of overdose and death, and validating that process or algorithm with chart review or a similar activity.

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)

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Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

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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)

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Other

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

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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.*

## PMR/PMC Development Template

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

NDA # NDA 207975  
Product Name: Vantrela ER (hydrocodone bitartrate extended-release) tablets

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PMR Description: 3033-7 An observational study to develop and validate an algorithm using coded medical terminologies to identify patients experiencing prescription opioid abuse or addiction, among patients receiving an ER/LA opioid analgesic.

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PMR Schedule Milestones:

Final Protocol Submission:	11/2014
Study Completion:	10/2016
Final Report Submission:	01/2017

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

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

The data needed to validate coded medical terminologies (e.g., ICD9, ICD10, SNOMED) used to identify the opioid-related adverse events: misuse, abuse, addiction, overdose, and death would optimally be drawn from a source that includes at least some patients who have been taking opioids long-term.

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

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of important adverse effects of long-term opioid use, including misuse, abuse, addiction, overdose and death.

The goal of PMRs 3033-1 and 3033-2 is to determine those incidences, and identify risk factors for those outcomes. In order to conduct such studies, the coded medical terminologies (e.g., ICD9, ICD10, SNOMED) used to identify opioid-related adverse events of misuse, abuse, addiction, overdose, and death need to be validated.

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

***If not a PMR, skip to 4.***

– **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

An observational study would likely be conducted that includes identifying patients with a specifically developed algorithm solely using coded medical terminologies (e.g., ICD9, ICD10, SNOMED) for opioid-related adverse events: misuse abuse, and addiction, and then conducting chart review or a similar activity to determine whether the identified patients actually meet the clinical definition. The validation process would be conducted in multiple data resources to ensure applicability in diverse populations and settings.

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)

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Other

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

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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.*

## PMR/PMC Development Template

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

NDA #	NDA 207975	
Product Name:	Vantrela ER (hydrocodone bitartrate extended-release) tablets	
PMR Description:	3033-8 An observational study using coded medical terminologies and other electronic healthcare data to define and validate doctor and/or pharmacy shopping outcomes by examining their association with abuse and/or addiction.	
PMR Schedule Milestones:	Final Protocol Submission:	<u>03/2015</u>
	Study Completion:	<u>10/2017</u>
	Final Report Submission:	<u>01/2018</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

The data needed to validate “doctor/pharmacy shopping” as outcomes suggestive of misuse, abuse, and/or addiction would optimally be drawn from a source that includes at least some patients who have been taking opioids long-term.

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

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of important adverse effects of long-term opioid use, including misuse, abuse, addiction, overdose and death.

The goal of PMRs 3033-1 and 3033-2 is to determine those incidences, and identify risk factors for those outcomes. In order to conduct such studies, the outcome of doctor/pharmacy shopping needs to be defined and validated, and its relationship to misuse, abuse, and/or addiction must be better characterized.

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

***If not a PMR, skip to 4.***

- **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

An observational study would likely be conducted that includes identifying patients who were prescribed opioids and conducting chart reviews or similar activities to determine if there is a pattern of activity suggestive of doctor and/or pharmacy shopping and identify common characteristics of those patients.

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)

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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)

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Other

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

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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.*

## PMR/PMC Development Template

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

NDA #	NDA 207975	
Product Name:	Vantrela ER (hydrocodone bitartrate extended-release) tablets	
PMR Description:	3033-9 An observational study using a validated patient survey to evaluate the association between doctor/pharmacy shopping outcomes and self-reported misuse and abuse.	
PMR Schedule Milestones:	Final Protocol Submission:	03/2015
	Study Completion:	09/2018
	Final Report Submission:	12/2018

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

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

The data needed to validate “doctor/pharmacy shopping” as outcomes suggestive of misuse, abuse, and/or addiction would optimally be drawn from a source that includes at least some patients who have been taking opioids long-term.

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

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of important adverse effects of long-term opioid use, including misuse, abuse, addiction, overdose and death.

The goal of PMRs 3033-1 and 3033-2 is to determine those incidences, and identify risk factors for those outcomes. In order to conduct such studies, the outcome of doctor/pharmacy shopping needs to be defined and validated, and its relationship to misuse, abuse, and/or addiction must be better characterized.

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

***If not a PMR, skip to 4.***

- **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

An observational study would likely be conducted that includes identifying patients who meet one or more definitions of doctor and/or pharmacy shopping, and then conducting chart review or a similar activity to determine whether the identified patients have an indication of opioid misuse and/or abuse.

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)

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Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

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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)

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Other

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

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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.*

## PMR/PMC Development Template

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

NDA # NDA 207975  
Product Name: Vantrela ER (hydrocodone bitartrate extended-release) tablets

PMR Description: 3033-10 An observational study using medical record review to evaluate the association between doctor/pharmacy shopping outcomes and patient behaviors suggestive of misuse, abuse and/or addiction.

PMR Schedule Milestones: Final Protocol Submission: 03/2015  
Study Completion: 03/2017  
Final Report Submission: 06/2017

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

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

The data needed to validate “doctor/pharmacy shopping” as outcomes suggestive of misuse, abuse, and/or addiction would optimally be drawn from a source that includes at least some patients who have been taking opioids long-term.

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

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of important adverse effects of long-term opioid use , including misuse, abuse, addiction, overdose and death.

The goal of PMRs 3033-1 and 3033-2 is to determine those incidences, and identify risk factors for those outcomes. In order to conduct such studies, the relationship between doctor/pharmacy shopping and misuse, abuse, and/or addiction needs to be more clearly elucidated.

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

***If not a PMR, skip to 4.***

- **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

An observational study would likely be conducted that includes identifying patients who meet one or more definitions of “doctor/pharmacy shopping”, and then conducting chart review or a similar activity to determine whether the patterns and characteristics of behaviors indicative of misuse, abuse, or addiction can also be identified in the patient population.

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)

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Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

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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)

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Other

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

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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.*

## PMR/PMC Development Template

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

NDA # NDA 207975  
Product Name: Vantrela ER (hydrocodone bitartrate extended-release) tablets

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PMR Description: 3033-11 Conduct a clinical trial to estimate the serious risk for the development of hyperalgesia following the long-term use of high-dose ER/LA opioid analgesics for at least one year to treat chronic pain. Include an assessment of risk relative to efficacy.

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PMR Schedule Milestones:	Final Protocol Submission:	<u>11/2014</u>
	Trial Completion:	<u>02/2019</u>
	Final Report Submission:	<u>08/2019</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

In order to estimate the risk for the development of hyperalgesia following use of opioid analgesics for at least one year, we must be able to access data from adequate numbers of patients who were treated long-term with opioids.

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

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of serious adverse effects of opioids, including hyperalgesia. The goal of the trial is to determine the risk of developing hyperalgesia.

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

***If not a PMR, skip to 4.***

- **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

A clinical trial is needed to determine the risk of hyperalgesia following long-term treatment with opioids because this condition can be distinguished most easily with a randomized withdrawal design.

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)

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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)

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Other

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

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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.*

## PMR/PMC Development Template

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

NDA # NDA 207975  
Product Name: Vantrela ER (hydrocodone bitartrate extended-release) tablets

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PMR Description: 2981-2 In order to provide the baseline data to support the hypothesis-testing studies required under PMR 2981-3, conduct a descriptive study that analyzes data on the following:

- 1) Utilization of VANTRELA ER and selected comparators. Reports should include nationally-projected quarterly retail dispensing, overall and by age group and census region;

AND

- 2) Abuse of VANTRELA ER and related clinical outcomes. These studies should utilize multiple data sources in different populations to establish the scope and patterns of abuse for VANTRELA ER as well as mutually agreed-upon, selected comparators to provide context.
- Data should include route-specific abuse outcomes, be nationally-representative or from multiple large geographic areas, and use meaningful measures of abuse.
  - Additional information, either qualitative or quantitative, from sources such as internet forums, spontaneous adverse event reporting, or small cohort studies may also be included to help better understand abuse of this drug, including routes and patterns of abuse in various populations.
  - Formal hypothesis testing is not necessary during this phase, but provide information on the precision of abuse-related outcome estimates (e.g., 95% confidence intervals for quarterly estimates) and calculate utilization-adjusted outcome estimates where possible.

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PMR Schedule Milestones:	Draft Protocol Submission:	05/2017
	Final Protocol Submission:	09/2017
	Study Completion:	09/2018
	Final Report Submission:	03/2019
	Other: N/A	N/A

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

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

This PMR requires marketing and use in the community over the long-term in order to assess whether the abuse-deterrent characteristics of VANTRELA ER actually deter abuse of the product in “real world” use.

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.”

FDA has determined that the sponsor must conduct individual post-marketing studies of VANTRELA ER to assess the known serious risks of misuse, abuse, and their consequences, and in particular to assess whether the opioid antagonist properties of VANTRELA ER that are intended to deter misuse and abuse actually result in a decrease in misuse and abuse and their consequences.

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.

Descriptive observational studies to document the patterns of use of VANTRELA ER and describe the patterns of misuse and abuse that are occurring in the "real world".

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.*

## PMR/PMC Development Template

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

NDA # NDA 207975  
Product Name: Vantrela ER (hydrocodone bitartrate extended-release) tablets

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PMR Description: 2981-3 Conduct formal observational studies to assess whether the properties intended to deter misuse and abuse of VANTRELA ER actually result in a meaningful decrease in misuse and abuse, and their consequences, addiction overdose, and death, in post-approval settings. The studies should allow FDA to assess the impact, if any, attributable to the abuse-deterrent properties of VANTRELA ER and should incorporate recommendations contained in *Abuse-Deterrent Opioids—Evaluation and Labeling: Guidance for Industry* (April 2015). Assessing the impact of the abuse-deterrent formulation on the incidence of clinical outcomes, including overdose and death, is critical to fulfilling this PMR. Any studies using electronic healthcare data should use validated outcomes and adhere to guidelines outlined in FDA’s guidance for industry and FDA staff, *Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data*.

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PMR Schedule Milestones:	Draft Protocol	05/2019
	Final Protocol Submission:	09/2019
	Study Completion:	09/2021
	Final Report Submission:	03/2022
	Other: N/A	N/A

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

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

This PMR requires marketing and use in the community over the long-term in order to assess whether the abuse-deterrent characteristics of VANTRELA ER actually deter abuse of the product in “real world” use.
--

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.”

FDA has determined that the sponsor must conduct individual post-marketing studies of VANTRELA ER to assess the known serious risks of misuse, abuse, and their consequences, and in particular to assess whether the properties of VANTRELA ER that are intended to deter misuse and abuse actually result in a decrease in misuse and abuse and their consequences.

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.

The design of the hypothesis-testing studies for VANTRELA ER will be informed by the patterns of use and the patterns of misuse/ abuse documented in PMR XXXX-2. The hypothesis testing studies must incorporate recommendations contained in the FDA draft guidance *Abuse-Deterrent Opioids—Evaluation and Labeling* (January 2013) and must allow FDA to assess the impact, if any, that is attributable to the abuse-deterrent properties of VANTRELA ER. In particular, post-marketing studies for VANTRELA ER must include individual assessments of all relevant routes of abuse and must employ multiple appropriate comparators, including but not limited to 1) immediate and extended release formulations of morphine sulfate and other opioid analgesics and 2) both products with and without properties intended to deter abuse. The study program must include geographically diverse populations that include both opioid-dependent and non-dependent individuals and must address all the abuse-related outcomes of interest: misuse, abuse, addiction, overdose, and death.

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)

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- 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)

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- Other

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

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?

- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
  
- 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.*

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/s/  
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KIMBERLY A COMPTON  
01/13/2017

JUDITH A RACOOSIN  
01/13/2017



Division of Pediatric and Maternal Health  
Office of New Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Silver Spring, MD 20993  
Tel 301-796-2200  
FAX 301-796-9744

### Maternal Health Review Addendum

**Date:** January 11, 2017

**From:** Tamara Johnson, MD, MS, Team Leader, Maternal Health  
Division of Pediatric and Maternal Health

**Through:** Lynne Yao, MD, Division Director  
Division of Pediatric and Maternal Health

**To:** Division of Analgesia, Anesthesia and Addiction Products

**Drug:** Vantrela (Hydrocodone, Extended Release)

**NDA:** 207-975

**Applicant:** Teva Pharmaceuticals Industries Ltd.

**Subject:** Addendum to October 19, 2015 Maternal Health consult review for Vantrela  
NDA 207-975

On October 19, 2015, the Division of Pediatric and Maternal Health (DPMH) completed a consult review for Vantrela which provided labeling recommendations for the Pregnancy and Lactation sections of the labeling, as well as the Patient Counseling Information.<sup>1</sup>

We note that the October 19, 2015 Vantrela consult review refers to the January 28, 2015 consult review prepared by DPMH for Zohydro (hydrocodone bitartrate) extended-release capsules, NDA 202880, S003. To clarify, DPMH did not rely on data in the Zohydro NDA or the Agency's finding of safety and effectiveness for Zohydro to support labeling sections of the Vantrela NDA referenced above. Rather, the cross-reference to the Zohydro consult was included to avoid duplicating background information relevant to this class of products; and the literature referenced in the consult review is supportive and/or for background purposes only.

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<sup>1</sup> DARRTS Reference ID: 3834438.

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TAMARA N JOHNSON  
01/12/2017

LYNNE P YAO  
01/12/2017

# Internal Consult

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

**Please Note: The following review is for DRISK only and should not be used to provide comments to the sponsor.**

**To:** Joan Blair, Health Communications Analyst, DRISK

**From:** Koung Lee, Regulatory Review Officer, OPDP

**CC:** Sam Skariah, Team Leader, OPDP  
Vaishali Jarral, Regulatory Project Manager, OSE  
Kimberly Lehrfeld, Team Leader, DRISK  
Sangeeta Tandon, DRISK  
Jamie Wilkins-Parker, Senior Risk Management Analyst, DRISK  
CDER-OPDP-RPM  
Olga Salis, Regulatory Project Manager, OPDP

**Date:** December 13, 2016

**Re:** **VANTRELA™ ER (hydrocodone bitartrate) extended-release tablets  
NDA 207975**  
Product Specific Information for the Extended-Release/Long-Acting (ER/LA) Opioid Single Shared System (SSS) Risk Evaluation and Mitigation Strategies (REMS) Materials

### Material Reviewed

OPDP has reviewed the VANTRELA™ ER “Specific Drug Information for Extended-release and Long—Acting Opioid Analgesics (ER/LA opioid analgesics)” for the SSS REMS for ER/LA opioid products website. This material was sent by DRISK to OPDP via email (Joan Blair, Health Communication Analyst) on Tuesday, December 13, 2016, and is attached at the end of this review.

OPDP offers the following comment.

### General Comment

Please remind the sponsor that REMS materials are not appropriate for use in a promotional manner.

**REMS Materials**

OPDP does not object to the VANTRELA ER specific drug information for Extended-Release and Long—Acting Opioid Analgesics REMS.

OPDP notes that no changes were proposed for the other parts of the ER/LA Opioid REMS other than the specific drug.

We have no additional comments on this proposed REMS material at this time.

Thank you for your consult.

Enclosure:

Joan Blair's December 13, 2016 email of VANTRELA ER product specific information

**From:** Blair, Joan E. (CDER)

**Sent:** Tuesday, December 13, 2016 3:19 PM

**To:** Lee, Koung U

**Cc:** Lehrfeld, Kimberly

**Subject:** Vantrela: NDA-207975 Patient Labeling Consult Request: OPDP's Review of Product-Specific Information in ER/LA REMS Blueprint

Hi Koung,

Attached you will find the product-specific information for Vantrela, which (upon approval) will be added to the ER/LA REMS Blueprint. I have also attached the latest SCPI, which DAAAP views as final, but what has not yet been shared with the sponsor.

If possible, could you please review the product specific information by COB, Wednesday, December 14<sup>th</sup>?

Thanks,

Joan

<b>Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)</b>	
<b>Vantrela ER</b>	Hydrocodone Bitartrate Extended-Release Tablets, 15 mg, 30 mg, 45 mg, 60 mg, and 90 mg
Dosing Interval	Every 12 hours
Key Instructions	<ul style="list-style-type: none"><li>▪ Opioid naïve and opioid nontolerant patients: Initiate with 15 mg every 12 hours. Dose can be increased from the current dose to the next higher dose every 3 to 7 days as needed.</li><li>▪ Swallow tablets whole (do not chew, crush, or dissolve).</li><li>▪ Mild or moderate hepatic and moderate to severe renal impairment: Initiate therapy with 1/2 of the recommended initial dose in patients with either of these impairments. If a dose less than 15 mg is needed, use alternative analgesic options.</li></ul>
Specific Drug Interactions	<ul style="list-style-type: none"><li>▪ CYP3A4 inhibitors may increase hydrocodone exposure.</li><li>▪ CYP3A4 inducers may decrease hydrocodone exposure.</li></ul>
Use in Opioid-Tolerant Patients	A 90 mg tablet, a single dose greater than 60 mg, or a total daily dose greater than 120 mg are for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	None
Relative Potency To Oral Morphine	See individual product information for conversion recommendations from prior opioid.

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KOUNG U LEE  
12/13/2016

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

Date: May 2, 2016

Reviewer(s): Joann H. Lee, Pharm.D.  
Drug Use Data Analyst  
Division of Epidemiology II (DEPI II)

Team Leader Rajdeep Gill, Pharm.D.  
Drug Use Data Analysis Team Leader  
DEPI II

Division Director  
For Drug Utilization LCDR Grace Chai, Pharm.D  
DEPI II

Drug Name(s): Vantrela (hydrocodone) Extended-Release (ER)

Application Type/Number: NDA 20-7975

Applicant/sponsor: Teva Branded Pharmaceutical Products R and D, Inc.

OSE RCM #: 2016-572

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## 1 INTRODUCTION

In preparation for the upcoming joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) scheduled for June 7, 2016, this review summarizes the drug utilization patterns of hydrocodone ER and other extended-release/long-acting (ER/LA) opioid analgesics to provide context and background information.

### 1.1 BACKGROUND<sup>1</sup>

NDA 20-7975 was submitted by the Sponsor as a single-entity hydrocodone (Vantrela) extended-release (ER) formulation tablet (15, 30, 45, 60, and 90 mg). Its proposed indication is for the management of chronic pain that may require daily, around the-clock, opioid treatment and for which alternative treatment options are inadequate. The Sponsor is requesting that Vantrela ER be labeled as an abuse deterrent product because the tablet is resistant to rapid release of the drug when the tablet is crushed.

This drug utilization review is provided as context for the discussions to be held at the upcoming Advisory Committee Meeting on June 7, 2016.

### 1.2 PRODUCT INFORMATION

Table 1 below provides the list of all brand and generic drug products covered under the ER/LA opioid analgesic REMS program included in this review:

**Table 1. Hydrocodone ER and all other ER/LA opioid analgesic products<sup>2</sup>**

Active Ingredient	Trade Name	Approval Date
Methadone tablets or liquid	Dolophine	March 14, 1973
<b>Extended-release, Oral-dosage Forms Containing Active Ingredient</b>		
Morphine ER	MS Contin	May 29, 1987
	Kadian	July 3, 1996
	Avinza	Feb 20, 2002
	Embeda (morphine/naltrexone)*	Aug 13, 2009
	Morphabond**	October 2, 2015
Oxycodone ER	Oxycontin	December 12, 1995
	Targiniq (oxycodone/naloxone) <sup>†</sup>	July 23, 2014

<sup>1</sup> Klein, M. Memorandum for Vantrela (hydrocodone bitartrate) ER Tablets: CEP-33237/NDA 207975 submitted to S. Hertz (Division of Anesthesia, Analgesia and Addiction Products - DAAAP). 28 Sept 2015

<sup>2</sup> Drugs at FDA: Approved Risk Evaluation and Mitigation Strategies (REMS) at <http://www.accessdata.fda.gov/scripts/cder/remis/index.cfm?event=RemsDetails.page&REMS=17>. Accessed March-2016.

Active Ingredient	Trade Name	Approval Date
Hydromorphone ER	Exalgo	March 1, 2010
Oxymorphone ER	Opana ER	June 22, 2006
Tapentadol ER	Nucynta ER	August 25, 2011
Hydrocodone ER	Zohydro ER	October 25, 2013
	Hysingla ER	November 20, 2014
<b>Transdermal Delivery Systems</b>		
Fentanyl Transdermal	Duragesic	August 7, 1990
Buprenorphine Transdermal	Butrans	June 30, 2010
<p><i>*Embeda ER (morphine/naltrexone) was withdrawn from the market in March 2011 because of stability issues. It was approved with a manufacturing supplement in November 2013.</i></p> <p><i>**Morphabond approved in October 2015, drug utilization data not available for this review.</i></p> <p><i>†Targiniq ER (oxycodone/naloxone) is currently not marketed in the United States.</i></p>		

## 2 METHODS AND MATERIALS

Proprietary drug utilization databases available to the Agency were used to conduct the analyses (see Appendix B for full database description).

### 2.1 DETERMINING SETTING OF CARE

The IMS Health, *IMS National Sales Perspectives*<sup>TM</sup> was used to determine various retail and non-retail channels of distribution for the ER/LA opioid analgesics. The sales data for 2015 shows that approximately 94% of hydrocodone ER were distributed to outpatient retail pharmacies (including chain, independent, and food stores). The sales data for the other ER/LA opioids (Table 1, Section 1.2) also show that majority of sales were towards retail pharmacies (including chain, independent, and food stores). Therefore, outpatient retail pharmacy utilization patterns were examined in this review for the opioid ER/LA analgesic products. Mail order/specialty and non-retail settings were not included in this review.<sup>3</sup>

### 2.2 DATA SOURCES USED

The IMS, *National Prescription Audit*<sup>TM</sup> (NPA) database was used to obtain nationally estimated number of prescriptions dispensed for hydrocodone ER and all other ER/LA opioid analgesics (Table 1, Section 1.2) from U.S. outpatient retail pharmacies, from

<sup>3</sup> Source: *The IMS Health, IMS National Sales Perspectives*<sup>TM</sup> Extracted March-2016 Year 2015. File: NSP 2016-574 Opioid ERLA AC March-25-2016.xlsx

2011 through 2015, annually. NPA database was also used to obtain the nationally estimated number of prescriptions dispensed for hydrocodone ER from U.S. outpatient retail pharmacies, stratified by top 10 prescriber specialties for 2015.

*The IMS, Total Patient Tracker™ (TPT) database* was used to obtain the nationally estimated number of patients who received a dispensed prescription for hydrocodone ER from U.S. outpatient retail pharmacies for 2015.

### 3 RESULTS

#### 3.1 PRESCRIPTION AND PATIENT DATA

**Figure 1 below and Table 2** in Appendix A show the nationally estimated number of ER/LA opioid analgesic prescriptions dispensed from U.S. outpatient retail pharmacies from 2011 through 2015.

Approximately 21-22 million ER/LA opioid analgesic prescriptions were dispensed annually from 2011 through 2015. In 2015, morphine ER accounted for 31% (6.4 million prescriptions) of the total ER/LA prescriptions dispensed, followed by fentanyl TD (23%, 4.8 million prescriptions), and oxycodone ER (21%, 4.4 million prescriptions). Methadone prescriptions accounted for 14% (2.8 million prescriptions) of the total ER/LA prescriptions dispensed.

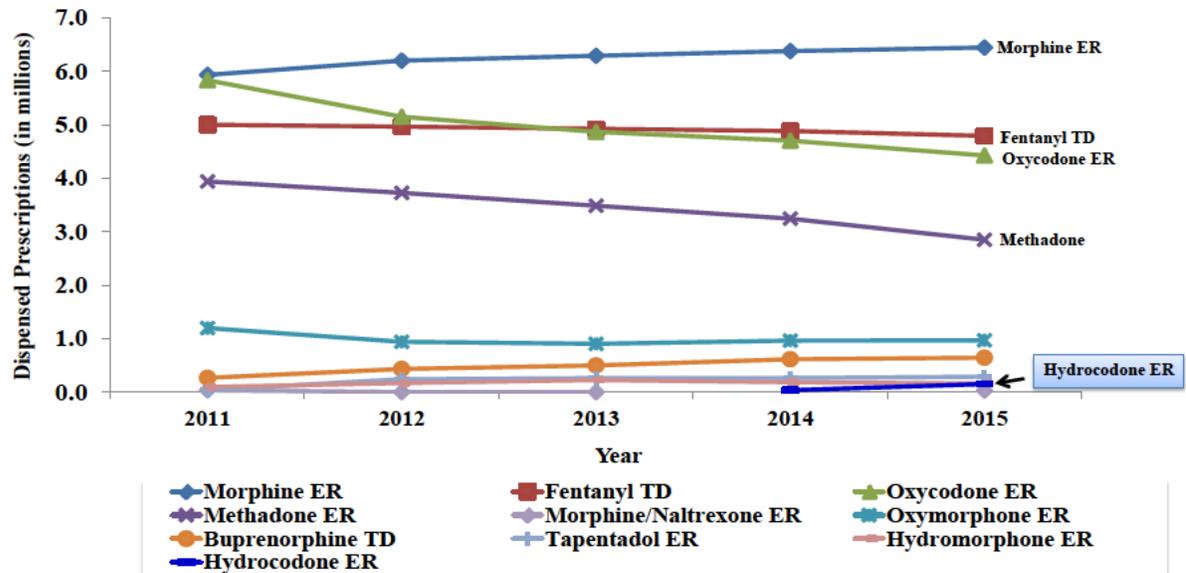
Since marketing of hydrocodone ER products (Zohydro and Hysingla) began in 2014, the uptake in prescriptions dispensed increased to approximately 150,000 prescriptions in 2015, accounting for less than 1% of prescriptions dispensed for the ER/LA opioid analgesics market. There were approximately 60,400 patients who received prescriptions dispensed for hydrocodone ER in 2015 from U.S. outpatient retail pharmacies (data not shown)<sup>4</sup>.

---

<sup>4</sup> Source: IMS, Total Patient Tracker (TPT). Year 2015. Data extracted March 2016.

**Figure 1.**

**Nationally estimated number of prescriptions dispensed for opioid ER/LA analgesics from U.S. outpatient retail pharmacies from 2011 - 2015**



Source: IMS, National Prescription Audits (NPA) Data extracted March 2015. File: NPA 2016-574 Rx Troxyca ERLA AC 04-04-16.xlsx  
 \*\*No data for years 2011, 2012, and 2013 for hydrocodone products: Zohydro ER approved in 10/2013 and Hysingla ER approved 11/2014

**3.2 PRESCRIBER SPECIALTY FOR HYDROCODONE ER**

Table 3 in Appendix A provides the total number of prescriptions dispensed for hydrocodone ER from U.S. outpatient retail pharmacies by the top prescribing specialties for year 2015. Family Practice/general practice/osteopathy were the top prescribing specialties (21% of total prescriptions), followed by anesthesiology (18%) and physical medicine & rehabilitation (13%).

**4 LIMITATIONS**

Findings from this review should be interpreted in the context of the known limitations of the databases used. Based on the IMS Health, IMS National Sales Perspectives™, sales data for 2015 showed that a vast majority of various ER/LA opioids bottles or packages were distributed to outpatient retail pharmacies. We focused our analysis on only the outpatient retail pharmacy settings; therefore, these estimates may not apply to other settings of care in which these products are used (e.g. mail-order setting, clinics, non-federal hospitals, etc.). The estimates provided are national estimates, but no statistical tests were performed to determine statistically significant changes over time or between products. All changes over time or between products should be considered approximate and may be due to random error.

## **5 CONCLUSION**

In preparation for the upcoming Advisory Committee for single-entity hydrocodone (Vantrela) extended-release (ER) tablets, this review summarizes the drug utilization patterns of hydrocodone ER and other extended-release/long-acting (ER/LA) opioid analgesics. Since marketing of hydrocodone ER products (Zohydro and Hysingla) began in 2014, the uptake in prescriptions dispensed increased to approximately 150,000 prescriptions in 2015, accounting for less than 1% of prescriptions dispensed for the ER/LA opioid analgesics market.

## 6 APPENDICES

### 6.1 APPENDIX A. TABLES

**TABLE 2.**

**Nationally estimated number of prescriptions dispensed for ER/LA opioid analgesics from U.S. outpatient retail pharmacies, 2011-2015**

	2011		2012		2013		2014		2015	
	Prescriptions (N)	Share (%)								
<b>Grand Total</b>	<b>22,330,862</b>	<b>100.0%</b>	<b>21,817,818</b>	<b>100.0%</b>	<b>21,446,002</b>	<b>100.0%</b>	<b>21,256,647</b>	<b>100.0%</b>	<b>20,742,630</b>	<b>100.0%</b>
Morphine ER	5,931,628	26.6%	6,198,303	28.4%	6,288,088	29.3%	6,375,570	30.0%	6,441,121	31.1%
Fentanyl TD	4,997,384	22.4%	4,961,133	22.7%	4,923,139	23.0%	4,881,447	23.0%	4,791,686	23.1%
Oxycodone ER	5,831,523	26.1%	5,148,631	23.6%	4,865,489	22.7%	4,699,154	22.1%	4,423,455	21.3%
Methadone	3,938,607	17.6%	3,725,332	17.1%	3,484,537	16.2%	3,242,281	15.3%	2,846,882	13.7%
Oxymorphone ER	1,196,953	5.4%	939,908	4.3%	901,305	4.2%	960,933	4.5%	968,029	4.7%
Buprenorphine TD	266,332	1.2%	431,793	2.0%	497,697	2.3%	613,086	2.9%	643,634	3.1%
Tapentadol ER	37,531	0.2%	242,059	1.1%	259,294	1.2%	264,048	1.2%	289,459	1.4%
Hydromorphone ER	95,823	0.4%	170,654	0.8%	226,452	1.1%	185,035	0.9%	160,632	0.8%
Hydrocodone ER	—	—	—	—	—	—	<b>35,093</b>	<b>0.2%</b>	<b>149,957</b>	<b>0.7%</b>
Morphine/Naltrexone ER	35,081	<1%	5	<0.1%	1	<0.1%	—	—	27,775	<1%

Source: IMS, National Prescription Audit (NPA). Extracted April 2016. File: NPA 2016-574 Rx Troxyca ERLA AC 04-22-16.xlsx

**TABLE 3.**

**Nationally estimated number of prescriptions dispensed for hydrocodone ER from U.S. outpatient retail pharmacies, stratified by top 10 prescriber specialties, 2015**

PRESCRIBER SPECIALTY	Prescriptions (N)	Share (%)
<b>Total Prescriptions</b>	<b>149,957</b>	<b>100.0%</b>
Family Practice/General Practice/Osteopathy	31,191	20.8%
Anesthesiology	27,413	18.3%
Physical Medicine & Rehab	18,783	12.5%
Nurse Practitioner	17,107	11.4%
Pain Medicine	15,535	10.4%
Physician Assistant	15,456	10.3%
Internal Medicine	7,644	5.1%
Neurology	3,290	2.2%
Rheumatology	1,612	1.1%
Orthopedic Surgery	1,223	0.8%
All Other specialties	10,703	7.1%

Source: IMS, National Prescription Audit (NPA). Year 2015. Extracted April-2016  
File: NPA 2016-572 specialty hydrocodone ERLA AC.xlsx

## **6.2 APPENDIX B: DRUG USE DATABASE DESCRIPTIONS**

### **IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail**

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

### **IMS, National Prescription Audit**

The National Prescription Audit (NPA™) measures the “retail outflow” of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers via formal prescriptions in the U.S. The NPA audit measures what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies. NPA™ receives over 2.7 billion prescription claims per year, captured from a sample of the universe of approximately 57,000 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 86% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions.

Data is also collected from approximately 40 - 70% (varies by class and geography) of mail service pharmacies and approximately 45-55% of long-term care pharmacies. Data are available on-line for 72- rolling months with a lag of 1 month.

### **IMS, Total Patient Tracker (TPT)**

Total Patient Tracker (TPT) is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time. TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 2.1 billion prescription claims per year.

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/s/  
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JOANN H LEE

08/08/2016

hydrocodone ERLA drug utilization review for Vantrela ERLA AC held June 7, 2016/NDA 207975

RAJDEEP K GILL

08/08/2016

GRACE CHAI

08/09/2016

**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: April 27, 2016

To: Sharon Hertz, MD  
Acting Director  
**Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)**

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

Barbara Fuller, RN, MSN, CWOCN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Morgan Walker, PharmD, MBA, CPH  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Subject: Focused Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)

Drug Name (established name): VANTRELA ER (hydrocodone bitartrate) extended-release tablets, for oral use, CII

Dosage Form and Route:

Application Type/Number: 207975

Applicant: Teva Branded Pharmaceutical Products R&D, Inc.

## **1 INTRODUCTION**

On September 30, 2014, Teva Branded Pharmaceutical Products R&D, Inc. submitted for the Agency's review a 505(b)(2) New Drug Application (NDA) 207975 for VANTRELA ER (hydrocodone bitartrate) extended-release tablets, an abuse-deterrent opioid. The Applicant obtained the right of reference of Vicoprofen (NDA 020716) from AbbVie, Inc. and submitted a letter of confirmation for the right of reference on July 7, 2015. Therefore, this Application has been changed from a 505(b)(2) to a 505(b)(1).

A collaborative review of the VANTRELA ER (hydrocodone bitartrate) extended-release tablets Medication Guide was completed on September 28, 2015 by the Division of Medical Policy Programs (DMPP) and Office of Prescription Drug Promotion (OPDP). Subsequently, a safety labeling change was issued for the class of extended-release/long-acting (ER/LA) opioid analgesic products. The Prescribing Information was updated to include a new Warning and Precaution (section 5.7 Adrenal Insufficiency) and Drug Interaction (section 7 serotonergic drugs) with corresponding information added to the Medication Guide.

The proposed indication for VANTRELA ER (hydrocodone bitartrate) extended-release tablets is for the management of pain severe enough to require daily around-the-clock, long-term opioid treatment and for which alternative treatments are inadequate.

This focused review is written by DMPP in response to a request by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) on April 21, 2016 for DMPP to provide a focused review of the Applicant's proposed Medication Guide (MG) for VANTRELA ER (hydrocodone bitartrate) extended-release tablets.

## **2 MATERIAL REVIEWED**

- Draft VANTRELA ER (hydrocodone bitartrate) extended-release tablets MG received on September 30, 2014, and received by DMPP on April 21, 2016.
- Draft VANTRELA ER (hydrocodone bitartrate) extended-release tablets Prescribing Information (PI) received on September 30, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on April 21, 2016.
- DMPP and OPDP Patient Labeling Review of VANTRELA ER (hydrocodone bitartrate) extended-release tablets MG dated September 28, 2015.

## **3 REVIEW METHODS**

In our focused review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)

#### **4 CONCLUSIONS**

The MG is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

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

Please let us know if you have any questions.

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

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/s/  
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MORGAN A WALKER  
04/27/2016

BARBARA A FULLER  
04/27/2016



**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service

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Food and Drug Administration  
Office of New Drugs, Office of Drug  
Evaluation IV  
Division of Pediatric and Maternal Health  
Silver Spring, MD 20993  
Telephone 301-796-2200  
FAX 301-796-9744

**Division of Pediatric and Maternal Health Review**

**Date:** October 16, 2015      **Consult Received:** February 13, 2015

**From:** Carol H. Kasten, MD, Medical Officer  
Division of Pediatric and Maternal Health, Maternal Health Team  
Office of Drug Evaluation IV (ODE IV)

**Through:** Tamara Johnson, MD, MS, Acting Team Leader  
Maternal Health Team  
Division of Pediatric and Maternal Health, ODE IV

Lynne P. Yao, MD, Director  
Division of Pediatric and Maternal Health, ODE IV

**To:** Division of Analgesia, Anesthesia and Addiction Products

**Drug:** Vantrela (Hydrocodone, Extended Release) NDA 207-975  
Schedule II Controlled Substance

**Sponsor:** Teva Pharmaceutical Industries Ltd.

**Proposed Indication:** for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

**Subject:** PLLR labeling for a new extended release/long acting (ER/LA) opioid drug product

**Consult Request:** "This NDA will require labeling in PLLR format. Please provide guidance in the review of that portion of the label."

## INTRODUCTION

This new drug application (NDA 207-975) for Vantrela (hydrocodone, extended release tablets) from Teva Pharmaceutical Industries was received on December 23, 2014. The submission is a 505(b)(2) application referencing the immediate-release hydrocodone component of Vicoprofen<sup>1</sup> as the reference listed drug (RLD). On February 13, 2015 the Division of Anesthesia, Analgesia and Addiction Products (DAAAP) consulted the Division of Pediatric and Maternal Health (DPMH) to provide labeling recommendations for the Vantrela labeling to the Pregnancy and Lactation Labeling Rule (PLLR) format.

DPMH recently reviewed another long acting hydrocodone drug product, Zohydro (NDA 202-880, S03) dated January 27, 2015; Carol H. Kasten, MD, primary author.<sup>2</sup> Pertinent differences between the Vantrela and Zohydro drug products are:

- Type and quantity of excipients
- Animal data which is described in the Pregnancy (8.1) subsection as the applicant completed their own for animal reproductive toxicology studies

In addition, there have been no new publications with human data that have been identified since the recent DPMH review for Zohydro.

For the remaining sections of this review, hydrocodone mechanism of action, class labeling for Extended Release/Long Acting (ER/LA) Opioids and Neonatal Opioid Withdrawal Syndrome, toxicology databases and published literature reviews, conclusions and recommendations, a summary of the information will be included. The reader is referred to the DPMH Zohydro Consult for the complete discussion.

## BACKGROUND

The applicant has submitted two clinical trials to support this application. The first trial (3079) failed to meet its primary endpoint. The second trial (3103) also failed to meet its primary endpoint and was complicated by a large amount of missing subject data per the statistical review.<sup>3</sup> On July 21, 2015 the applicant submitted a request to convert the application to a 505(b)(1) after having obtained the right of reference for Vicoprofen from AbbVie. At the time of this review, the Division's decision on the action to be taken for this application is undecided.

### Vantrela Formulation

Vantrela tablets have been formulated to extend the release of hydrocodone adequately to permit twice daily dosing and to confer abuse deterrent properties. The applicant states that this is accomplished by [REDACTED] (b) (4)

[REDACTED] The reader is referred to the pharmacology toxicology review for additional information on the safety of the excipients used in this formulation.

<sup>1</sup> NDA 20-716 license holder AbbVie, Inc.

<sup>2</sup> DARRTS Reference ID: 3693127

<sup>3</sup> Statistical Review and Evaluation, Office of Translational Sciences, Office of Biostatistics, CDER, Bradley McEvoy, DrPH, primary author. Dated September 11, 2015.

### Teva Animal Reproductive Toxicology Data

Animal studies in rats and rabbits were completed using hydrocodone doses that were approximately five times higher than the maximum recommended human dose (MRHD) of 180 mg/day did not produce any fetal malformations. Embryofetal studies in rats at doses that were approximately 1.8 times the MRHD did demonstrate an increased number of post-implantation embryonic losses. These data are consistent with other hydrocodone animal studies including those reported for Zohydro.

### Hydrocodone Mechanism of Action

Hydrocodone is biotransformed to the opioid hydromorphone. Its analgesic effect is attributable to both hydrocodone and hydromorphone, which is the more potent opioid.<sup>4</sup>

### Class Labeling for Opioid Drug Products

As part of the class labeling, boxed warnings are required for addiction, abuse and misuse, respiratory depression that can lead to overdose and death and Neonatal Opioid Withdrawal Syndrome (NOWS) which may be life threatening in neonates whose mothers required prolonged opioid therapy while pregnant. In addition to the boxed warnings, there is class labeling in several sections and sub-sections. The basis for the NOWS class labeling is contained in the PMHS *Citizen Petition and Petition for Stay Regarding Neonatal Opioid Withdrawal Syndrome (NOWS) labeling changes* consult review.<sup>5</sup>

### **Database and Literature Review**

#### Pregnancy - conclusions in the recent DPMH Zohydro review

- Two large epidemiologic studies, the Collaborative Perinatal Project (CPP)<sup>6,7</sup> and the National Birth Defects Prevention Study (NBDPS)<sup>8</sup> do not indicate there is an increased risk of teratogenesis from prenatal exposure to hydrocodone.
- Reviews in the toxicology databases TERIS<sup>9</sup> and Reprotox<sup>10</sup> indicate that there is minimal risk of teratogenesis from prenatal hydrocodone exposure.

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<sup>4</sup> Clinical pharmacology online©, [www.clinicalpharmacology-ip.com](http://www.clinicalpharmacology-ip.com) Elsevier. Gold Standard.

Revision date: November 26, 2015. Accessed January 11, 2015.

<sup>5</sup> Co-Primary Authors Leyla Sahin, MD, Amy Taylor, MD, MHS. *Citizen Petition and Petition for Stay regarding Neonatal Opioid Withdrawal Syndrome (NOWS) labeling changes*. April 11, 2014. DARRTS Reference ID: 3488324

<sup>6</sup> See Heinonen OP, Slone D, Shapiro S: *Birth Defects and Drugs in Pregnancy*. Publishing Sciences Group Inc., Littleton, MA, pgs 287, 434, 1977.

<sup>7</sup> Pettersen J. Book Review of Heinonen, *et al*.

<sup>8</sup> Broussard CS, Rasmussen SA, Reefhuis J, Friedman JM, Jann MW, Riehle-Colarusso T, and Honein MA (2011) Maternal treatment with opioid analgesics and risk for birth defects. *Am J Obstet Gynecol* 204 (4):314-11

<sup>9</sup> TERIS is the TERatology Information Service located at University of Washington. It is an online database designed to assist physicians or other healthcare professionals in assessing the risks of possible teratogenic exposures in pregnant women. Review date 07/14. Accessed 2015.

[http://www.micromedexsolutions.com/micromedex2/librarian/ND\\_T/evidencexpert/ND\\_PR/evidencexpert/](http://www.micromedexsolutions.com/micromedex2/librarian/ND_T/evidencexpert/ND_PR/evidencexpert/)

<sup>10</sup> [www.Reprotox.org](http://www.Reprotox.org). REPROTOX® system was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 2015.

## Lactation - conclusions in the recent DPMH Zohydro review

- Lactating women should not be treated with hydrocodone. There are reports of excess sedation and death in breastfeeding infants of women treated with hydrocodone in the published literature.
- The LactMed<sup>11</sup> review recommends that alternative, non-narcotic analgesics be used in women who breastfeed.

## **DISCUSSION**

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the “Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling,”<sup>12</sup> also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and creates a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule<sup>13</sup> format to include information about the risks and benefits of using these products during pregnancy and lactation.

The risk of teratogenesis for hydrocodone is low based on both human and animal studies as described previously.<sup>14</sup> However, there are significant risks to the breastfeeding infant of a Vantrela treated lactating women. As noted in previous reviews of labeling for other hydrocodone-containing products, hydrocodone can cause drowsiness, central nervous system depression and death in breastfeeding infants. Therefore, DPMH does not recommend breastfeeding while a lactating woman is treated with a hydrocodone-containing drug product.

## **CONCLUSIONS AND RECOMMENDATIONS**

There are no new data or reviews which change our previous conclusions and recommendations discussed in the recent DPMH Zohydro review. These conclusions formed the basis of the Zohydro labeling recommendations and are the same as for other hydrocodone products. Those conclusions are:

- The risk of teratogenesis from prenatal Vantrela exposure is low.
- There is a risk of serious adverse events, including death, if a lactating woman treated with Vantrela breastfeeds an infant. Therefore, breastfeeding is not recommended during treatment with Vantrela.

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<sup>11</sup> LactMed® The LactMed database is a National Library of Medicine database with information on drugs and lactation geared toward healthcare practitioners and nursing women. LactMed Record Number: 990; Last revised January 7, 2015

<sup>12</sup> *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

<sup>13</sup> *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

<sup>14</sup> DPMH Review - Zohydro (NDA 202-880, S03) dated January 27, 2015; Carol H. Kasten, MD, primary author; DARRTS Reference ID: 3693127

DPMH attended meetings with DAAAP in April, May, June, August and September, 2015. DPMH presented its labeling recommendations at the September 15, 2015 meeting with the Division.

The following are the DPMH Maternal Health Team recommendations for the proposed labeling For Vantrela in PLLR format.

**VANTRELA ER (hydrocodone bitartrate) extended-release tablets, for oral use, CII  
Initial U.S. Approval: 1943**

**WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE THREATENING  
RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID  
WITHDRAWAL SYNDROME; and CYTOCHROME P450 3A4 INTERACTION**

*See full prescribing information for complete boxed warning.*

- **Prolonged use of VANTRELA ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.3)**

—————**INDICATIONS AND USAGE**—————

VANTRELA ER is an opioid agonist indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. (1)

—————**USE IN SPECIFIC POPULATIONS**—————

- Pregnancy: May cause fetal harm. (8.1)
- Lactation: Not recommended. (8.2)

**FULL PRESCRIBING INFORMATION: CONTENTS\***

**5 WARNINGS AND PRECAUTIONS**

5.3 Neonatal Opioid Withdrawal Syndrome

**8 USE IN SPECIFIC POPULATIONS**

8.1 Pregnancy

8.2 Lactation

## FULL PRESCRIBING INFORMATION

### BOXED WARNING

**WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; and CYTOCHROME P450 3A4 INTERACTION**

#### Neonatal Opioid Withdrawal Syndrome

**Prolonged use of VANTRELA ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see Warnings and Precautions (5.3)].**

## 1 INDICATIONS AND USAGE

VANTRELA™ ER is an opioid agonist indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

### 5.3 Neonatal Opioid Withdrawal Syndrome

Prolonged use of VANTRELA ER during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. [REDACTED] (b) (4)

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn [see Use in Specific Populations (8.1)].

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### *Risk Summary*

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome [see Warnings and Precautions (5.3)]. There are no available data on VANTRELA ER use in pregnant women to inform any drug associated risks. [REDACTED] (b) (4)

(b) (4)

Advise pregnant women of the potential risks to a fetus. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

### *Clinical Considerations*

#### Fetal/neonatal adverse reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, (b) (4) and manage accordingly [see *Warnings and Precautions (5.3)*].

#### Labor and Delivery

Opioids cross the placenta and may produce respiratory depression (b) (4) and psychophysiological effects in neonates. An opioid antagonist such as naloxone must be available for reversal of opioid induced respiratory depression in the neonate. VANTRELA ER is not recommended for use in women immediately prior to labor, when shorter-acting analgesics or other analgesic techniques are more appropriate. Opioid analgesics, including VANTRELA ER, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor.

### *Data*

#### Animal Data

(b) (4)

## **8.2 Lactation**

### *Risk Summary*

Hydrocodone is present in human milk. (b) (4)

Lactation studies have not been conducted with extended-release hydrocodone, including VANTRELA ER, and no information is available on the effects of the drug on the breastfed infant or the effects of the drug on milk production. Because of the potential for serious adverse

reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with VANTRELA ER.

#### *Clinical Considerations*

Infants exposed to VANTRELA ER through breast milk should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

## **17 PATIENT COUNSELING INFORMATION**

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

#### Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential that prolonged use of VANTRELA ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated [*see Warnings and Precautions (5.3)*].

(b) (4)

(b) (4) female patients that VANTRELA ER (b) (4) cause fetal harm and to inform (b) (4) health care provider with a known or suspected pregnancy [*see Use in Specific Populations (8.1)*].

#### Lactation

Advise patients that breastfeeding is not recommended during treatment with VANTRELA ER [*see Use in Specific Populations (8.2)*].

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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CAROL H KASTEN  
10/16/2015

LYNNE P YAO  
10/19/2015

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

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

## Memorandum

Date: October 2, 2015

To: Kimberly Compton, Senior Regulatory Project Manager  
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)  
  
Sharon Hertz, MD, Director - DAAAP

From: Koungh Lee, Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

Through: Jessica Fox, Regulatory Review Officer - OPDP

CC: Olga Salis, Senior Regulatory Project Manager - OPDP

Subject: NDA 207975  
Vantrela ER (hydrocodone bitartrate) Extended-release Tablets  
Professional Labeling Review

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As requested in DAAAP's consult dated February 13, 2015, OPDP has reviewed the substantially complete prescribing information and container and carton labeling for Vantrela ER. The substantially complete prescribing information was provided to OPDP on September 17, 2015, via email by Kimberly Compton with the file name "[\\fdafs01\ODE2\DAAAP\NDA and sNDA\NDA 207975 \(ER Hydrocodone Teva\)\Labeling\N 207-975 PI from EDR 4-22-15 \(USE FOR EDITS\).doc](#)".

OPDP has provided comments on the substantially complete prescribing information in the attached document below. Specifically, we made comments on pages 11, 16, 18, 29 and 30.

OPDP has no comments at this time on the carton and container labeling submitted September 28, 2015.

Please note that our comments on the Medication Guide will be provided under a separate cover as a collaborative review between OPDP and the Division of Medical Policy Programs (DMPP).

Thank you for your consult. OPDP appreciates the opportunity to provide comments. If you have any questions, please contact me at (240) 402-8686 or by email, [Koung.Lee@fda.hhs.gov](mailto:Koung.Lee@fda.hhs.gov).

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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KOUNG U LEE  
10/02/2015

# Center for Devices and Radiological Health

(ODE/DOED/ENTB)

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## Audiology Review

To: Robert A. Levin CDER/DNP  
From: Ting Zhang, Ph.D., Audiology ENTB/DOED/ODE  
Date: September 18, 2015  
Thru: Srinivas Nandkumar, Ph.D.  
Branch Chief, Ear, Nose, and Throat Devices  
Re: NDA 207975  
Name of Firm: Teva Branded Pharmaceutical Products  
Name of Product: Vantrela ER (hydrocodone ER) tabs  
Intended Use: Mgmt of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate

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Thank you for your request of a consultative review re. NDA208975. I have reviewed the study reports C33237/3079 and C33237/3103 from an audiology perspective. The following memo presents a summary of the audiology report and an evaluation of the information provided in that report for the assessment of potential ototoxic effects from the study drug from the audiology perspective. You can find a list of my comments at the end of the memo in the section titled "Conclusions & Recommendations."

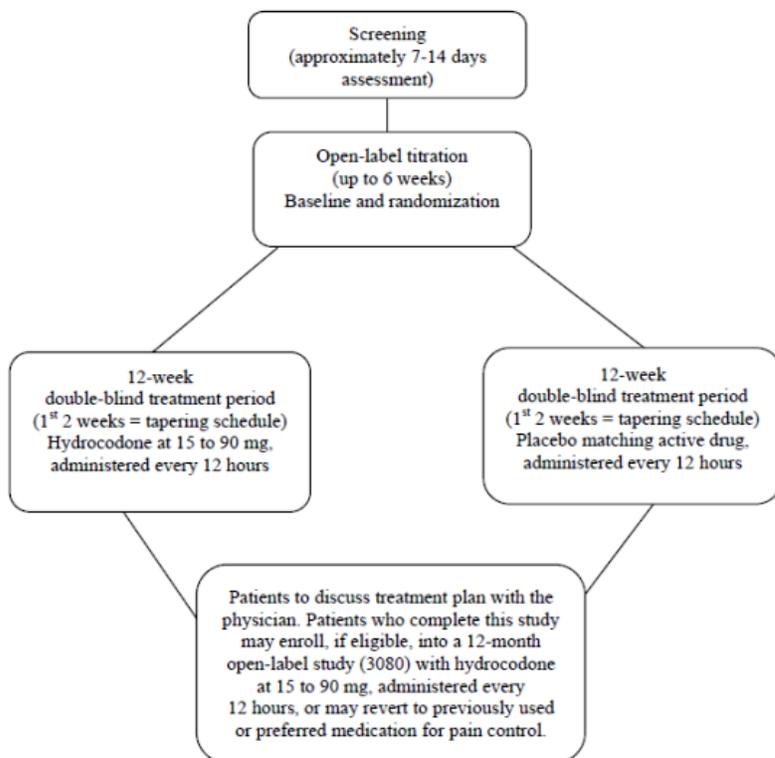
### **I. Purpose**

Teva has submitted NDA 20795 for Vantrela (hydrocodone bitartrate extended-release tablets) for the management of <sup>(b) (4)</sup> pain.

There have been reports in the literature of hearing loss associated with the use of hydrocodone, usually with a hydrocodone/acetaminophen combination. These reports describe a sensorineural hearing loss that is typically sudden or rapidly progressive in nature, and often severe in degree. Currently, there is no clear consensus on the extent of hydrocodone's risk for ototoxic effects on hearing and vestibular function. Factors that contribute to the unclear nature of hydrocodone-associated hearing loss include: drug dosage, drug use period, patient risk factors (e.g., existing hearing loss, history of noise exposure) that may make them more susceptible to ototoxic effects, and the use of hydrocodone in conjunction with other agents (e.g., acetaminophen, NSAIDs). Since progressive hearing loss has been associated with the abuse of hydrocodone/acetaminophen combination products, and the potential exposure to hydrocodone from this product is higher than the labeled doses from combination products, the FDA requested that audiometry evaluations be performed. The Applicant submitted the audiometry findings and individual clinically significant hearing changes for two clinical studies (3103 and 3079) in their 12/23/14 submission.

## II. Review of Clinical Protocol Study C33237/3079

Figure 1: Overall Study Schema



### 7.6.2 Pure Tone Audiometry

Pure tone audiometry will be performed at visit 2 and 3 (before and during open-label titration, respectively), at the first visit of the double-blind treatment period (day 0), and at the final visit (double-blind week 12 or early termination)

Pure tone audiometry will be performed by trained personnel and total testing time will take approximately 20 to 25 minutes. During the test, the patient will wear headphones and be seated in a quiet room; trained personnel will manipulate the audiometry equipment to test the patient's hearing.

Hearing loss is classified in degrees of hearing from normal to profound. This classification is determined by the hearing threshold (or the softest sound detected at a specific frequency). The exact ranges that classify hearing loss depend on the exact technique used during testing and on the patient's age. These values will be provided by each audiology laboratory performing the test (Appendix C). For serial audiograms, the criteria for a clinically significant hearing change will be based on the guidance from the

American Speech-Language-Hearing Association (ASHA 1994, cited in [Konrad-Martin et al 2005](#)). These criteria include the following: greater than 20 dB pure-tone threshold shift at 1 frequency; greater than 10 dB shift at 2 consecutive test frequencies; or threshold response shifting to “no response” at 3 consecutive test frequencies. Change must be confirmed by retest.

### **III. Review of Clinical Protocol Study C33237/3103**

#### **3.1.1 Overall Design and Screening Period**

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, randomized-withdrawal study to assess the efficacy and safety of hydrocodone bitartrate extended-release tablets in patients with moderate to severe chronic low back pain who require continuous opioid treatment for an extended period of time. The study will consist of a screening period of approximately 7 to 14 days (visit 1), an open-label titration period of up to 6 weeks (visit 2 [titration baseline] through visit 6), a double-blind treatment period of up to 12 weeks (visit 7 [day 0/baseline]; visits 8 through 11 [weeks 1, 2, 4, and 8, respectively; a final on-treatment visit [if applicable; referred to herein as visit 11.5]); and a final study visit (visit 12/week 12 [or early termination]).

Pure tone audiometry will be performed by a qualified audiologist and will not be done at the study center. During the test, the patient will wear headphones and be seated in a quiet room; trained personnel will manipulate the audiometry equipment to test the patient’s hearing.

Hearing loss is classified in degrees of hearing from normal to profound. This classification is determined by the hearing threshold (or the softest sound detected at a

specific frequency). The exact ranges that classify hearing loss depend on the exact technique used during testing and on the patient’s age. These values will be provided by each audiology laboratory performing the test ([Appendix F](#)). For serial audiograms, the criteria for a clinically significant hearing change will be based on the guidance from the American Speech-Language Hearing Association (ASHA 1994, cited in ([Konrad-Martin et al 2005](#))). These criteria include the following: greater than 20 dB pure tone threshold shift at 1 frequency; greater than 10 dB shift at 2 consecutive test frequencies; or threshold response shifting to “no response” at 3 consecutive test frequencies.

The study center will refer patients to an audiologist for testing at each of the specified visits. The audiologist will perform testing and record results on an audiology study report form. The investigator will review the results from this form, and study center personnel will record the results on the CRF.

Some clinically significant findings may require further testing by the audiologist. Clinically significant findings may be discussed with the audiologist to determine if a patient should have study drug discontinued or should be withdrawn from the study. NOTE: A change in audiology findings is not necessarily an adverse event.

**Reviewer’s Comments:** *From an audiology perspective, the clinical protocol regarding pure tone audiometry proposed to monitor pure tone thresholds before, during, and after the 12-week hydrocodone use. Generally speaking, we would expect to see ototoxic drug effects on hearing and vestibular function (especially as measured by pure-tone audiometry) within 12 months of treatment with the drug. Furthermore, the type of hearing loss most typically reported in association with hydrocodone use is sudden in onset and/or rapid in progression. Therefore, from an audiology perspective, the proposed pure tone audiometry measures are able to capture ototoxic drug effect from the hydrocodone use.*

#### IV. Review of “Pure Tone Audiometry” reported under “12.5.4 Other Observations Related to Safety” in the clinical report C33237/3079

##### 12.5.4.1 Pure Tone Audiometry

Pure tone audiometry was performed by the individual study centers before and during the open-label titration period (before study drug exposure at visit 2 and after 1 week of exposure to the study drug at visit 3 [or visit 7, if the patient achieved a successful dose before or during visit 3]), and at the 1<sup>st</sup> and final visits of the double-blind treatment period (day 0 and week 12, or early termination).

##### (a) Audiometry Findings Over Time

Overall, there were no clinically meaningful trends in mean changes from baseline to final values in pure tone audiometry results for patients treated with hydrocodone extended-release tablets. Mean changes from baseline to final values were minimal at all hearing thresholds (range -2.6 to 1.3 decibel levels), and there were no changes in median changes from baseline to final values at all hearing thresholds (Table 61 and Table 62).

**Table 61: Changes From Baseline to Final Values in Pure Tone Audiometry by Hearing Threshold and Patient Opioid Status (Safety Analysis Set)**

Threshold	Statistic	Open-label titration periods			
		Opioid naïve (N=189)		Opioid experienced (N=200)	
		Left ear	Right ear	Left ear	Right ear
-500 Hz	n	174	174	184	185
	Mean	-0.1	-0.3	-0.7	-1.9
	SD	9.10	7.65	9.22	12.01
	Median	0.0	0.0	0.0	0.0
-1000 Hz	n	176	176	183	185
	Mean	-0.1	0.3	-0.3	-0.2
	SD	5.73	5.79	6.59	6.52
	Median	0.0	0.0	0.0	0.0
-2000 Hz	n	176	176	183	185
	Mean	-0.4	-0.1	-0.3	0.3
	SD	5.93	4.91	7.32	7.92
	Median	0.0	0.0	0.0	0.0
-3000 Hz	n	176	176	183	185
	Mean	-0.5	1.0	0.0	-0.1
	SD	6.12	8.87	8.19	7.64
	Median	0.0	0.0	0.0	0.0
-4000 Hz	n	176	176	183	184
	Mean	-0.2	0.0	-0.4	-0.4
	SD	8.97	6.96	8.94	8.66
	Median	0.0	0.0	0.0	0.0
-6000 Hz	n	174	176	183	184
	Mean	-0.3	0.1	-1.7	-0.2
	SD	11.87	11.59	13.94	14.07
	Median	0.0	0.0	0.0	0.0
-8000 Hz	n	173	174	182	184
	Mean	0.1	-0.6	-0.4	-0.7
	SD	11.96	11.54	11.86	14.70
	Median	0.0	0.0	0.0	0.0

SOURCE: Summary 15.29.4, Listing 16.2.8.20.

<sup>a</sup> Pure tone audiometry was performed before and during the open-label titration period at visits 2 and 3 (or visit 7 if the patient achieved a successful dose before or during visit 3), and at the 1<sup>st</sup> and final visits of the double-blind treatment period (day 0 and week 12, or early termination).

NOTE: Pure tone audiometry values are in decibels for each frequency threshold. Baseline and final assessment values were summarized for each patient.  
Hz=Hertz; SD=standard deviation.

**Table 62: Changes From Baseline to Final Values in Pure Tone Audiometry by Threshold, Treatment Group, and Study Period (Full Analysis Set)**

Threshold	Statistic	Open-label titration period <sup>a</sup>				Double-blind treatment period <sup>b</sup>			
		Placebo (N=147)		Hydrocodone (N=146)		Placebo (N=147)		Hydrocodone (N=146)	
		Left ear	Right ear	Left ear	Right ear	Left ear	Right ear	Left ear	Right ear
-500 Hz	n	135	136	138	138	132	132	134	134
	Mean	0.3	-0.7	-0.1	-1.4	-0.4	-1.3	-0.2	-2.0
	SD	7.40	10.16	10.34	7.13	8.78	11.08	11.41	7.88
	Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
-1000 Hz	n	136	137	139	139	133	133	135	134
	Mean	-0.1	0.7	0.1	-0.6	-0.4	-0.3	1.1	-0.6
	SD	6.35	6.69	6.31	5.74	6.99	6.75	11.24	6.80
	Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
-2000 Hz	n	136	137	139	139	132	133	135	135
	Mean	0.2	0.0	-1.2	-0.1	0.6	-0.2	-0.1	-0.3
	SD	5.91	7.29	6.71	4.74	5.66	6.96	9.91	7.36
	Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
-3000 Hz	n	136	137	139	139	132	132	135	135
	Mean	-0.4	-0.6	-0.4	1.0	-0.1	-0.9	-1.6	-0.6
	SD	6.17	7.05	7.58	9.63	7.08	8.50	14.82	9.72
	Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
-4000 Hz	n	136	136	139	139	132	132	135	135
	Mean	-0.5	-0.4	-0.4	-0.8	1.1	-0.8	-1.3	-0.7
	SD	9.46	7.30	8.54	7.29	9.13	7.92	14.57	10.98
	Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Footnotes and abbreviations are provided at the end of the table.

(continued)

**Table 62: Changes From Baseline to Final Values in Pure Tone Audiometry by Threshold, Treatment Group, and Study Period (Full Analysis Set) (Continued)**

Threshold	Statistic	Open-label titration period <sup>a</sup>				Double-blind treatment period <sup>b</sup>			
		Placebo (N=147)		Hydrocodone (N=146)		Placebo (N=147)		Hydrocodone (N=146)	
		Left ear	Right ear	Left ear	Right ear	Left ear	Right ear	Left ear	Right ear
-6000 Hz	n	136	136	138	139	132	133	134	135
	Mean	1.0	-0.1	-2.6	-0.1	-1.1	-0.9	-2.4	-2.4
	SD	12.91	13.80	10.57	12.15	14.07	11.99	15.51	14.21
	Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
-8000 Hz	n	134	135	137	138	131	132	133	134
	Mean	0.8	0.4	-1.0	-2.0	1.3	-0.7	-1.8	-1.9
	SD	11.51	13.65	12.40	12.42	11.33	9.22	14.89	18.36
	Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

SOURCE: Summary 15.29.5, Listing 16.2.8.20.

<sup>a</sup> Pure tone audiometry was performed before study drug exposure (visit 2, baseline) and after 1 week of exposure to study drug (visit 3, final) (before and during the open-label titration period, respectively). Baseline and final assessment values were summarized for patients in the placebo and hydrocodone treatment groups.

<sup>b</sup> Pure tone audiometry was performed at the 1<sup>st</sup> visit of the double-blind treatment period (day 0, baseline) and at the final visit of the double-blind treatment period (week 12 or early termination). Baseline and final assessment values were summarized for patients in the placebo and hydrocodone treatment group.

NOTE: Pure tone audiometry was performed before and during the open-label titration period at visits 2 and 3 (or visit 7 if the patient achieved a successful dose before or during visit 3), and at the 1<sup>st</sup> and final visits of the double-blind treatment period (day 0 and week 12, or early termination). Pure tone audiometry values are in decibels for each frequency threshold.

Hz=Hertz; SD=standard deviation.

Pure tone audiometry tests results are summarized in [Summary 15.29.4](#) (by threshold [safety analysis set]) and [Summary 15.29.5](#) (by threshold and study period [full analysis set]), and individual results are provided in section 16.2.8, [Listing 16.2.8.20](#) (enrolled patients) and [Listing 16.2.8.22](#) (enrolled patients).

**Reviewer's Comments:**

*Pure tone audiometry was performed before and after the open-label titration period, and before and after the double-blind treatment period. Overall, mean hearing threshold changes from baseline to final values for both open-label titration period and double-blind treatment period ranged -2.6 to 1.3 dB across conventional frequencies of 500-8000 Hz. From an audiology perspective, a change of hearing threshold > 10 dB is considered clinically significant. The reported mean threshold change of -2.6 to 1.3 dB is judged minimal.*

*However, it is unknown whether there are any significant mean threshold changes from the very beginning to the end of the study for those patients who participated in both the open-label titration period and the double-blind study period, i.e., the baseline of the open-label titration period (Visit 2) to the final assessment of the double-blind study period (Visit 12). We believe this is an important individual data analysis on to evaluate the extent of hydrocodone's risk for ototoxic effects on hearing. The sponsor will be asked to provide further analysis on the pure tone audiometry data from pure tone audiometry to support the absence of ototoxic effect of hydrocodone bitartrate extended-release tablets for the management of chronic pain.*

*The sponsor did not include ultra-high frequency audiometry as part of the pure tone audiometry. Although we typically expect to see ototoxic medication effects first in the ultra-high frequencies, it is also reasonable to assume that if there is no impact on conventional frequencies after 3 months of the hydrocodone use, then there likely are not ototoxic effects on hearing function, particularly for speech understanding. Given the minimal hearing threshold changes from conventional pure tone audiometry, we would expect that changes of hearing thresholds in the ultra-high frequency range are minimal as well.*

**(b) Individual Clinically Significant Hearing Changes**

The criteria for clinically significant changes from baseline in hearing were predefined for the study (see section 9.5.1.2(f)(ii)). Hearing loss was classified in degrees of hearing from normal to profound and was determined by the hearing threshold (or the softest sound detected at a specific frequency).

Overall, the patients who had clinically significant changes in hearing from baseline to final assessment in each study period were comparable for the patients in the hydrocodone and placebo treatment groups, and no clinically meaningful differences were seen between the treatment groups (Table 63). A total of 73 (19%) patients enrolled in the study had at least 1 clinically significant change from baseline in hearing, and of these 73 patients, 29 (20%) patients in the hydrocodone treatment group and 30 (20%) patients in the placebo treatment group had at least 1 clinically significant change in hearing that occurred during the double-blind treatment period.

Few patients in the hydrocodone or placebo treatment groups had clinically significant changes in hearing from baseline values (Table 64). Of note, patients did not all have normal hearing at baseline. Small numerical differences were observed between the treatment groups, but overall the findings were not clinically meaningful. No patient with a clinically significant change in hearing had an adverse event leading to withdrawal from the study.

**Table 63: Overall Clinically Significant Hearing Changes From Baseline to Final Assessment in Pure Tone Audiometry Test Results (Safety Analysis Set)**

Analysis group	Number (%) of patients <sup>a</sup>		
	Placebo (N=147)	Hydrocodone (N=146)	Total (N=293)
<b>Safety analysis set</b>			389 (100)
≥1 CS value during study	—	—	73 (19)
≥1 CS value during open-label titration period	—	—	55 (14)
<b>Full analysis set</b>	147 (100)	146 (100)	293 (100)
≥1 CS value during study	30 (20)	29 (20)	59 (20)
≥1 CS value during open-label titration period	22 (15)	19 (13)	41 (14)
≥1 CS value during double-blind treatment period	13 (9)	16 (11)	29 (10)
≥1 CS value at endpoint	12 (8)	15 (10)	27 (9)
<b>Number of patients with CS values who rolled over to participate in study C33237/3080</b>	9 (6)	9 (6)	18 (6)

SOURCE: Summary 15.29.3, Listing 16.2.8.20, Listing 16.2.8.21, and Listing 16.2.8.22.

<sup>a</sup>Patients in the placebo and hydrocodone treatment groups.

CS=clinically significant.

**Table 64: Clinically Significant Hearing Changes From Baseline to Final Assessment in Pure Tone Audiometry by Study Period and Treatment Group (Full Analysis Set)**

Study period	Hearing category at baseline <sup>a</sup>	Criteria for significant change	Number of patients with CS change of the number of patients at baseline in that hearing category			
			Placebo (N=147)		Hydrocodone (N=146)	
			Left ear	Right ear	Left ear	Right ear
Open-label titration period	Normal hearing	>10 dB shift at 2 consecutive test frequencies	3 of 32	0	2 of 23	3 of 30
		>20 dB shift at 1 test frequency	1 of 32	1 of 31	1 of 23	1 of 30
	Mild	>10 dB shift at 2 consecutive test frequencies	1 of 61	3 of 62	4 of 68	4 of 65
		>20 dB shift at 1 test frequency	1 of 61	4 of 62	2 of 68	1 of 65
		shift to no response at 3 consecutive test frequencies	0	0	1 of 68	0
	Moderate	>10 dB shift at 2 consecutive test frequencies	4 of 22	2 of 25	0	1 of 24
		>20 dB shift at 1 test frequency	3 of 22	1 of 25	1 of 28	2 of 24
	Moderately severe	>10 dB shift at 2 consecutive test frequencies	2 of 14	2 of 10	0	1 of 17
		>20 dB shift at 1 test frequency	1 of 14	2 of 10	0	0
	Severe	>10 dB shift at 2 consecutive test frequencies	0	1 of 10	0	0
		>20 dB shift at 1 test frequency	0	2 of 10	0	0
	Profound	>10 dB shift at 2 consecutive test frequencies	0	1 of 3	1 of 7	0
		>20 dB shift at 1 test frequency	0	1 of 3	4 of 7	1 of 5

Footnotes and abbreviations are provided at the end of the table.

(continued)

**Table 64: Clinically Significant Hearing Changes From Baseline to Final Assessment in Pure Tone Audiometry by Study Period and Treatment Group (Full Analysis Set) (Continued)**

Study period	Hearing category at baseline <sup>a</sup>	Criteria of significant change	Number of patients with CS change of the number of patients at baseline in that hearing category			
			Placebo (N=147)		Hydrocodone (N=146)	
			Left ear	Right ear	Left ear	Right ear
Double-blind treatment period	Normal hearing	>10 dB shift at 2 consecutive test frequencies	2 of 32	1 of 31	1 of 23	0
		>20 dB shift at 1 test frequency	2 of 32	0	2 of 23	0
	Mild	>10 dB shift at 2 consecutive test frequencies	2 of 61	2 of 62	6 of 68	6 of 65
		>20 dB shift at 1 test frequency	2 of 61	1 of 62	5 of 68	5 of 65
	Moderate	>10 dB shift at 2 consecutive test frequencies	3 of 22	1 of 25	1 of 28	0
		>20 dB shift at 1 test frequency	3 of 22	0	0	0
	Moderately severe	>10 dB shift at 2 consecutive test frequencies	1 of 14	1 of 10	0	1 of 17
		>20 dB shift at 1 test frequency	1 of 14	2 of 10	0	0
	Severe	>20 dB shift at 1 test frequency	0	1 of 10	0	0
	Profound	>10 dB shift at 2 consecutive test frequencies	0	0	2 of 7	0
		>20 dB shift at 1 test frequency	0	1 of 3	2 of 7	0

SOURCE: Summary 15.29.2, Listing 16.2.8.20, and Listing 16.2.8.21.

<sup>a</sup>Hearing category for baseline value: normal=0 to 20dB, mild=21 to 40dB, moderate=41 to 55dB, moderately severe=56 to 70dB, severe=71 to 90dB, profound=91 and greater. The worst value at baseline was used for the classification.

NOTE: Pure tone audiometry was performed before study drug exposure (visit 2), after 1 week of exposure to study drug (visit 3, or visit 7 if the patient achieved a successful dose during visit 2), at the 1<sup>st</sup> visit of the double blind treatment period (day 0), and at the final visit of the double blind treatment period (week 12, or early termination).

dB=decibels; CS=clinically significant.

Clinically significant hearing changes from baseline in pure tone audiometry are summarized in section 15, [Summary 15.29.1](#) (to titration [safety analysis set]), [Summary 15.29.2](#) (by study period [full analysis set]), and [Summary 15.29.3](#) (overall changes [safety analysis set]), and individual data are provided in section 16.2.8, [Listing 16.2.8.21](#) (enrolled patients).

**Reviewer's Comments:**

*Overall, the number of patients who had clinically significant changes in hearing from baseline to final assessment in both open-label titration period and double-blind study period were comparable between the hydrocodone and placebo treatment groups. We agree that no clinically meaningful differences were seen between the hydrocodone and placebo treatment groups.*

*The clinical significant hearing changes are reported in a percentage rate of the number of subjects whose hearing changes exceed ASHA criteria and the results of hearing changes are stratified according to the degrees of hearing loss from normal to profound (Table 64, Clinical Study Report C33237/3079). However, the magnitude of clinical significant hearing change is not reported for individual subjects. Hearing loss associated with hydrocodone use is typically severe degrees of hearing loss with a rapid onset. It is unknown whether there are any clinical significant hearing changes that have the similar characteristics of hearing loss associated with hydrocodone use. The sponsor will be asked to provide results, analysis, interpretation on the magnitude of clinical significant hearing changes for individual subjects.*

**V. Review of “Pure Tone Audiometry” reported under “12.5.4 Other Observations Related to Safety” in the clinical report C33237/3103**

**12.5.4.1. Pure Tone Audiometry**

Pure tone audiometry was performed by a qualified audiologist within 2 weeks before the start of open-label titration period (before the patient was enrolled in the study at visit 2), about 2 weeks before or after the start (visit 7 [day 0/baseline]) of double-blind study treatment, within 2 weeks of the final on-treatment visit, and within 2 weeks of the final study visit (week 12 [or early termination]) and was not done at the study center.

**12.5.4.1.1. Audiometry Findings Over Time**

During the open-label titration period, mean changes from baseline to final values were small at all hearing thresholds for both opioid status groups (range, -1.1 to 0.1 dB for opioid-naïve patients and -1.3 to 0.5 dB for opioid-experienced patients) (Table 70). There were no changes in median values from baseline to final value at all hearing thresholds.

**Table 70: Changes From Baseline to Final Values During the Open-Label Titration Period in Pure Tone Audiometry by Hearing Threshold and Patient Opioid Status (Safety Analysis Set)**

Threshold	Statistic	Open-label titration period <sup>a</sup>			
		Opioid-naïve (N=368)		Opioid-experienced (N=255)	
		Left ear (dB)	Right ear (dB)	Left ear (dB)	Right ear (dB)
500 Hz	n	186	186	108	109
	Mean	-0.1	-0.3	-1.0	-0.6
	SD	4.46	4.08	4.86	4.58
	Median	0.0	0.0	0.0	0.0
1000 Hz	n	186	186	108	109
	Mean	-0.4	-0.1	-0.5	0.0
	SD	3.69	4.40	3.84	4.11
	Median	0.0	0.0	0.0	0.0
2000 Hz	n	186	186	108	109
	Mean	-1.1	0.0	-0.8	-0.8
	SD	8.52	4.01	4.33	4.09
	Median	0.0	0.0	0.0	0.0
3000 Hz	n	186	185	107	108
	Mean	0.1	-0.2	-0.9	-0.6
	SD	5.00	4.67	5.36	4.18
	Median	0.0	0.0	0.0	0.0
4000 Hz	n	186	186	108	109
	Mean	-0.5	-0.4	-1.3	-0.3
	SD	5.64	5.01	4.91	4.97
	Median	0.0	0.0	0.0	0.0
6000 Hz	n	185	185	108	108
	Mean	-0.2	-0.3	-0.2	-0.2
	SD	5.89	6.69	6.60	5.44
	Median	0.0	0.0	0.0	0.0
8000 Hz	n	186	186	108	109
	Mean	-0.4	0.0	-0.5	0.5
	SD	5.73	8.85	7.20	6.65
	Median	0.0	0.0	0.0	0.0

Source: Summary 15.25.4, Listing 16.2.8.20.

<sup>a</sup> Pure tone audiometry was performed before enrollment in the open-label titration period, about 2 weeks before or after the start of double-blind study treatment, within 2 weeks of the final on-treatment visit, and within 2 weeks of the final study visit.

dB=decibels; Hz=Hertz; n=number of patients; SD=standard deviation.

Among patients who participated in both the open-label titration period and the double-blind treatment period, mean changes from baseline to final values were small at all hearing thresholds for both treatment groups and generally comparable during the open-label titration period (range, -2.4 to 0.3 dB for the hydrocodone treatment group and -1.2 to 0.0 dB for the placebo treatment group) and the double-blind treatment period (range, -1.3 to 0.4 dB for the hydrocodone treatment group and -1.4 to 0.5 dB for the placebo treatment group) (Table 71 and Figure 10 [500 Hz only]).

**Table 71: Changes From Baseline to Final Values in Pure Tone Audiometry by Threshold, Treatment Group, and Study Period (Full Analysis Set)**

Threshold	Statistic	Open-label titration period <sup>a</sup>				Double-blind treatment period <sup>a</sup>			
		Placebo (N=179)		Hydrocodone (N=191)		Placebo (N=179)		Hydrocodone (N=191)	
		Left ear (dB)	Right ear (dB)	Left ear (dB)	Right ear (dB)	Left ear (dB)	Right ear (dB)	Left ear (dB)	Right ear (dB)
500 Hz	n	80	80	79	80	162	162	179	180
	Mean	-0.5	-0.2	-0.2	-0.9	-0.8	-0.5	-0.9	-0.4
	SD	4.68	4.80	3.62	4.34	5.44	5.19	5.56	5.42
	Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
1000 Hz	n	80	80	79	80	162	162	179	180
	Mean	-0.1	0.0	-0.6	-0.3	-0.5	-1.4	-0.8	-1.3
	SD	3.90	4.28	3.34	4.13	4.50	9.78	5.23	4.94
	Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2000 Hz	n	80	80	79	80	162	162	179	180
	Mean	-1.2	-0.3	-2.4	-0.5	-1.2	-0.6	-0.5	0.2
	SD	3.92	4.38	12.37	4.03	4.97	4.97	5.50	5.51
	Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
3000 Hz	n	79	78	79	80	158	158	175	175
	Mean	-1.1	-0.6	-0.6	-0.4	-1.3	-1.0	-0.5	-0.3
	SD	5.06	5.16	5.27	3.91	5.86	5.60	5.86	5.41
	Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
4000 Hz	n	80	80	79	80	162	162	179	180
	Mean	-0.7	-0.6	-0.4	0.1	-0.6	-1.0	-0.6	0.4
	SD	4.55	4.84	5.53	4.74	7.10	7.28	5.95	5.97
	Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
6000 Hz	n	79	78	79	80	159	160	175	175
	Mean	-1.0	-0.1	-0.3	0.3	-0.4	-0.8	-0.3	-0.5
	SD	5.13	7.96	6.95	5.79	7.91	8.61	8.69	8.07
	Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

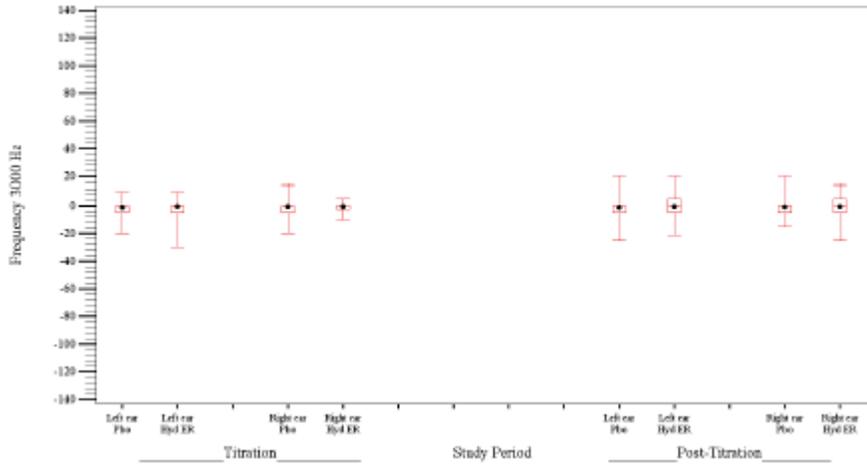
**Table 71: Changes From Baseline to Final Values in Pure Tone Audiometry by Threshold, Treatment Group, and Study Period (Full Analysis Set) (Continued)**

Threshold	Statistic	Open-label titration period <sup>a</sup>				Double-blind treatment period <sup>a</sup>			
		Placebo (N=179)		Hydrocodone (N=191)		Placebo (N=179)		Hydrocodone (N=191)	
		Left ear (dB)	Right ear (dB)	Left ear (dB)	Right ear (dB)	Left ear (dB)	Right ear (dB)	Left ear (dB)	Right ear (dB)
8000 Hz	n	80	80	79	80	162	162	179	180
	Mean	-1.0	-0.6	-0.1	0.1	-1.2	-0.9	-0.5	-0.4
	SD	5.81	6.13	7.88	6.68	9.17	11.42	8.14	7.38
	Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

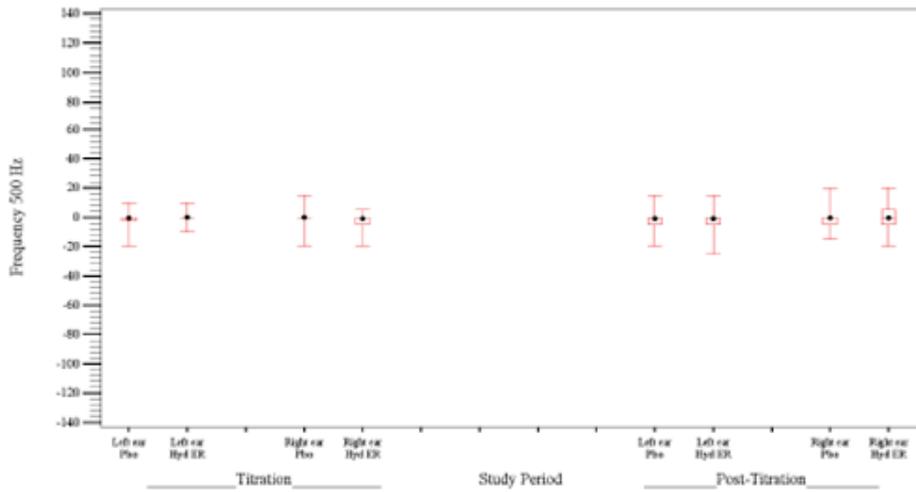
Source: Summary 15.25.5, Listing 16.2.8.20.

<sup>a</sup> Pure tone audiometry was performed before enrollment in the open-label titration period, about 2 weeks before or after the start of double-blind study treatment, within 2 weeks of the final on-treatment visit, and within 2 weeks of the final study visit.

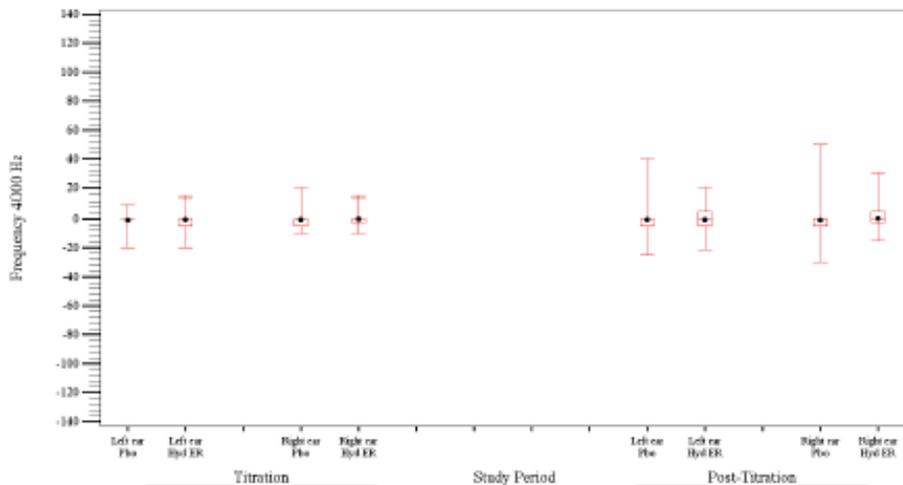
dB=decibels; Hz=Hertz; n=number of patients; SD=standard deviation.

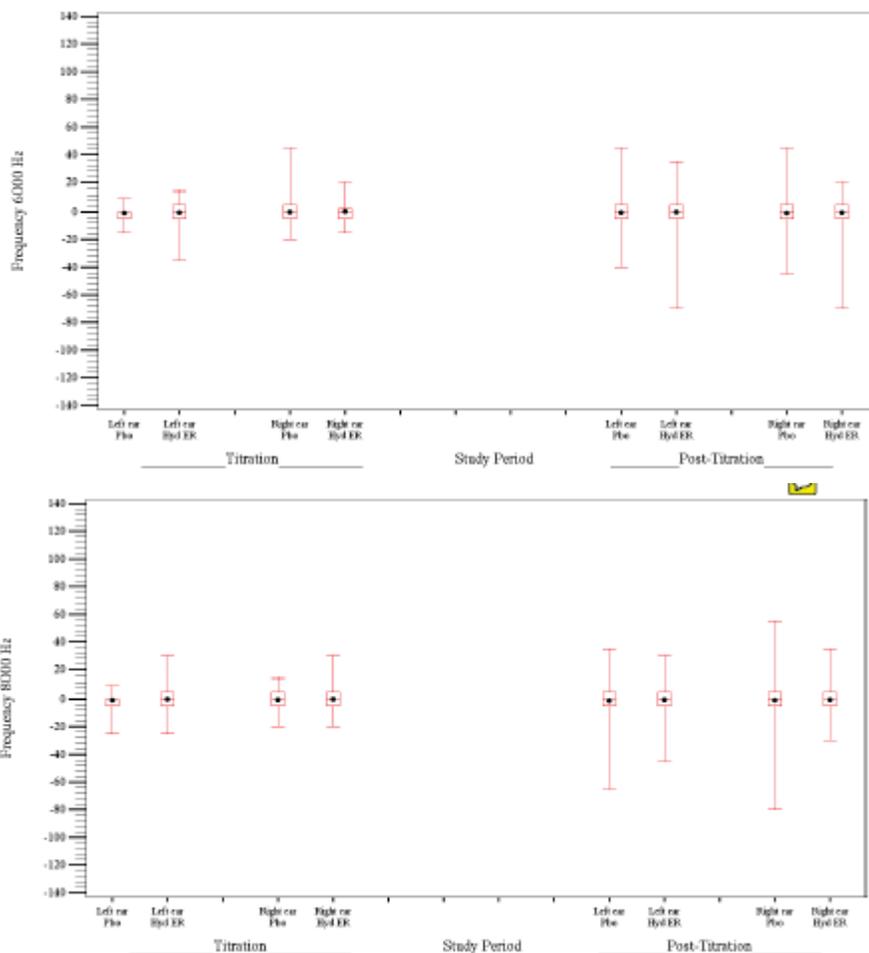


**Figure 10: Box Plots of Changes From Baseline for Pure Tone Audiometry by Threshold and Study Period (Full Analysis Set)**



Source: Graph 5.  
Hyd ER=hydrocodone extended-release tablets; Hz=Hertz; Pbo=matching placebo tablets.





Summaries of changes from baseline in pure tone audiometry results are provided in Section 15, [Summary 15.25.4](#) (safety analysis set) by opioid status and [Summary 15.25.5](#) (full analysis set) by treatment group and study period. A box plot of the changes from baseline in pure tone audiometry results is provided in Section 15, [Graph 5](#) (full analysis set) by treatment group. Individual patient data are provided in Section 16, [Listing 16.2.8.20](#).

**Reviewer's Comments:**

*Conventional pure tone audiometry (500-8000 Hz) was performed before and after the open-label titration period, and before and after the double-blind treatment period. During the open-label titration period, mean hearing threshold changes from baseline to final values range -1.1 to 0.1 dB for opioid-naïve patients and -1.3 to 0.5 dB for opioid-experienced patients. Among patients who participated in both the open-label titration period and the double-blind treatment period, mean changes from baseline to final values range -2.4 to 0.3 dB for the hydrocodone treatment group and -1.2 to 0.0 dB for the placebo treatment group during the open-label titration period; mean changes from baseline to final values range -1.3 to 0.4 dB for the hydrocodone treatment group and -1.4 to 0.5 dB for the placebo treatment group for the double-blind treatment period. Overall, the mean hearing changes from baseline to final assessment in both open-label titration period and double-blind study period were comparable between the hydrocodone and placebo treatment groups. From an audiology perspective, a change of hearing threshold > 10 dB is considered clinically significant. The*

*reported mean threshold change of -2.4 to 0.5 dB is judged minimal and the mean threshold changes in the placebo group are judged equivalent to those in the hydrocodone treatment group.*

*The mean threshold changes from the baseline of each open-label titration/double-blind study period to the final assessment in each period are considered minimal and we agree that overall the pure tone audiometry data does not indicate a significant signal of treatment-emergent hearing loss. However, all thresholds are compared before and after the open-label titration/double-blind treatment period. Based on the box plot of threshold changes reported in Graph5 (C33237/3103 Clinical Study Report), it appears that the standard deviations around the mean thresholds are much larger at the final assessment in the double-blind treatment period than that at the final assessment in the open titration period at 4000, 6000, and 8000 Hz testing frequencies. It is unknown whether there are any threshold changes from the very beginning to the end of the study for those patients who participated in both the open-label titration period and the double-blind study period, i.e., the baseline of the open-label titration period to the final assessment of the double-blind study period. We believe this is an important data analysis to evaluate the extent of hydrocodone's risk for ototoxic effects on hearing. The sponsor will be asked to provide further analysis on the pure tone audiometry data to support the absence of ototoxic effect of hydrocodone bitartrate extended-release tablets for the management of chronic pain.*

#### **12.5.4.1.2. Individual Clinically Significant Hearing Changes**

The criteria for potentially clinically significant changes from baseline in hearing were predefined for this study (see Section 9.5.1.3.6.1). Hearing loss was classified in degrees of hearing from normal to profound and was determined by the hearing threshold (ie, the softest sound detected at a specific frequency).

Overall during the study, 29 (5%) patients had at least 1 clinically significant change in hearing from baseline to final assessment, with 13 (2%) patients having at least 1 clinically significant change in hearing during the open-label titration period. Among patients who participated in the double-blind treatment period, 18 (5%) patients had at least 1 clinically significant change in hearing during the study, with at least 1 clinically significant change in hearing reported for 7 (2%) patients during the open-label titration period and 14 (4%) patients during the double-blind treatment period. The proportions of patients having at least 1 clinically significant change in hearing during the study were comparable between the hydrocodone and placebo treatment groups during the different study periods (Table 72). Of note, 30% of opioid-naïve patients and 37% of opioid-experienced patients had a medical history of ear and labyrinth disorders, the majority of which consisted of some level of deafness (eg, unilateral, bilateral, or neurosensory) (Summary 15.4.2).

**Table 72: Overall Clinically Significant Hearing Changes From Baseline to Final Assessment in Pure Tone Audiometry Test Results (Safety Analysis Set)**

Analysis group	Number (%) of patients		
	Placebo	Hydrocodone	Total
Safety analysis set	—	—	623
≥1 CS value during study	—	—	29 (5)
≥1 CS value during open-label titration period	—	—	13 (2)
Full analysis set	179 (100)	191 (100)	370 (100)
≥1 CS value during study	10 (6)	8 (4)	18 (5)
≥1 CS value during open-label titration period	5 (3)	2 (1)	7 (2)
≥1 CS value during the double-blind treatment period	8 (4)	6 (3)	14 (4)
≥1 CS value at endpoint	8 (4)	7 (4)	15 (4)
Number of patients with CS values who rolled over to participate in Study C33237/3104	4 (2)	6 (3)	10 (3)

Source: Summary 15.25.1, Listing 16.2.8.20, Listing 16.2.8.21.  
CS=clinically significant.

During the open-label titration period, the number of patients with a clinically significant change from baseline in hearing was low and generally comparable between opioid-naïve and opioid-experienced patients (Table 73).

**Table 73: Clinically Significant Hearing Changes From Baseline to Final Assessment in Pure Tone Audiometry During the Open-Label Titration Period by Opioid Status (Safety Analysis Set)**

Hearing category at titration baseline*	Criteria for significant change	Number of patients with CS change of the number of patients at baseline in that hearing category			
		Opioid-naïve (N=368)		Opioid-experienced (N=255)	
		Left ear	Right ear	Left ear	Right ear
Normal hearing (0 to 20 dB)	>10 dB shift at 2 consecutive test frequencies	1/110	—	—	—
	>20 dB shift at 1 test frequency	—	—	—	—
	Shift to no response at 3 consecutive test frequencies	—	—	—	—
Mild (21 to 40 dB)	>10 dB shift at 2 consecutive test frequencies	—	—	—	—
	>20 dB shift at 1 test frequency	1/97	2/96	1/75	—
	Shift to no response at 3 consecutive test frequencies	—	—	—	—
Moderate (41 to 55 dB)	>10 dB shift at 2 consecutive test frequencies	—	—	—	—
	>20 dB shift at 1 test frequency	—	—	—	—
	Shift to no response at 3 consecutive test frequencies	—	—	—	—
Moderately severe (56 to 70 dB)	>10 dB shift at 2 consecutive test frequencies	—	—	—	—
	>20 dB shift at 1 test frequency	—	—	—	—
	Shift to no response at 3 consecutive test frequencies	—	—	—	—
Severe (71 to 90 dB)	>10 dB shift at 2 consecutive test frequencies	—	—	—	—
	>20 dB shift at 1 test frequency	—	—	—	—
	Shift to no response at 3 consecutive test frequencies	—	—	—	—
Profound (>91 dB)	>10 dB shift at 2 consecutive test frequencies	—	—	—	1/5
	>20 dB shift at 1 test frequency	1/8	—	—	1/5
	Shift to no response at 3 consecutive test frequencies	—	—	—	—

Source: Summary 15.25.2, Listing 16.2.8.20, Listing 16.2.8.21.

\*The highest value for dB reached for any of the 7 threshold frequencies (ie, 500, 1000, 2000, 3000, 4000, 6000, and 8000 Hz) was used to determine hearing category at baseline.

dB=decibels; CS=clinically significant.

Note: Pure tone audiometry was performed before enrollment in the open-label titration period, about 2 weeks before or after the start of double-blind study treatment, within 2 weeks of the final on-treatment visit, and within 2 weeks of the final study visit.

Among patients who participated in both the open-label titration and double-blind treatment periods, the number of patients with a clinically significant change from baseline in hearing was generally comparable between the hydrocodone and placebo treatment groups during both study periods (Table 74 and Table 75). Relatively more clinically significant changes in hearing were reported during the double-blind treatment period compared with the open-label treatment period. Of note, 36% of patients in the hydrocodone treatment group and 34% of patients in the placebo treatment group had a medical history of ear and labyrinth disorders, the majority of which consisted some level of deafness (eg, unilateral, bilateral, or neurosensory) (Summary 15.4.1). No patient with a clinically significant change in hearing had an adverse event leading to withdrawal from the study.

**Table 74: Clinically Significant Hearing Changes From Baseline in Pure Tone Audiometry During Open-Label Titration by Treatment Group (Full Analysis Set)**

Hearing category at baseline <sup>a</sup>	Criteria for significant change	Number of patient: with CS change of the number of patients at baseline in that hearing category			
		Placebo (N=179)		Hydrocodone (N=191)	
		Left ear	Right ear	Left ear	Right ear
Normal hearing (0 to 20 dB)	>10 dB shift at 2 consecutive test frequencies	—	—	—	—
	>20 dB shift at 1 test frequency	—	—	—	—
	Shift to no response at 3 consecutive test frequencies	—	—	—	—
Mild (21 to 40 dB)	>10 dB shift at 2 consecutive test frequencies	—	—	—	—
	>20 dB shift at 1 test frequency	—	1/67	1/68	—
	Shift to no response at 3 consecutive test frequencies	—	—	—	—
Moderate (41 to 55 dB)	>10 dB shift at 2 consecutive test frequencies	—	—	—	—
	>20 dB shift at 1 test frequency	—	—	—	—
	Shift to no response at 3 consecutive test frequencies	—	—	—	—
Moderately severe (56 to 70 dB)	>10 dB shift at 2 consecutive test frequencies	—	—	—	—
	>20 dB shift at 1 test frequency	—	—	—	—
	Shift to no response at 3 consecutive test frequencies	—	—	—	—
Severe (71 to 90 dB)	>10 dB shift at 2 consecutive test frequencies	—	—	—	—
	>20 dB shift at 1 test frequency	—	—	—	—
	Shift to no response at 3 consecutive test frequencies	—	—	—	—
Profound (>91 dB)	>10 dB shift at 2 consecutive test frequencies	—	—	—	1/4
	>20 dB shift at 1 test frequency	—	—	1/6	1/4
	Shift to no response at 3 consecutive test frequencies	—	—	—	—

Source: Summary 15.25.3, Listing 16.2.8.20, Listing 16.2.8.21.

<sup>a</sup> The highest value for dB reached for any of the 7 threshold frequencies (ie, 500, 1000, 2000, 3000, 4000, 6000, and 8000 Hz) was used to determine hearing category at baseline.

dB=decibels; CS=clinically significant.

Note: Pure tone audiometry was performed before enrollment in the open-label titration period, about 2 weeks before or after the start of double-blind study treatment, within 2 weeks of the final on-treatment visit, and within 2 weeks of the final study visit.

**Table 75: Clinically Significant Hearing Changes From Baseline in Pure Tone Audiometry During the Double-Blind Treatment Period by Treatment Group (Full Analysis Set)**

Hearing category at baseline <sup>a</sup>	Criteria for significant change	Number of patient: with CS change of the number of patients at baseline in that hearing category			
		Placebo (N=179)		Hydrocodone (N=191)	
		Left ear	Right ear	Left ear	Right ear
Normal hearing (0 to 20 dB)	>10 dB shift at 2 consecutive test frequencies	—	—	1/56	—
	>20 dB shift at 1 test frequency	1/54	—	—	1/76
	Shift to no response at 3 consecutive test frequencies	—	—	—	—
Mild (21 to 40 dB)	>10 dB shift at 2 consecutive test frequencies	1/60	3/67	—	2/49
	>20 dB shift at 1 test frequency	1/60	1/67	2/68	2/49
	Shift to no response at 3 consecutive test frequencies	—	—	—	—
Moderate (41 to 55 dB)	>10 dB shift at 2 consecutive test frequencies	1/28	—	1/27	—
	>20 dB shift at 1 test frequency	2/28	1/21	1/27	—
	Shift to no response at 3 consecutive test frequencies	—	—	—	—
Moderately severe (56 to 70 dB)	>10 dB shift at 2 consecutive test frequencies	—	1/15	—	—
	>20 dB shift at 1 test frequency	—	—	1/15	—
	Shift to no response at 3 consecutive test frequencies	—	—	—	—
Severe (71 to 90 dB)	>10 dB shift at 2 consecutive test frequencies	—	—	—	—
	>20 dB shift at 1 test frequency	1/12	—	1/14	—
	Shift to no response at 3 consecutive test frequencies	—	—	—	—
Profound (>91 dB)	>10 dB shift at 2 consecutive test frequencies	—	1/5	—	—
	>20 dB shift at 1 test frequency	—	—	—	—
	Shift to no response at 3 consecutive test frequencies	—	—	—	—

Source: Summary 15.25.3, Listing 16.2.8.20, Listing 16.2.8.21.

<sup>a</sup> The highest value for dB reached for any of the 7 threshold frequencies (ie, 500, 1000, 2000, 3000, 4000, 6000, and 8000 Hz) was used to determine hearing category at baseline.

dB=decibels; CS=clinically significant.

Note: Pure tone audiometry was performed before enrollment in the open-label titration period, about 2 weeks before or after the start of double-blind study treatment, within 2 weeks of the final on-treatment visit, and within 2 weeks of the final study visit.

An overall summary of pure tone audiometry results is provided in Section 15, [Summary 15.25.1](#). Summaries of clinically significant pure tone audiometry results are provided in Section 15, [Summary 15.25.2](#) (safety analysis set) by opioid status and [Summary 15.25.3](#) (full analysis set) by treatment group and study period. Individual patient data are provided in Section 16, [Listing 16.2.8.20](#) and [Listing 16.2.8.21](#).

**Reviewer's Comments:**

*Overall, the proportions of patients having at least 1 clinically significant change in hearing during the study were comparable between the hydrocodone and placebo treatment groups during both open titration period and double-blind study period. We agree that no clinically meaningful differences were seen between the hydrocodone and placebo treatment groups.*

*However, for those patients who participated in both the open-label titration and double-blind treatment periods, relatively more clinically significant changes in hearing were reported during the double-blind treatment period compared with the open-label treatment period. Again this is related to the observation of larger standard deviations around the mean thresholds at the final assessment in the double-blind treatment period than that at the final assessment in the open titration period at 4000, 6000, and 8000 Hz testing frequencies reported in Graph 5 (C33237/3103 Clinical Study Report). It is unknown whether there are any individual clinically significant threshold changes between the hydrocodone and placebo treatment groups from the very beginning to the end of the study for those patients who participated in both the open-label titration period and the double-blind study period, i.e., the baseline of the open-label titration period to the final assessment of the double-blind study period. We believe this is an important individual data analysis to evaluate the extent of hydrocodone's risk for ototoxic effects on hearing. The sponsor will be asked to provide further analysis on the individual data from pure tone audiometry to support the absence of ototoxic effect of hydrocodone bitartrate extended-release tablets for the management of chronic pain.*

*Again, the clinical significant hearing changes are reported in a percentage rate of the number of subjects whose hearing changes exceed ASHA criteria and the results of hearing changes are stratified according to the degrees of hearing loss from normal to profound (Table 73,74,75, Clinical Study Report C33237/3103). However, the magnitude of clinical significant hearing change is not reported for individual subjects. Hearing loss associated with hydrocodone use is typically severe degrees of hearing loss with a rapid onset. It is unknown whether there are any clinical significant hearing changes that have the similar characteristics of hearing loss associated with hydrocodone use. The sponsor will be asked to provide results, analysis, and interpretation on the magnitude of clinical significant hearing changes for individual subjects.*

**VI. Interactive review:**

Overall, the sponsor followed the agreed upon ototoxicity monitoring protocol from the audiology perspective. Mean hearing threshold changes from baseline to final values for both open-label titration period and double-blind treatment period ranged -2.6 to 1.3 dB (Study 3079) and -2.4 to 0.5 dB (Study 3103) across conventional frequencies of 500-8000 Hz. Given the nature of a typical hydrocodone-associated hearing loss (i.e., sudden onset, rapidly progressing

severe sensorineural hearing loss) from reports in the literature, the reported mean threshold changes are judged minimal and clinically insignificant. However, the sponsor will need to conduct additional analyses on the pure tone audiometry data and adverse events associated with vestibular function submitted as part of the Clinical Study Report for study 3079 and 3103 in order to adequately support no significant signal of acute decrements in hearing or vestibular function in the population studied, during the time course of the study, and under the dosage conditions studied (see deficiencies below).

Following are the comments and sponsor's responses regarding the additional data analyses on the data of pure tone audiometry and adverse events associated with vestibular function in order to adequately address our concerns about the potential for ototoxic effects from hydrocodone use.

1. In both clinical studies (3079 and 3103), conventional pure tone audiometry (500-8000 Hz) was performed before and after the open-label titration period (Visit 2 to Visit 3 or 7), and before and after the double-blind treatment period (Visit 7 to Visit 12). Mean hearing threshold changes from baseline to final values after the open-label titration or double-blind treatment period) ranged -2.6 to 1.3 dB for Clinical Study 3079 and -2.4 to 0.5 dB for Clinical Study 3103 across conventional frequencies of 500-8000 Hz. We acknowledge that the reported mean threshold changes are minimal and clinically insignificant. However, all thresholds are compared before and after the open-label titration/double-blind treatment period. Based on the box plot of threshold changes reported in Graph5 (Clinical Study Report 3103) and Figure 3 (Clinical Study Report 3079), it appears that the standard deviations around the mean thresholds are much larger at the final assessment in the double-blind treatment period than that at the final assessment in the open titration period (e.g., at 4000, 6000, and 8000 Hz testing frequencies in Graph5, Clinical Study Report 3103). It is unknown whether there are any significant mean threshold changes from the very beginning to the end of the study for those patients who participated in both the open-label titration period and the double-blind study period, i.e., from the baseline of the open-label titration period (Visit 2) to the final assessment of the double-blind study period (Visit 12). We believe this is an important data analyses to evaluate the extent of hydrocodone's risk for ototoxic effects on hearing. Please conduct additional analysis on the pure tone audiometry data to compare the hearing thresholds values between Visit 2 and Visit 12 for both 3079 and 3103 clinical studies in order to adequately support no significant signal of acute decrements in hearing in the population studied, during the time course of the study, and under the dosage conditions studied.

Response:

We would like to clarify that the requested comparison of the hearing thresholds values between Visit 2 and Visit 12 is presented in Tables 61 and 62 for Clinical Study Report C33237/3079 and in Tables 70 and 71 for Clinical Study Report C33237/3103.

In these tables, the term “Baseline” refers to Visit 2 for both the titration and double-blind treatment periods. The term “Final Values” in the titles of Table 61 and 62 (Study C33237/3079), and Tables 70 and 71 (Study C33237/3103) are the final assessments performed during each study period. The term “Final values” for the titration period refers to the last assessment before taking the randomized treatment, whereas the term “Final values” for the double-blind period is the final study visit or at early termination (Visit 12). All changes from baseline in the tables are changes from Visit 2. There was no significant difference in individual

clinically significant hearing changes between the hydrocodone ER and placebo treatment groups for those patients who participated in both the open-label titration and double-blind treatment periods. Based on these data, no evidence of ototoxicity with hydrocodone ER was observed.

***Reviewer’s Comments: The sponsor clarified the data for threshold comparisons from Visit 2 to Visit 12 was included in Tables 61 and 62 for Clinical Study Report C33237/3079 and in Tables 70 and 71 for Clinical Study Report C33237/3103. I reviewed the tables and agree that the mean hearing changes from baseline to final assessment in both open-label titration period and double-blind study period were considered minimal or non-clinically significant, and also comparable between the hydrocodone and placebo treatment groups. The response is judged adequate and acceptable.***

2. In both clinical studies (3079 and 3103), individual clinically significant hearing changes are reported in a percentage rate of the number of subjects whose hearing changes exceed ASHA criteria and the results of hearing changes are stratified according to the degrees of hearing loss from normal to profound (Table 63 and 63 in Clinical Study Report C33237/3079; Table 73, 74, and 75 in Clinical Study Report C33237/3103). Overall, the proportions of patients having at least 1 clinically significant change in hearing during the study were comparable between the hydrocodone and placebo treatment groups during both open titration period and double-blind study period. Please address following issues:
  - a. For those patients who participated in both the open-label titration and double-blind treatment periods, relatively more clinically significant changes in hearing were reported during the double-blind treatment period compared with the open-label treatment period (Table 74 and 75 in C33237/3103 Clinical Study Report). Again this is related to the observation of larger standard deviations around the mean thresholds at the final assessment in the double-blind treatment period than that at the final assessment in the open titration period at 4000, 6000, and 8000 Hz testing frequencies reported in Graph 5 (C33237/3103 Clinical Study Report). It is unknown whether there are any significant individual clinically significant threshold changes between the hydrocodone and placebo treatment groups from the very beginning to the end of the study for those patients who participated in both the open-label titration period and the double-blind study period, i.e., from the baseline of the open-label titration period (Visit 2) to the final assessment of the double-blind study period (Visit 12). We believe this is an important individual data analysis to evaluate the extent of

hydrocodone's risk for ototoxic effects on hearing. For both 3079 and 3103 clinical studies, please conduct further analysis on the individual clinically significant hearing changes from Visit 2 to Visit 12 and report if there is any significant difference in individual clinically significant hearing changes between the hydrocodone and placebo treatment groups for those patients who participated in both the open-label titration and double-blind treatment periods.

Response:

We would like to clarify that the requested comparison of clinically significant hearing changes from Visit 2 to Visit 12 is presented in Tables 63 and 64 of [Clinical Study Report C33237/3079](#) and in Tables 72 and 73 of [Clinical Study Report C33237/3103](#). The baseline in all safety analyses is defined as "Visit 2". The term "Final Assessment" in the titles of these tables is defined the same way as the term "Final Values" in the titles of the Tables discussed in "Teva Response to FDA Comment 1." The larger standard deviation observed for the change from baseline to the end of double-blind treatment period was caused by a few outliers, however, the standard deviations of change from baseline to the end of double-blind treatment period are comparable between the hydrocodone ER and placebo groups. There was no significant difference in individual clinically significant hearing changes between the hydrocodone ER and

placebo treatment groups for those patients who participated in both the open-label titration and double-blind treatment periods. Based on these data, no evidence of ototoxicity with hydrocodone ER was observed.

***Reviewer's Comments: The sponsor clarified the data for threshold comparisons from Visit 2 to Visit 12 was included in Tables 63 and 64 for Clinical Study Report C33237/3079 and in Tables 72 and 73 for Clinical Study Report C33237/3013. I reviewed the table. Overall, the proportions of patients having at least 1 clinically significant change in hearing during the study were comparable between the hydrocodone and placebo treatment groups during both open titration period and double-blind study period. We agree that no clinically meaningful differences were seen between the hydrocodone and placebo treatment groups. The response is judged adequate and acceptable.***

- b. You report the clinical significant hearing changes in a percentage rate of the number of subjects whose hearing changes exceed ASHA criteria and the results of hearing changes are stratified according to the degrees of hearing loss from normal to profound. We acknowledge that the proportions of patients having at least 1 clinically significant change in hearing during both open titration period and double-blind study period were comparable between the hydrocodone and placebo treatment groups. However, the magnitude (i.e., dB shift) of clinical significant hearing changes is not reported for individual subjects. Hearing loss associated with hydrocodone use is typically severe degrees of hearing loss with a rapid onset. It is unknown whether there are any clinical significant hearing changes that have the similar characteristics of hearing loss associated with hydrocodone use. Please provide a summary of the results, analyses, and interpretation on the magnitude of clinical significant hearing changes for individual subjects for both 3079 and 3103 clinical studies.

Response:

As requested, Teva performed additional analyses of the magnitude of clinical significant hearing changes for both study C33237/3079 and C33237/3103. Changes in hearing denoting clinical significance were classified as category I (greater than 10 dB shift at 2 consecutive test frequencies), category II (greater than 20 dB shift at 1 frequency), and category III (no response at 3 consecutive test frequencies).

During the open-label titration period of Study C33237/3079 (Ad Hoc Listing 16.2.8.34 for Study C33237/3079), 44 patients (15%) had shifts in audiometry that were considered clinically significant. Changes from baseline considered clinically significant ranged from 15 to 75dB. The highest absolute change reported in category I and II was 75 dB. There was 1 patient [ $<1\%$ ] with shifts from baseline meeting the definition of category III.-There were no hearing or vestibular-related adverse events reported in patients with the highest absolute change reported.

During the posttitration double-blind treatment period of Study C33237/3079, the number of patients with reported shifts in audiometry considered clinically significant was comparable in the placebo (15, 10.2%) and hydrocodone ER (17, 11.6%) groups. Changes from baseline considered clinically significant ranged from 15 to 85 dB and from 15 to 45 dB in patients in the placebo and hydrocodone ER group, respectively. The highest absolute change reported in category I and II was 85 dB for the placebo and 45 dB for the hydrocodone ER groups. There were no patients with shifts from baseline meeting the definition of category III. There were no hearing or vestibular-related adverse events reported in patients with the highest absolute change reported.

In Study C33237/3079, patient 039006 reported mild hypoacusis (day 137 to day 285; considered related to hydrocodone ER by the investigator) and mild dizziness (day 4; considered not related to hydrocodone ER by the investigator) had a dB shift of category I on day 137. Two additional patients with dB shifts of category II reported adverse events of dizziness in Study C33237/3079. Patient 049001, who had a clinically significant category II dB shift on day 8, reported mild dizziness (day 16 to day 22; considered related to hydrocodone ER by the investigator). Patient 064011, who had a clinically significant category II dB shift on day 5, reported mild dizziness (day 23 to day 24; considered related to hydrocodone ER by the investigator).

Two patients in the placebo group in Study C33237/3079 had category II dB shifts and vestibular adverse events. Patient 062002, who reported mild deafness unilateral (day 8 to day 15; considered related to treatment [placebo] by the investigator) and mild tinnitus (day 6 to day 13; considered related to treatment [placebo] by the investigator) had a dB shift of category II on day 8. Patient 046007, who reported moderate hypoacusis (day 90 onset; considered related to treatment [placebo] by the investigator), had a dB shift of category II on day 90.

During the open-label titration period of Study C33237/3103 (Ad Hoc Listing 16.2.8.34 for Study C33237/3103), changes from baseline considered clinically significant ranged from 30 to 45 dB. There were no hearing or vestibular-related adverse events reported in patients with the highest absolute change reported. There were no patients with shifts from baseline meeting the definition of category III.

During the posttitration double-blind treatment period of Study C33237/3103, the number of patients with reported shifts in audiometry considered clinically significant was comparable in the placebo (11, 6.1%) and hydrocodone ER (10, 5.2%) groups. Changes from baseline considered clinically significant ranged from 15 to 180 dB and from 15 to 40 dB in patients in the placebo and hydrocodone ER group, respectively. The highest absolute change reported in category I was 55 dB for placebo and 35 dB for hydrocodone ER. In category II, the highest absolute change reported was 180 dB and 40 dB in the placebo and hydrocodone ER groups, respectively. There were no hearing or vestibular-related adverse events reported in patients with the highest absolute change reported. There were no patients with shifts from baseline meeting the definition of category III.

In Study C33237/3103, patient 10412004, who reported mild tinnitus (day 104; considered not related to hydrocodone ER by the investigator), had a dB shift of category II on day 104. Patient 1037007, who reported moderate deafness neurosensory (day 23, considered related to study drug [placebo] by the investigator), had a dB shift of category II on day 23.

In summary, clinically significant hearing changes were reported during Studies C33237/3079 and C33237/3103; however, there is no clinically significant difference in the magnitude, as defined as the maximum change from baseline (in dB), of clinical significant hearing changes for individual patients when placebo and hydrocodone ER groups were compared for both studies. There were no hearing or vestibular-related adverse events reported in patients with the highest absolute change reported. Seven patients (4 patients in the hydrocodone ER group and 3 in the placebo group) with non-serious hearing or vestibular adverse events (9 adverse events total) also had clinically significant dB shifts. Of these 7 patients, 5 (2 patients in hydrocodone ER group and 3 patients in the placebo group) had vestibular adverse events which were temporally associated with a clinically significant dB shift. In conclusion, the percentage of patients with any hearing or vestibular-related adverse events among patients with clinically significant dB shifts were low, and comparable between the placebo (n=3, <1%) and hydrocodone ER (n=4, <1%) groups. These adverse events were generally mild in intensity, non-serious, and reversible. No new significant safety findings were identified.

The following ad hoc listings from these analyses are provided in Module 5, under the respective study folders for studies C33237/3079 and C33237/3103:

- [Ad Hoc Listing 16.2.8.34 Listing of Clinically Significant Change-From-Baseline Audiometry Data Full Analysis Set for Study CEP-33237/3079](#)
- [Ad Hoc Listing 16.2.8.34 Listing of Clinically Significant Change-From-Baseline Audiometry Data Full Analysis Set for Study CEP-33237/3103](#)

***Reviewer's Comments: The sponsor conducted additional statistical analysis on the magnitude of clinically significant threshold shift between placebo and treatment groups. I agree that there is no significant difference in the magnitude of threshold shift between the placebo and treatment groups. Many of these subjects who had significant threshold shift have also pre-study, sensorineural hearing loss that may contribute to the increase of threshold over the study period that is not associated with HYD use. The response is judged adequate and acceptable.***

3. Typically the ototoxic effect of drug use is associated with hearing or vestibular function. You provide pure tone audiometry data to support no significant signal of acute decrements in hearing after hydrocodone use. However, you do not provide a separate report about the data analyses on vestibular function to evaluate whether there is any impact on vestibular function after the hydrocodone use. Instead you report adverse events associated with vestibular function (e.g., dizziness, vertigo). Please provide a cumulative summary and your interpretation of the percentage of subjects with confirmed treatment-emergent adverse events related to vestibular function (e.g., dizziness, vertigo, vestibular disorder etc.) for both 3079 and 3103 clinical studies in order to adequately support no significant signal of acute decrements in vestibular function in the population studied, during the time course of the study, and under the dosage conditions studied.

Response:

As requested, Teva performed additional analyses of the percentages of patients with treatment-emergent adverse event related to vestibular function. Specifically, treatment-emergent adverse events regardless of their reported causality were run using the *Hearing and Vestibular Disorders* Standardised MedDRA Queries (SMQ; Broad, MedDRA version 16.0) for the open-label titration period of the combined C33237/3079 and C33237/3103 studies (Safety Analysis Set; Adhoc Summary 3) and for posttitration double-blind treatment period of the combined 3079 and 3103 studies (Posttitration Analysis Set; Adhoc Summary 4). Of note, the Hearing and Vestibular Disorders SMQ, which includes 2 SubSMQs (Hearing Impairment SMQ and Vestibular Disorders SMQ), is used to capture all the relevant adverse events related to vestibular function including dizziness, vertigo, and vestibular disorders.

During the open-label titration period of the 2 combined studies (Adhoc Summary 3), 68 (7%) patients reported at least 1 SMQ hearing impairment or vestibular disorders adverse events with the highest percentage for dizziness (5%) followed by  $\leq 1\%$  for tinnitus, vertigo, hyperacusis, and balance disorder.

During the posttitration double-blind treatment period of the two combined studies (Adhoc Summary 4), at least 1 SMQ hearing impairment or vestibular disorders adverse events was reported in 11 (3%) and 12 (4%) patients in the placebo and hydrocodone ER group, respectively. Hypoacusis and dizziness were reported in both placebo and hydrocodone ER groups. Hypoacusis was  $<1\%$  in both groups and dizziness was reported in 2% and 1% of patients in the placebo and hydrocodone ER groups, respectively. Deafness neurosensory, deafness unilateral, and acoustic stimulation tests abnormal were reported in the placebo group whereas deafness, mixed deafness, and tinnitus were reported in the hydrocodone ER group. No specific adverse event pattern was identified in the hydrocodone ER group as compared to the placebo group. Overall, the incidence of none of the adverse events exceeded 2% and there was no more than 1% difference in the percentage of any adverse event between the placebo and hydrocodone ER groups.

In summary, no clinically significant findings were identified by analyses of the percentages of patients with treatment-emergent adverse event related to vestibular function (MedDRA SMQ of *Hearing and vestibular disorders*) in the population studied, during the time course of the studies, and under the dosage conditions studied. Thus, these findings support findings from the pure tone audiometry assessments as described in the original clinical study reports for studies C33237/3079 and C33237/3103.

The following ad hoc tables from these analyses are provided in Module 5, under the respective folder for the Integrated Summary of Safety/4-Month Safety Update:

- Adhoc Summary 3 Hearing impairment or Vestibular disorders Standardized MedDRA Query (SMQ) Adverse Events by System Organ Class, High Level Term, Preferred Term, and Opioid Status During the Titration Treatment Period Safety Analysis Set for Studies 3079 and 3103
- Adhoc Summary 4 Hearing impairment or Vestibular disorders Standardized MedDRA Query (SMQ) Adverse Events by System Organ Class, High Level Term, Preferred Term, and Treatment Group During the Posttitration Treatment Period Posttitration Analysis Set For Double-Blind Studies 3079 and 3103

***Reviewer's Comments: The sponsor conducted additional statistical analysis on the***

*percentages of patients with treatment emergent adverse event related to vestibular function. I reviewed the results and agree that there is no significant difference in the percentages of patients with treatment emergent adverse event related to vestibular function between the placebo and treatment groups. The response is judged adequate and acceptable.*

## **VII. Conclusions & Recommendations:**

The data submitted in the audiology report and follow-up response has adequately addressed our concerns about the potential for ototoxic effects from HYD use. There is no significant signal of acute decrements in hearing or vestibular function in the population studied, during the time course of the study, and under the dosage conditions studied.

Please feel free to contact me if you have any questions or concerns about this review.

*Reviewed by*



Ting Zhang -S  
2015.09.25  
12:10:04 -04'00'

*Ting Zhang, Ph.D.  
Scientific Reviewer/Audiology*

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KIMBERLY A COMPTON  
10/01/2015  
Entering for CDRH reviewer

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

**PATIENT LABELING REVIEW**

Date: September 28, 2015

To: Sharon Hertz, MD  
Director  
**Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)**

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

Barbara Fuller, RN, MSN, CWOCN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Morgan Walker, PharmD, MBA  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Koung Lee, RPh, MSHS  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

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

Drug Name (established name): VANTRELA ER (hydrocodone bitartrate)

Dosage Form and Route: extended-release tablets, CII

Application Type/Number: 207975

Applicant: Teva Branded Pharmaceutical Products R&D, Inc.

## 1 INTRODUCTION

On September 30, 2014, Teva Branded Pharmaceutical Products R&D, Inc. submitted for the Agency's review 505(b)(2) New Drug Application (NDA) 207621 for VANTRELA ER (hydrocodone bitartrate) extended-release tablets, an abuse-deterrent formulation. The Applicant obtained the right of reference of Vicoprofen (NDA 020716) from AbbVie, Inc. and submitted a letter of confirmation for the right of reference on July 7, 2015. Therefore, this Application has been changed from a 505(b)(2) to a 505(b)(1). The proposed indication for VANTRELA ER (hydrocodone bitartrate) extended-release tablets is for the management of pain severe enough to require daily around-the-clock, long-term opioid treatment and for which alternative treatments are inadequate.

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 Anesthesia, Analgesia, and Addiction Products (DAAAP) on February 13, 2015, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for VANTRELA ER (hydrocodone bitartrate) extended-release tablets.

## 2 MATERIAL REVIEWED

- Draft VANTRELA ER (hydrocodone bitartrate) extended-release tablets MG received on September 30, 2014, and received by DMPP and OPDP on September 17, 2015.
- Draft VANTRELA ER (hydrocodone bitartrate) extended-release tablets Prescribing Information (PI) received on September 30, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 17, 2015.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the MG the target reading level is at or below an 8<sup>th</sup> grade 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 APFont 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/  
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MORGAN A WALKER  
09/28/2015

KOUNG U LEE  
09/29/2015

BARBARA A FULLER  
09/29/2015

LASHAWN M GRIFFITHS  
09/30/2015

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## 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)

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**Date of This Memorandum:** September 30, 2015

**Requesting Office or Division:** Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

**Application Type and Number:** NDA 207975

**Product Name and Strength:** Vantrela ER (hydrocodone bitartrate extended-release tablets), 15 mg, 30 mg, 45 mg, 60 mg, 90 mg

**Submission Date:** September 28, 2015

**Applicant/Sponsor Name:** Teva Branded Pharmaceutical Products R and D, Inc.

**OSE RCM #:** 2014-2515

**DMEPA Primary Reviewer:** Millie Shah, PharmD, BCPS

**DMEPA Team Leader:** Vicky Borders-Hemphill, PharmD

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#### 1 PURPOSE OF MEMO

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that we review the revised container labels for Vantrela ER (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.<sup>1</sup>

#### 2 CONCLUSION

The revised container labels for Vantrela ER are acceptable from a medication error perspective. We have no further recommendations at this time.

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<sup>1</sup> Brahmbhatt M. Label and Labeling Review for Vantrela ER (NDA 207975). 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 Mar 12. 10 p. OSE RCM No.: 2014-2515.

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/s/  
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MILLIE C BRAHMBHATT  
09/30/2015

BRENDA V BORDERS-HEMPHILL  
09/30/2015

**PeRC Meeting Minutes  
September 9, 2015**

**PeRC Members Attending:**

Lynne Yao  
Linda Lewis  
Hari Cheryl Sachs  
Lily Mulugeta  
Belinda Hayes  
Wiley Chambers  
Meshaun Payne  
George Greeley  
Michelle Roth-Cline  
Lisa Faulcon  
Julia Pinto  
Dianne Murphy  
Gregory Reaman  
Adrienne Homatko-Munoz  
Barb Buch  
Maura O'Leary (

NON-RESPONSIVE

NON-RESPONSIVE

NON-RESPONSIVE

Freda Cooner

NON-RESPONSIVE



NON-RESPONSIVE

**Hydrocodone Bitartrate (Extended Release Tablets) Agreed iPSP Partial Waiver/Deferral**

- Proposed Indication: Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
- The division noted that this product has an agreed iPSP and that this product is developed as an abuse deterrent form of Hydrocodone (coating that prevents diversion). The PeRC agreed that development of this product in patients less than 7 years of age would likely require different formulation development which would defeat the abuse deterrent properties of the drug. For this reason, the PeRC agrees that waiver in patients < 7 years of age is acceptable. However, the PeRC also noted that patients less than 7 years of age

also suffer from pain severe enough to require daily, around-the- clock, long-term opioid treatment. Therefore, in the future, formulations that may be suitable for use in younger patients would potentially need to be studied in younger patients with chronic, severe pain.

- The PeRC also notes the expanding scope of narcotic addiction in this country. However, the PeRC continues to conclude that pediatric patients should have access to drugs which have been appropriately studied to provide accurate dosing, efficacy and safety information. Furthermore, the PeRC does not agree that approval of such products for pediatric patients with severe, chronic pain would lead to addiction and abuse problems in pediatric patients if used and prescribed appropriately. Finally, the PeRC also does not agree that approval of such products for use in pediatric patients with severe, chronic pain would lead to worsening addiction/abuse in adults.
- ***PeRC Recommendations:***
  - The PeRC concurred with the sponsor's plan for a partial waiver and deferral in their Agreed iPSP.

NON-RESPONSIVE

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/s/  
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MESHAUN L PAYNE  
09/28/2015



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

**Date:** September 28, 2015

**To:** Sharon Hertz, M.D., Director  
Division of Anesthesia, Analgesia and Addiction Products

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

**From:** Katherine Bonson, Ph.D., Pharmacologist  
Silvia Calderon, Ph.D., Pharmacologist  
Controlled Substance Staff

**Subject:** CEP-33237 (hydrocodone bitartrate ER; Vantrela) in 15, 30, 45, 60, and 90 mg tablets  
NDA 207,975 (IND 105,587)  
Indication: [REDACTED] (b) (4)  
Sponsor: Teva Pharmaceutical Products  
PDUFA Goal Date: October 23, 2015

**Materials reviewed:** In vitro physical manipulation and chemical extraction studies as well as two human abuse potential studies submitted in of the NDA. (submission #000, 12/23/14)

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## **1. Background**

CEP-33237 (Vantrela; NDA 207,975) is a Schedule II single-entity hydrocodone bitartrate tablet (15, 30, 45, 60, and 90 mg) in an extended-release formulation (b) (4) that is being developed by CIMA Labs, Inc. (a corporate affiliate of Teva Branded Pharmaceutical Products). Teva submitted the NDA as a 505(b)(2) application that references the immediate-release hydrocodone component of Vicoprofen (NDA 020716). Vantrela is indicated for the management of “pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate”.

Vantrela extended-release tablets, 15 mg, 30 mg, 45 mg, 60 mg and 90 mg (b) (4) polymers that are intended to impart abuse deterrent properties to the formulation. Vantrela tablets do not contain polyethylene oxide (PEO).

The Sponsor accepts that their product is Schedule II under the Controlled Substances Act and is not requesting a schedule change.

However, the Sponsor is seeking a label claim that their product is abuse deterrent, based on their assertion that their tablet is resistant to rapid release of the drug when the tablet is comminuted (e.g., crushed), and is resistant to dose-dumping when co-administered with alcohol. They conducted numerous abuse-deterrent related studies, including:

- Category 1 *in vitro* manipulation studies of intact and manipulated drug product
- Category 2 clinical pharmacokinetic studies (alcohol interaction study plus PK data from intranasal clinical abuse potential study [Category 3] with crushed tablets)
- Category 3 clinical abuse potential studies (oral and intranasal administration), as well as evaluation of loss and diversion data from Phase 3 clinical studies

## **2. Conclusions**

CSS has reviewed the nonclinical and clinical abuse-related data submitted in NDA 207,975 for CEP-33237 (Vantrela; hydrocodone extended release, abuse deterrent) concludes the following:

### ***a) In vitro Studies (Category 1 Studies)***

Extraction studies using small volumes (30 ml) of solvents (water, buffers, 20% and 40% alcohol) showed that extraction of hydrocodone from manipulated tablets into

aqueous solutions intended for ingestion increases with agitation and temperature. However, reduction in particle size of the sample doesn't seem to affect the levels of extraction (extractability).

- i) High percentages of hydrocodone bitartrate can be extracted from Vantrela tablets into aqueous solutions intended for ingestion. Compared to Zohydro (the comparator used by the Sponsor in some of the in vitro studies), Vantrela tablets required longer extraction times, agitation and high water temperatures to accomplish the extraction. For example, approximately 84 % of hydrocodone bitartrate is released in hot water (95°C) without agitation from intact Zohydro tablets at 15 minutes, whereas approximately 10 % is extracted from either the 15 mg or 90 mg strengths Vantrela tablets under the same conditions of the study. Extraction times of 30 minutes in hot water (95°C) without agitation of the solution afforded a range of hydrocodone bitartrate solution containing 4.5 mg and 39 mg, from intact 15 mg and 90 mg Vantrela tablets, respectively, and the entire 50 mg of hydrocodone bitartrate when using Zohydro tablets.
- ii) The extraction of Vantrela tablets in 30 ml of aqueous solvents produced somewhat viscous solutions that contained some undissolved viscous materials. However, upon filtration the solutions were not too viscous to be ingested, with viscosities of representative samples similar to or less than Pepto-Bismol.
- iii) The pH of the aqueous extraction solvents doesn't seem to have an effect on the percent of hydrocodone bitartrate extracted from Vantrela 15 and 90 mg tablets.
- iv) Extraction efficiency and drug release seems to decrease with tablet strength, for example 65.2% of hydrocodone was extracted at 30 minutes from intact 90 mg (58.7 mg) Vantrela tablets from 30 ml of water heated at 95 °C with agitation (500 RPM), whereas 81.6 % of hydrocodone bitartrate was extracted from the 15 mg tablets (12.2 mg) under the same conditions.
- v) In 30 ml of 20 % and 40 % alcohol, under the most aggressive conditions (60°C, 500 rpm agitation), extraction from manipulated tablets (comminuted with a coffee mill or rotary abrasion tool) is relatively rapid: about 70–80% extraction efficiency is reached within 30 minutes. Under similar conditions greater than 90 % of hydrocodone bitartrate was extracted from Zohydro 50 mg within the first 5 minutes of extraction.
- vi) With organic solvents, hydrocodone bitartrate can be readily extracted from comminuted Vantrela tablets. The same is true of manipulated Zohydro ER comparator. However, the purity of the extracted Vantrela residues is significantly lower than residues extracted from manipulated Zohydro ER comparator.
- vii) Syringeability/injectability studies show that a solution for injection could be obtained under very specific conditions of extraction using the high strength 90 mg tablets, though the extraction of hydrocodone bitartrate may not be very efficient in that a small percentage of the active ingredient was extracted and abusers would have to inject volumes of 5-7 ml to feel the reinforcing effects of the opioid.
- viii) Syringeability/injectability studies show that extraction in 5ml and 10 ml of aqueous solvent ( water, pH 6.3 phosphate buffer and pH 10.3 borate buffer) render mixtures difficult to filter, and that retain in part the color of the tablets. Comminution of the tablets increased the efficiency of the extractions, affording

samples of higher viscosity that required larger volumes of extraction; however, the extracts were more difficult to handle.

- ix) Syringeability/injectability study results show that extraction from lower strength tablets was inefficient under most of the conditions tested, and that only under specific conditions of extraction, comminuted 90 mg tablets afforded a solution that could potentially be abused by injection.

***b) Oral Human Abuse Potential Study***

In the human abuse potential study conducted using oral administration of 45 mg hydrocodone in various forms, finely crushed CEP-33237 produced responses on positive and negative subjective measures (Drug Liking, Overall Drug Liking, Take Drug Again, Drug Value, Good Drug Effects, Euphoria, as well as Bad Drug Effects, Nausea, Sedation and Drowsiness) that were statistically significantly greater than the responses on these measures produced by intact CEP-33237 and placebo, but statistically significantly less than the responses produced by hydrocodone powder (as an immediate-release condition).

Notably, the 45 mg dose of hydrocodone tested is in the mid-range of the dosage strengths (range of 15 to 90 mg) that will be marketed, if approved. Thus, this study does not test the highest proposed therapeutic dose of hydrocodone (60 mg), and it also does not test suprathreshold doses of hydrocodone. However, these doses are adequate for assessing abuse potential of an opioid without exposing subjects to undue risk.

An analysis of adverse events showed that each hydrocodone treatment condition reliably produced known opioid AEs such as nausea, vomiting, somnolence and pruritis. The order of these opioid responses statistically was hydrocodone powder > crushed CEP-33237 > intact CEP-33237  $\geq$  placebo, which is consistent with the results of the subjective measure analysis.

The 45 mg dose of hydrocodone ingested orally produced different pharmacokinetic responses, based on the formulation. The order of C<sub>max</sub> and AUC values produced by each of the hydrocodone levels was: hydrocodone powder > crushed CEP-33237 > intact CEP-33237. Scores on all subjective measures paralleled the peak plasma concentrations (C<sub>max</sub> values) of hydrocodone that were produced by each drug condition, demonstrating a close correlation between drug levels and drug response. Similarly, the occurrence of opioid-related adverse events also paralleled C<sub>max</sub> values from each drug condition.

The results of this study show that when CEP-33237 is taken as directed as an intact oral tablet, it produces no adverse events that are indicative of abuse. Crushing the CEP-33237 tablet prior to oral ingestion significantly increases its abuse potential compared to placebo, but these responses from crushed CEP-33237 are significantly less than those produced by orally-ingested hydrocodone powder. This suggests that CEP-33237 has abuse deterrent properties when it is physically manipulated and ingested orally.

***c) Intranasal Human Abuse Potential Study***

In the human abuse potential study conducted with 45 mg hydrocodone in various forms, each of the three intranasal conditions (hydrocodone powder, finely milled Zohydro and finely milled CEP-33237) produced statistically significant increases in the responses to positive and negative subjective measures (Drug Liking, Overall Drug Liking, Take Drug Again, Drug Value, Good Drug Effects, Euphoria, as well as Bad Drug Effects, Nausea, Sedation and Drowsiness) compared to placebo. In contrast, oral administration of intact CEP-33237 produced responses on these measures that were comparable to placebo, similar to the results in the oral administration human abuse potential study (see above).

Notably, the 45 mg dose of hydrocodone tested is in the mid-range of the dosage strengths (range of 15 to 90 mg) that will be marketed, if approved. Thus, this study does not test the highest proposed therapeutic dose of hydrocodone (60 mg), and it also does not test suprathreshold doses of hydrocodone. However, these doses are appropriate because larger doses would not be easily insufflated when crushed.

A statistical analysis of the three intranasal conditions showed that intranasally administered hydrocodone powder was statistically equivalent to intranasal finely milled Zohydro on the subjective measures, and that these responses were statistically significantly greater than those produced by intranasal finely milled CEP-33237. oral intact CEP-33237  $\geq$  placebo.

An analysis of adverse events showed that each hydrocodone treatment condition reliably produced known opioid AEs such as nausea, vomiting, somnolence and pruritis. Hydrocodone powder and finely milled Zohydro produced the greatest degree of these AEs, followed by finely milled CEP-33237 and then oral intact CEP-33237. This order of opioid response is consistent with the results of the subjective measure analysis.

The 45 mg dose of hydrocodone ingested intranasally and orally produced different pharmacokinetic responses, based on the formulation. The order of C<sub>max</sub> and AUC values produced by each of the hydrocodone levels were: intranasal hydrocodone powder = intranasal finely milled Zohydro > intranasal finely milled CEP-33237 >> oral intact CEP-33237. Scores on all subjective measures paralleled the peak plasma concentrations (C<sub>max</sub> values) of hydrocodone that were produced by each drug condition, suggesting a close correlation between drug levels and drug response. Similarly, the occurrence of opioid-related adverse events also paralleled C<sub>max</sub> values from each drug condition.

The results of this study show that when CEP-33237 is taken as directed as an intact oral tablet, it produces a signal of abuse potential similar to that of placebo. Crushing the CEP-33237 tablet prior to intranasal use significantly increases its abuse potential compared to placebo, although the abuse signals are significantly less than those produced by intranasal hydrocodone powder or crushed Zohydro. This suggests that CEP-33237 has abuse deterrent properties when it is physically manipulated and utilized intranasally.

### **3. Recommendations**

CSS recommends that:

- a) Based on the study results from human abuse potential studies, Vantrela should be allowed a label claim that it has abuse deterrence with regard to oral and intranasal abuse of manipulated tablets.

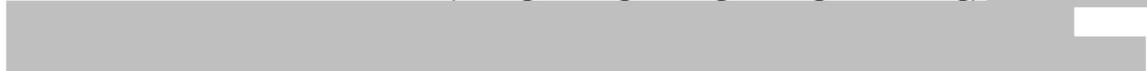
- b)  (b) (4)

### **4. Discussion**

#### **A. Chemical Manipulation Studies in Support of Abuse Deterrent Claim**

##### **1. Product Information**

Vantrela extended-release tablets (15 mg, 30 mg, 45 mg, 60 mg and 90 mg)  (b) (4)

 polymers that impart abuse deterrent properties to the formulation. Vantrela tablets do not contain polyethylene oxide (PEO).

The quantitative composition of the various strengths of the product is shown below in Table 1.

**Table 1: Quantitative Composition of Hydrocodone Bitartrate Extended Release  
Tablets 15 mg, 30 mg, 45 mg, 60 mg and 90 mg (Source NDA 207-975, Module  
3.2.P.1).**

Component	Reference to standard	Function	mg /tablet				
			15 mg tablet	30 mg tablet	45 mg tablet	60 mg tablet	90 mg tablet
Hydrocodone bitartrate (b) (4)	USP	Active ingredient	15.00	30.00	45.00	60.00	90.00
Lactose monohydrate (b) (4)	NF	(b) (4)					
Ethyl cellulose (b) (4)	NF						
Hypromellose (b) (4)	USP						
Glyceryl behenate	NF						
Magnesium stearat (b) (4)	NF						
(b) (4) (Varies for each strength)	various						
<b>Total weight / Tablet</b>							

The manufacturing steps of the product are as follows:



The total weight of Vantrela 15 mg, 30 mg and 45 mg is 575mg, and the weight of 60 mg and 90 mg tablets is 1150 mg.

In early development, [REDACTED] (b) (4)  
[REDACTED] During the pharmaceutical  
development of the formulation, lots containing [REDACTED] (b) (4)  
[REDACTED] were used for the lower product strengths, whereas a  
(b) (4) was used for the highest strengths. Thus, for the  
lowest strengths the majority of the *in vitro* studies were not conducted with the to-  
be-marketed formulation of the lower strengths. At the request of the Agency, the  
Sponsor conducted a series of *in vitro* studies to validate prior study results obtained  
with the lower strengths tablets.

## 2. *In Vitro* Studies

The Sponsor conducted several studies to assess the abuse deterrent properties of the formulation. These studies were reviewed by Office of Pharmaceutical Quality (OPQ) (see Appendix, page 45).

The sections below supplement the OPQ review and summarize CSS's review of the two study reports: 1) Teva Study report Larger Volume Extractions, and 2) Teva Study Report Simulated Intravenous Manipulation and Small Volume Extraction (NDA 207-975, 3.2.P.2 Pharmaceutical Development).

### a) *General considerations*

These extraction studies were conducted using intact and comminuted tablets. The Sponsor evaluated the use of a pill crusher, hammer, coffee mill, grinder and rotary abrasion to comminute the formulation. Based on particle size distribution and drug release in simulated gastric fluid (simulated oral ingestion), the Sponsor selected a subset of tools and conditions of comminution such as milling time, and the number of strokes for each tool.

The use of a coffee mill for 30 seconds and the use of a rotary abrasion tool to complete total comminution of the sample were selected as the best tools for *in vitro* manipulation studies and for the manipulation of the samples used in the oral and intranasal abuse potential studies

Physical manipulation experiments were conducted on Vantrela tablets stored at ambient, heated, and frozen conditions to simulate common forms of manipulation of opioid medications. Resultant powders were characterized by particle size distribution. Various controls were used for comparison during each type of *in vitro* study conducted on the drug product, including: Hydrocodone bitartrate drug substance (API) for all extraction experiments; Vicoprofen (AbbVie) tablets for simulated oral ingestion, simulated insufflation, and simple chemical extraction (pH 2 and 8 buffers) tests after manipulation (two Vicoprofen® tablets were used

simultaneously to represent a 15 mg hydrocodone dose); and Zohydro ER capsules for large volume extractions and small volume extractions.

The HPLC method used in all in vitro studies is the same as the method used for quantitation of the released drug during in vitro dissolution studies from finished drug product. The results presented are mean values for six replicates (with a few exceptions) for study product and three replicated for reference products; and are expressed both as percent of extracted from one dose unit and as absolute mass of hydrocodone bitartrate drug extracted. Much of the in vitro manipulation data for the 15-, 30-, and 45-mg strengths was obtained on development lots containing coated (b) (4) granule (b) (4), while all data for the 60-mg and 90-mg tablets were obtained on tablets with a (b) (4) coated (b) (4), representing the to-be-marketed formulation.

***b) In vitro extraction studies with large volume of solvents***

The Sponsor conducted simple extractions with solvents suitable for oral ingestion (water, pH 2 and pH 8 buffers, 20% and 40% alcohol), simple extractions using organic solvents that, upon evaporation, could render a residue that could be insufflated or reconstituted for injection, as well as complex multi-step extraction intended for extraction and purification of the hydrocodone base.

*Extraction in solvents suitable for oral ingestion*

Aqueous and ethanolic solvents were considered for this category of extraction. An extraction volume of 30 ml of water, pH 2 and pH 8 buffers, and 20% and 40% alcohol were selected based on the solubility of hydrocodone bitartrate<sup>1</sup> in these solvents. Intact or comminuted dosage forms (using the coffee mill or the rotary abrasion) were used in these experiments.

A variety of extraction times (5-180 minutes), temperatures (ambient, 60°C, and 100°C) and agitation conditions (without agitation and at 500 rpm) were investigated. These conditions cover a range of extractions from “passive” (ambient, no agitation) to “aggressive” (60°C and 100°C, 500 rpm stirring). After extraction, samples were assayed by HPLC for quantitation of hydrocodone bitartrate.

The 30 ml extractions produced in these experiments contained some undissolved material and were somewhat viscous. Upon filtration, the solutions were not too viscous to be ingested, with viscosities of the representative samples similar to or lower than Pepto-Bismol.

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<sup>1</sup> The Sponsor reports that the solubility of hydrocodone bitartrate in aqueous solutions across the pH range of 2 to 8 is higher than 90 mg/ml and in 40% ethanolic solutions is approximately 70mg/ml.

### *Simple Aqueous Extractions*

As shown in Table 2, the extraction of hydrocodone from manipulated tablets into aqueous solutions intended for ingestion increases with agitation and temperature. Reduction in particle size of the sample does not seem to affect the levels of extraction.

As also shown in Table 2, higher levels of hydrocodone bitartrate were extracted from Zohydro than from Vantrela tablets, under all conditions. Intact Zohydro 50 mg tablets released 84% of the labeled amount of hydrocodone bitartrate at 15 min when taken in 30 ml water at 95°C, whereas under the same conditions, Vantrela 15 mg and 90 mg tablets release 34.7% and 27.7% respectively.

Extraction efficiency and drug release seem to decrease with increasing tablet strength. For example, 65.2% of hydrocodone was extracted at 30 minutes from intact 90 mg (58.7 mg) Vantrela tablets using 30 ml of water heated at 95°C with agitation (500 rpm), whereas 81.6% of hydrocodone bitartrate was extracted from the 15 mg tablets (12.2 mg) under the same conditions.

Although under certain conditions of extraction, high percentages of hydrocodone bitartrate can be extracted from Vantrela tablets, Vantrela may represent an incremental improvement over Zohydro, in that longer extraction times, agitation and high water temperatures are required to accomplish the extraction. For example, approximately 84% of hydrocodone bitartrate is released in hot water (95°C) without agitation from intact Zohydro tablets at 15 minutes, whereas approximately 10% is extracted from either the 15 mg or 90 mg strengths Vantrela tablets under the same conditions.

Under the same conditions and in absolute terms, hydrocodone bitartrate is extracted in 30 minutes ranges from 4.5 mg (from 15 mg tablets, intact) to 39 mg (from 90 mg tablets, intact). In contrast, the entire 50 mg dose of hydrocodone bitartrate is extracted from Zohydro under the same conditions.

**Table 2: Percent of Hydrocodone Bitartrate Extracted in Simple Aqueous Extractions in Water (30 ml) from Manipulated and Intact to be Marketed Vantrela Tablets ( (b) (4) ), and Comparators**

MANIPULATION CONDITION	TEMPERATURE	AGITATION	TEST ARTICLE	PERCENT OF HYDROCODONE BITARTRATE EXTRACTED AT DIFFERENT EXTRACTION TIMES				
				5 MIN	15 MIN	30 MIN	120 MIN	180 MIN
Intact	95 °C	500 RPM	Vantrela 15 mg	3.1	34.7	81.6	98.6	NA <sup>1</sup>
			Vantrela 90 mg	1.2	27.7	65.2	91.3	NA
			Zohydro 50 mg	36.7	104.5	105.4	106.1	NA
		Without agitation	Vantrela 15mg	0.5	11.0	30.0	78.9	NA
			Vantrela 90mg	0.4	15.6	44.2	85.5	NA
			Zohydro 50mg	23.2	84.0	103.7	105.9	NA
Coffee Grinder <sup>2</sup>	100 °C	500 RPM	Vantrela 15 mg	NA	NA	86.3	NA	98.8
			Vantrela 90 mg	NA	NA	65.8	93.8	95.4
			Zohydro 50 mg	99.9	100.2	101.0	101.8	NA
Rotary Tool <sup>3</sup>	100 °C	500 RPM	Vantrela 15 mg	NA	NA	85.3	NA	96.8
			Vantrela 90 mg	NA	NA	71.7	94.0	97.2
Coffee Grinder <sup>2</sup>	Ambient	500 RPM	Vantrela 15 mg	NA	NA	13.4	NA	52.2
			Vantrela 90 mg	NA	NA	12.2	39.0	51.6
			Zohydro 50 mg	NA	NA	99.4	103.4	NA

<sup>1</sup>NA- Not sampled, <sup>2</sup>Coffee Mill (Mr. Coffee) for 30 seconds. *Particle size distribution* for the 45 mg strength 25.9% <106 µm, 10.9 % >106-180 µm, 15.8 % >180-300 µm, 18.8% > 300-425 µm, 19.9% > 425-600 µm, 7.7 % >600-800 µm, 1.0 % >850 µm. <sup>3</sup>PediPaws™ pet grooming tool was selected as the rotary abrasion technique, with comminution accomplished by pressing the tablet against the rotary abrasive drum until the entire tablet is comminuted. *Particle size distribution* for the 45 mg strength 45 % <106 µm, 10.7 % >106-180 µm, 9.0 % >180-300 µm, 8.7% > 300-425 µm , 8.8% 425-600 µm, 7.1 % >600-800 µm, 3.6 % >850 µm.

*Extraction in pH 2 and pH 8 buffers*

The effect of pH on the extraction efficiency was investigated by comparing percentages of hydrocodone bitartrate extracted in water, and in pH 2 and pH 8 buffers. As seen in Table 3, the pH of the solution does not seem to have an effect on the extraction efficiency of manipulated Vantrela 15 mg and 90 mg tablets comminuted with the coffee mill and with a rotary abrasion tool at room temperature with 500 rpm agitation. The percentages of hydrocodone bitartrate extracted from Zohydro 50 mg tablets and from

Vicoprofen 15 tablets (2 tablets of 7.5 mg hydrocodone bitartrate) were in the range of 92-99 % at both pH 2 and pH 8 buffers under the same conditions of extraction. In conclusion, a change in pH doesn't seem to have an effect on the percent of hydrocodone bitartrate extracted from Vantrela 15 and 90 mg tablets.

**Table 3. Percent of Hydrocodone Bitartrate Extracted in Simple Aqueous Extractions in Water (30 ml), pH 2 Buffer (30 ml of 50 mM phosphate), and pH 8 Buffer (30 ml of 50 mM phosphate) from Manipulated and Intact to-be-Marketed Vantrela Tablets <sup>(b) (4)</sup> and Comparators, at Room Temperature and 500 rpm Agitation.**

Manipulation Condition	Temp.	Agitation	Percent of Hydrocodone bitartrate extracted			
			Test article	Water 30 min.	pH 2 Buffer 30 min.	pH 8 Buffer 30 min.
Coffee Grinder <sup>2</sup>	Ambient	500 RPM	Vantrela 15 mg (37.5)	28.7	28.7	27
			Vantrela 15 mg (40)	13.4	NA <sup>1</sup>	NA
			Vantrela 90 mg	12.2	13.5	11.4
			Zohydro 50 mg	99.4	97.0	97.6
Rotary Tool <sup>3</sup>	Ambient	500 RPM	Vantrela 15 mg (37.5)	59.1	44.3	60.2
			Vantrela 15 mg (40)	62.9	NA	NA
			Vantrela 90 mg	51.4	42.8	50.0
			Zohydro 50 mg	NA	NA	NA
			Vicoprofen 15mg	NA	99.1	92.7

<sup>1</sup>NA- Not sampled, <sup>2</sup>Coffee Mill (Mr. Coffee) for 30 seconds. *Particle size distribution* for the 45 mg strength 25.9% <106 µm, 10.9 % >106-180 µm, 15.8 % >180-300 µm, 18.8% > 300-425 µm, 19.9% > 425-600 µm, 7.7 % >600-800 µm, 1.0 % >850 µm. <sup>3</sup>PediPaws™ pet grooming tool was selected as the rotary abrasion technique, with comminution accomplished by pressing the tablet against the rotary abrasive drum until the entire tablet is

*Extraction in 40% and 20 % Ethanol*

In 30 ml of either 20% or 40%<sup>2</sup> ethanol, intact Vantrela tablets retain their extended release properties even when heated to 60°C and subjected to agitation. For example, under these conditions using 40% ethanol, 25.5% and 23.8% of hydrocodone is

<sup>2</sup> This medium mimics a shot of strong liquor, such as vodka.

extracted from the 15 and 90 mg strengths of intact Vantrela, respectively. In comparison, under the same conditions, 100% of hydrocodone is extracted within the first 5 minutes from intact Zohydro 50 mg capsules.

When tablets are comminuted, an alcohol-containing medium becomes a more efficient extraction solvent. As seen with other solvents, the efficiency of the extraction increases with temperature and agitation. At higher temperatures of extraction and high agitation, it seems that the particle size distribution of the sample does not have a pronounced effect.

Under the most aggressive conditions (60°C, 500 rpm agitation), extraction from manipulated tablets is relatively rapid: about 70–80% extraction efficiency is reached within 30 minutes for both manipulation tools. For example, as seen in Table 4, at room temperature, approximately 33.4% and 65.1% of the labeled hydrocodone is extracted in 40% ethanol (30 ml, 500 rpm) from 90 mg Vantrela tablet after tablets were comminuted with a coffee mill or a rotary abrasion tool, respectively. In contrast, when the temperature of the solution was increased to 60°C, 88.9 % (approximately 80 mg) and 74.9% percent (approximately 67 mg) of labeled hydrocodone is extracted at 30 minutes. Under similar conditions, over 90% of hydrocodone bitartrate was extracted from Zohydro 50 mg within the first 5 minutes of extraction.

**Table 4. Percent Extraction of Hydrocodone Bitartrate from Intact and Manipulated Vantrela 90 mg Tablets in 40% and 20% ethanol (30 ml, 500 rpm) at Room Temperature and at 60°C**

		PERCENT OF HYDROCODONE EXTRACTED IN 30 ML OF SOLVENT AT 30 MINUTES		
Agitation	Temperature	Vantrela 90 mg	40 % Ethanol	20 % Ethanol
500 RPM	Ambient	Intact	3.0	12.6
		Coffee Mill <sup>1</sup>	33.4	10.1
		Rotary Tool <sup>2</sup>	65.1	32.0
	60 °C	Intact	23.8	1.4
		Coffee Mill	88.9	69.5
		Rotary Tool	74.9	70.4

<sup>1</sup>Coffee Mill (Mr. Coffee) for 30 seconds. *Particle size distribution* for the 45 mg strength 25.9% <106 µm, 10.9 % >106-180 µm, 15.8 % >180-300 µm, 18.8% > 300-425 µm, 19.9% > 425-600 µm, 7.7 % >600-800 µm, 1.0 % >850 µm. <sup>2</sup>PediPaws™ pet grooming tool was selected as the rotary abrasion technique, with comminution accomplished by pressing the tablet against the rotary abrasive drum until the entire tablet is comminuted. *Particle size distribution* for the 45 mg strength 45 % <106 µm, 10.7 % >106-180 µm, 9.0 % >180-300 µm, 8.7% > 300-425 µm , 8.8% 425-600 µm, 7.1 % >600-800 µm, 3.6 % >850 µm.

*Extraction in organic volatile solvents*

An alternative approach to dissolving tablets in ingestible household solutions is to extract the drug from comminuted tablets using a volatile solvent, which can subsequently be removed by evaporation to yield an isolable residue. This residue could be directly insufflated or it could be reconstituted for ingestion or injection. Methanol, isopropanol, acetone, ethyl acetate, and methylene chloride were selected as solvents for extraction studies.

Because of the relatively low solubility of drug substance in the organic solvents selected, the extraction volume was increased proportionately with tablet strength (e.g., 30 ml for 15 mg strength, 180 ml for 90 mg strength). This was done to ensure that any changes in extraction efficiency as a function of dose strength were not due to reaching a solubility limit as the total amount of drug increased. These solvents are relatively volatile, so removal of excess solvent is not considered a large barrier for abusers.

Prior to extraction, tablets were comminuted using two manipulation methods (coffee mill and rotary abrasion tool). Extractions were performed at ambient temperature, using various extraction times (5, 15, 30 and 60 minutes) and agitation conditions. After extraction, samples were filtered, and the filtrate was dried (blown air or nitrogen gas) to remove solvent prior to weighing and assay by HPLC.

Results of these studies show that when using organic solvents, hydrocodone bitartrate can be readily extracted from comminuted Vantrela tablets. The same is true of manipulated Zohydro ER comparator. However, the purity of the extracted Vantrela residues after solvent removal is significantly lower than residues extracted from manipulated Zohydro ER comparator. The lower purity of the Vantrela residues indicates that hydrocodone is extracted with excipients. As such, this type of extraction requires investment of time and patience, but seems to offer minimal advantages compared to other forms of manipulation. Unlike aqueous extracts, solvent extracts are not potable, and although the solvent can be removed, doing so does not remove excipients or result in highly purified drug.

### ***Syringeability-Injectability***

Syringeability-injectability studies were conducted to assess the feasibility of preparing solutions for injection using Vantrela tablets.

Stoops *et al.* (2010) showed that 10 mg or 20 mg, but not 5 mg, of hydrocodone hydrochloride are associated with high levels of Drug Liking when administered intravenously by opioid-experienced non-dependent individuals in a human abuse potential study. Based on the findings by Stoops *et al.*, notwithstanding the differences in salt forms used (hydrochloride vs. bitartrate), CSS evaluated the potential for abuse of the solutions prepared for injection based on the volume of the extracted solution that an abuser would have to inject to deliver at least 10 mg of hydrocodone bitartrate.

Syringeability studies consisted of the extraction of manipulated dosage forms in water (5 and 10 ml), and intact tablets in pH 6.3 and 10.3 buffers (5 and 10 ml), and samples were drawn into the syringe without a needle as well as through 22 and 27 gauge needles.

Experimental conditions were designed to mimic the small volume extraction operation in the controlled laboratory setting. The resulting sample from each comminution technique (or intact tablet) was placed in a glass vial with addition of 5 ml of extraction medium preheated to approximately 100°C (water) or 90°C (pH 6.3 and 10.3 buffers).

Extractions were conducted with no agitation, or with agitation when vials were agitated continuously on a platform shaker at 150 rpm to simulate more aggressive conditions.

Extraction times of 1 and 5 minutes were employed in the water studies, and 1, 5, 10, and 30 minutes in the studies using pH 6.3 and pH 10.3 buffers. Continuous heat was applied through the 30 minute extraction time to maintain the extraction temperature at 90°C for the entire 30 minutes, whereas for the 5 minute extractions in water, pre-heated (100°C) water was used.

Hydrocodone bitartrate drug substance (API) was employed as a control for each set of experimental conditions. Zohydro ER capsules were included as a comparator when using buffers as extraction solvents.

Following extraction, the first assessment was whether drawing the mixture into a syringe through a needle or expelling the mixture from a syringe through a needle was feasible. These are termed syringeability and injectability, respectively. Drawing the sample into the syringe was performed without a needle as well as through 22 and 25 gauge needles. Extraction volumes were incrementally evaluated (5 ml to 10 ml) as needed to explore the range of the physical barriers and to achieve conditions where filtrates (at least 1.5 ml) could be collected.

Study results show that extraction in small volumes render mixtures that are difficult to filter, and that retain in part the color of the tablets. Comminution of the tablets increased the efficiency of the extractions, but the extracts were more difficult to handle.

Extraction from lower strength tablets was inefficient under most of the conditions tested. It is only under specific conditions of extraction that comminuted 90 mg tablets produced a solution that could potentially be abused. For example, a filtrate of 5.2 ml with a concentration of 4.3 mg of hydrocodone bitartrate per ml (22.3 mg/5.2 ml) was obtained after testing comminuted 90 mg tablets with a rotary abrasion tool in 10 ml of water at 100°C at 1 minute without agitation, whereas 5 minute extraction times did not give a filterable solution under the same conditions of extraction. Similar extraction results were seen when using pH 6.3 phosphate and pH 10.3 borate buffers. Extraction of hydrocodone bitartrate in 5 ml of these buffers at 90°C from the intact 90 mg tablet was negligible, though approximately 4 ml of filtrate was recuperated in these extractions. When testing intact Zohydro pellets in 5 ml of both buffers, without agitation, approximately 22 mg of hydrocodone bitartrate in 4.2 ml were obtained in the phosphate buffer, and 10.4 mg in 4.1 ml of borate buffer was extracted.

In conclusion, a solution for injection could be obtained under very specific conditions of extraction using the high strength 90 mg tablets, though the extraction of hydrocodone bitartrate may not be very efficient in that a small percentage of the active ingredient was extracted.

## **B. Pharmacokinetics**

Given that hydrocodone is a well-characterized drug, only absorption parameters related to the novel extended-release formulation are described for pharmacokinetics.

### *Absorption*

After a single oral dose of 90 mg CEP-33237, T<sub>max</sub> ranged from 5-12 hours and the mean t<sub>1/2</sub> was 10 ± 3 hours. The C<sub>max</sub> was 56 ± 14 ng/ml, with an AUC of 1073 ± 213 ng.h/ml.

In contrast, after twice-daily doses of 90 mg CEP-33237 for 10 days, T<sub>max</sub> was 5 hours and the mean t<sub>1/2</sub> was 11 ± 4 hours. The C<sub>max</sub> was 123 ± 25 ng/ml, with an AUC of 2453 ± 518 ng.h/ml.

Thus, T<sub>max</sub> and t<sub>1/2</sub> were similar between acute and chronic dosing with CEP-33237, but exposure was doubled with chronic dosing compared to acute dosing.

### *Alcohol Interaction Study*

The results of a Phase 1 food and alcohol interaction study (Study #1076) are reviewed by the Clinical Pharmacology Team in DAAAP. However, a cursory review of the data from this study shows that C<sub>max</sub> increased 45% when a 15 mg tablet of CEP-33237 was administered with food compared to the fasted state. In contrast, administration of 4%, 20%, or 40% alcohol solutions did not significantly alter plasma concentrations of hydrocodone from 15 mg tablets of CEP-33237, compared with administration with water. This suggests that alcohol does not cause dose-dumping of hydrocodone from the CEP-33237 tablets.

Despite the lack of changes in systemic exposure to hydrocodone with increasing concentrations of alcohol, there was an increase in depressant-associated adverse events, as shown in Table 5 below.

**Table 5: Effect of Food and Alcohol on AEs Produced by 15 mg Oral Vantrela**

<b>Preferred term</b>	<b>Number (%) of subjects<sup>a</sup></b>					<b>Overall<sup>b</sup></b>
	<b>A Fasted (N=32)</b>	<b>B Fed (N=33)</b>	<b>C 4% alc (N=36)</b>	<b>D 20% alc (N=35)</b>	<b>E 40% alc (N=33)</b>	
Nausea	4 (13%)	2 (6%)	1 (3%)	5 (14%)	13 (39%)	
Vomiting	1 (3%)	1 (3%)	1 (3%)	4 (11%)	9 (27%)	
Feeling drunk	0	0	1 (3%)	5 (14%)	10 (30%)	
Paresthesia	0	1 (3%)	0	5 (14%)	6 (18%)	
Somnolence	2 (6%)	1 (3%)	1 (3%)	1 (3%)	1 (3%)	

These data show that alcohol dose-dependently increases the stomach upset, euphoria, paresthesia and sedative effects of hydrocodone. Thus, patients who consume alcohol while taking Vantrela are likely to experience increased impairment compared to those who do not drink.

### **C. Clinical Safety, Efficacy and Physical Dependence Studies**

#### **1. Oral Administration Human Abuse Potential Study with CEP-33237 (Study #C-1085)**

This was a randomized, double-blind, triple-dummy, placebo-controlled crossover study that evaluated the oral abuse potential, safety, tolerability, and PK of CEP-33237 (intact and crushed) compared to placebo and hydrocodone powder (as an immediate release condition) in healthy nondependent recreational opioid users. The Sponsor did not submit the protocol to CSS prior to its initiation, so CSS did not provide any feedback on the design of the study.

The study consists of a Screening Phase, the Main Study (Qualification Phase and Treatment Phase) and a Follow-Up Visit.

#### **Subjects**

##### *Number of Subjects*

During the Main Study, 100 subjects (18 to 43 years of age, 79 men and 21 women) who were nondependent, recreational opioid users were enrolled in a Qualification Phase. A total of 35 subjects completed the Treatment Phase, out of 45 subjects who received any treatment in this phase.

*Inclusion Criteria* for participation are standard but include the following criteria that are relevant for a human abuse potential study:

- The subject had a history of recreational opioid use to achieve a “high” at least 10 times in the last year and at least on 1 occasion within the 12 weeks before screening. Subjects who abused multiple drugs were to express a preference for opioids.
- The subject had a negative urine drug screen (except for THC) and a negative alcohol test at screening. If a subject tested negative for THC at screening, the test result at baseline must have been negative for the subject to be considered for enrollment in the study.
- The subject was not physically dependent on opioids, as demonstrated by successful completion of a naloxone challenge; i.e., subject did not exhibit signs or symptoms of opioid withdrawal (as assessed by a Clinical Opiate Withdrawal

Scale score of <5) following administration of intravenous naloxone in the Naloxone Challenge.

*Exclusion Criteria* are standard but include the following criteria that are relevant for a human abuse potential study:

- The subject had habitually consumed, within the past 2 years, more than 28 units of alcohol per week for male subjects or 21 units of alcohol per week for female subjects, or had a history or current diagnosis of substance dependence, as assessed by using the DSM-IV-TR (American Psychiatric Association 2000).
- The subject had participated in, or at the time of the study, was participating in or seeking treatment for substance-related disorders (excluding nicotine).
- The subject was a heavy smoker (>20 cigarettes per day), chewed tobacco and/or was unable to abstain from smoking for 6 hours during any day, or abstain from caffeine intake for 20 hours during any day.

### **Naloxone Challenge Test**

All subjects passed the Naloxone Challenge Test at least 12 hours prior to the administration of study drug in the Qualification Phase and in the Treatment Phase (if subjects left the facility after the Qualification Phase), using the Clinical Opiate Withdrawal Scale (COWS).

A total of up to 0.8 mg naloxone HCl was administered. An initial dose of 0.2 mg naloxone HCl was administered as an intravenous (IV) bolus, followed by another IV bolus dose of 0.6 mg naloxone HCl for subjects who displayed no signs of withdrawal after the initial dose (COWS score of <5). Vital signs were recorded at 5 minutes, and at 0.25, 0.5, 1, 1.5, and 2 hours following administration of naloxone.

### **Main Study:**

Subjects must pass the following criteria in the Qualification Phase to be eligible to enter the Treatment Phase:

- The subject must have had a peak score in response to the immediate-release product of at least 15 points greater than that of placebo on Drug Liking as assessed by question 1 of the DLEQ and on overall Drug Liking as assessed by the Overall Drug Liking VAS.
- The subject must have had an acceptable placebo and hydrocodone response on all other measures (as judged by the investigator and/or designee).

## Oral Drug Doses

### *Main Study*

#### *Qualification Phase (single blinded)*

The following treatments were administered orally:

- 45 mg hydrocodone bitartrate powder in 60 ml noncarbonated flavored beverage
- 60 ml noncarbonated flavored beverage

The 45 mg dose of hydrocodone is the same as that used in the Treatment Phase.

There was a washout period of at least 48 hours in between treatments.

#### *Treatment Phase (double-blind)*

The following treatments were administered orally:

- One 45 mg CEP-33237 tablet (**intact**) + intact placebo tablet, taken with 60 ml noncarbonated flavored beverage
- One 45 mg CEP-33237 tablet (**crushed**) + intact placebo tablet, taken with 60 ml noncarbonated flavored beverage
- 45 mg hydrocodone bitartrate **powder (immediate release positive control condition)** in 60 ml noncarbonated flavored beverage + one crushed placebo tablet
- One intact placebo tablet + one crushed placebo tablet, taken with 60 ml noncarbonated flavored beverage

There was a washout period of at least 14 days in between treatments.

Notably, the 45 mg dose of hydrocodone tested in the Treatment Phase is the mid-range dosage strength of CEP-33237 that will be marketed (range of 15 to 90 mg). This was the same dose that was tested in the intranasal human abuse study (Study #C-10032, see below). Thus, this study not only does not test the highest proposed therapeutic dose of hydrocodone (60 mg), but it does not test suprathreshold doses of hydrocodone. CSS was not consulted regarding the design of this study.

This study was conducted from January 2012 through May 2012, prior to the marketing of Zohydro (ER single entity hydrocodone) in October 2013. Thus, although Zohydro would have been the ideal positive control, it was not available when this study was conducted. Since all other marketed IR hydrocodone products contain other drugs (such

as OTC analgesics), the Sponsor chose to use hydrocodone powder as the best available immediate release positive control condition.

The CEP-33237 tablet and matching placebo were finely crushed using the Silent Knight tool based on results of the *in vitro* physical manipulation studies. The Sponsor states that “specific considerations in selection of this method were the simulated oral ingestion dissolution profile and feasibility of the manipulation method in a clinical trial setting (including material loss and staff exposure). Particle size distribution was a secondary consideration for the method for this study due to the lack of correlation between particle size and simulated oral ingestion dissolution profile.”

#### *Pharmacodynamic Variables*

All subjective endpoints were assessed at baseline, 0.25, 0.75, 1.25, 1.75, 2.5, 4, 6, 7, 8, 9, 10, 12, and 24 hours after drug administration, except for VAS for Overall Drug Liking, Take Drug Again, and Price Value Assessment was assessed at 24 hours. During the Treatment Phase, additional measurements were taken for the subjective measures at 36, 48, 60, and 72 hours after drug administration (except for VAS for Overall Drug Liking, Take Drug Again, and Price Value Assessment).

#### Primary Measure:

Drug Liking VAS (Emax)

#### Secondary Measures:

##### *Balance of effects:*

- Drug Liking VAS (Emax, Emin and TA\_AUE)
- Overall Drug Liking VAS (Emax, Emin; end-of-day and next day scores)
- Take Drug Again VAS (Emax; end-of-day and next day scores)
- Price Value Assessment (end-of-day and next day scores)

##### *Positive effects:*

- Good Effects VAS (Emax and TA\_AUE)
- ARCI MBG scale (Emax and TA\_AUE)

##### *Negative effects:*

- Bad Effects VAS (Emax and TA\_AUE)
- Nausea VAS (Emax and TA\_AUE)
- ARCI LSD scale (Emax and TA\_AUE)

##### *Sedative effects:*

- ARCI PCAG scale (Emax and TA\_AUE)

##### *Other drug effects:*

- Any Effects VAS (Emax and TA\_AUE)

*Objective Measures:*

- Pupillometry

*Safety Variables*

- Adverse events
- Clinical laboratory parameters
- Vital signs measurements
- ECG and physical examination findings
- SpO<sub>2</sub> monitoring
- Concomitant medication usage.

During the Treatment Phase, blood samples were collected immediately before each study drug administration and 0.25, 0.75, 1.25, 1.75, 2.5, 4, 6, 7, 8, 9, 10, 12, 24, 36, 48, 60, and 72 hours after the start of each study drug administration.

**Results**

**Pharmacokinetics of Hydrocodone Conditions**

As shown in the Table 6 below, identical amounts of hydrocodone ingested orally produced different pharmacokinetic responses, based on the formulation. The hydrocodone powder (45 mg, representing an immediate release condition) produced the greatest C<sub>max</sub> value (91 ng/ml). The next highest C<sub>max</sub> of 41 ng/ml was produced by crushed CEP-33237 (45 mg), but this was less than one-half of the plasma concentration produced by the powder condition. The lowest C<sub>max</sub> of 29 ng/ml was produced by intact CEP-33237 (45 mg), which was one-third of the powder condition. Notably, crushing the CEP-33237 tablet only produced a slight increase in plasma concentrations of hydrocodone (41 ng/ml vs 29 ng/ml).

**Table 6: Pharmacokinetics of 45 mg CEP-33237 (Intact and Crushed) and Hydrocodone Powder**

PK Parameter	45 mg intact CEP-33237 N = 40	45 mg crushed CEP-33237 N = 41	45 mg powder hydrocodone N = 39
C <sub>max</sub> (ng/ml)	29 ± 1	41 ± 2	91 ± 3
AUC (0-inf) (ng*hr/ml)	584 ± 22	586 ± 22	625 ± 22
T <sub>max</sub> (hours)	7.7 ± 0.2	4.0 ± 0.2	1.1 ± 0.1

## Subjective Responses

The subjective responses produced by the three treatment conditions reflect the plasma levels of hydrocodone produced by these conditions, as shown in the pharmacokinetic data above. The order of plasma hydrocodone produced by each of these conditions was hydrocodone powder (immediate release) > crushed CEP-33237 > intact CEP-33237, which also reflects the order of subjective measures response, shown in the Table 7 below.

**Table 7: Effects of Oral Placebo, CEP-33237 (Intact and Crushed) and Hydrocodone Powder on Subjective Measures (VAS and ARCI)**

Measure	Placebo N = 35	45 mg intact CEP-33237 N = 35	45 mg crushed CEP-33237 N = 35	45 mg powder hydrocodone N = 33
Drug Liking VAS bipolar	53 ± 2	54 ± 1	66 ± 3	85 ± 2
Overall Drug Liking VAS bipolar	51 ± 1	51 ± 1	58 ± 4	74 ± 3
Take Drug Again VAS	47 ± 2	46 ± 3	59 ± 3	75 ± 3
PVAQ VAS (\$0.25-50.00)	1 ± 1	1 ± 1	7 ± 2	12 ± 1
Good Drug Effects VAS	9 ± 3	11 ± 3	33 ± 5	73 ± 4
ARCI-MGB Euphoria (0-16)	2.5 ± 0.5	2.8 ± 0.4	5.7 ± 0.7	8.6 ± 0.7
Bad Drug Effects VAS	3 ± 2	6 ± 2	13 ± 3	17 ± 3
Nausea VAS	4 ± 2	9 ± 3	11 ± 4	15 ± 4
ARCI LSD Dysphoria (0-14)	4.0 ± 0.3	4.4 ± 0.3	4.7 ± 0.3	6.2 ± 0.3
Any Drug Effect VAS	10 ± 3	12 ± 3	33 ± 5	74 ± 4
ARCI PCAG Sedation	4.7 ± 0.4	5.4 ± 0.4	6.6 ± 0.4	8.8 ± 0.4
Pupil Diameter	5.5 ± 0.1	3.2 ± 0.1	4.0 ± 0.1	3.2 ± 0.1

## Statistical Analysis of Subjective Measures

The primary measure of Drug Liking was evaluated for statistically significant differences between CEP-33237 (crushed and intact), hydrocodone powder and placebo by both the FDA Office of Biostatistics as well as by the Sponsor.

However, a similar evaluation of the secondary measures was only conducted by the Sponsor and was limited to comparisons of hydrocodone powder vs. placebo, crushed CEP-33237 and intact CEP-33237, as well as a comparison of crushed CEP-33237 vs.

intact CEP-33237. Thus, no comparisons of crushed CEP-33237 and intact CEP-33237 with placebo are available.

Drug Liking VAS (bipolar):

- Hydrocodone powder (immediate release) produced a significantly higher Emax score on Drug Liking compared to placebo ( $P < 0.0001$ ). These data show that hydrocodone powder was liked by subjects, which validates the study.
- Crushed CEP-33237 produced a significantly higher Emax scores on Drug Liking compared to placebo ( $P < 0.001$ ). However, intact CEP-33237 did not statistically differentiate from placebo on this measure ( $P = 0.675$ ), showing that when the drug product is used as intended, it does not produce Drug Liking.
- Crushed CEP-33237 produced a significantly higher Emax scores on Drug Liking compared to intact CEP-33237 ( $P < 0.001$ ).
- However, both intact and crushed CEP-33237 produced a significantly lower Emax scores on Drug Liking compared to hydrocodone powder ( $P < 0.001$ ).

Overall Drug Liking VAS:

- Hydrocodone powder (immediate release) produced a significantly higher Emax score on Overall Drug Liking compared to placebo ( $P < 0.0001$ ). These data show that hydrocodone powder was liked by subjects, which validates the study.
- Crushed CEP-33237 produced a slight but significantly higher Emax scores on Overall Drug Liking compared to placebo ( $P < 0.045$ ). However, intact CEP-33237 did not statistically differentiate from placebo on this measure ( $P = 0.92$ ), showing that when the drug product is used as intended, it does not produce Drug Liking.
- Crushed CEP-33237 produced a significantly higher Emax scores on Overall Drug Liking compared to intact CEP-33237 ( $P < 0.001$ ).
- However, both intact and crushed CEP-33237 produced a significantly lower Emax scores on Overall Drug Liking compared to hydrocodone powder ( $P < 0.001$ ).

Positive Subjective Measures -- Good Drug Effects VAS, ARCI-MBG, Take Drug Again VAS and Price Value Assessment Questionnaire (PVAQ):

- Hydrocodone powder (immediate release) produced a significantly higher Emax score on these measures compared to placebo ( $P < 0.001$ ).
- Hydrocodone powder produced a significantly higher Emax scores compared to both crushed CEP-33237 and intact CEP-33237 ( $P < 0.001$ ).
- Crushed CEP-33237 produced a significantly higher Emax scores compared to intact CEP-33237.

Bad Effects VAS:

- Hydrocodone powder (immediate release) produced a significantly higher Emax score on these measures compared to placebo ( $P < 0.001$ ).
- Hydrocodone powder produced a significantly higher Emax scores compared to intact CEP-33237 ( $P < 0.001$ ), but was statistically indistinguishable from crushed CEP-33237 ( $P = 0.259$ ).

- Crushed CEP-33237 produced a significantly higher Emax scores compared to intact CEP-33237 (P=0.036).

ARCI – LSD (dysphoria):

- Hydrocodone powder (immediate release) produced a significantly higher Emax score Dysphoria compared to placebo (P<0.001).
- Hydrocodone powder produced a significantly higher Emax scores for Dysphoria compared to both crushed CEP-33237 and intact CEP-33237 (P<0.001).
- Crushed CEP-33237 was statistically indistinguishable from intact CEP-33237 on the Dysphoria scale (P=0.278).

Nausea VAS:

- Hydrocodone powder (immediate release) produced a significantly higher Emax score Nausea compared to placebo (P=0.02).
- Hydrocodone powder produced a similar degree of Nausea compared to both crushed CEP-33237 and intact CEP-33237 (P>0.15).
- Crushed CEP-33237 and intact CEP-33237 produced a similar degree of Nausea (P=0.52).

ARCI – PCAG (Sedation):

- Hydrocodone powder (immediate release) produced a significantly higher Emax score Sedation compared to placebo (P<0.001).
- Hydrocodone powder produced a significantly higher Emax scores for Sedation compared to both crushed CEP-33237 and intact CEP-33237 (P<0.001).
- Crushed CEP-33237 produced greater Sedation than intact CEP-33237 (P=0.008).

Any Drug Effects VAS:

- Hydrocodone powder (immediate release) produced a significantly higher Emax score Sedation compared to placebo (P<0.001).
- Hydrocodone powder produced a significantly higher Emax scores for Sedation compared to both crushed CEP-33237 and intact CEP-33237 (P<0.001).
- Crushed CEP-33237 produced greater Sedation than intact CEP-33237 (P<0.001).

Pupillary Changes

- Hydrocodone powder produced a significant decrease in pupillary size compared to placebo, crushed CEP-33237 and intact CEP-33237. Crushed CEP-33237 produced a greater decrease in pupillary size compared to intact CEP-33237.

***Conclusions about Subjective Measures***

- The study was validated by the statistically significant increase in Drug Liking VAS in response to hydrocodone powder (immediate release) compared to placebo. Hydrocodone powder similarly statistically significantly increased scores on other positive subjective responses (Overall Drug Liking, Take Drug Again, Subjective Drug Value, Good Effects, and Euphoria), as well as on

negative subjective scales (Bad Effects, Dysphoria, Nausea), Sedation and Any Effects.

- In general, crushed CEP-33237 produced statistically significantly lower responses on all subjective measures compared to hydrocodone powder, but the crushed CEP-33237 produced statistically significantly greater responses compared to intact CEP-33237 and to placebo. Intact CEP-33237 was often statistically equivalent on subjective measures to placebo.
- Thus, the order of opioid subjective responses was hydrocodone powder > crushed CEP-33237 > intact CEP-33237 ≥ placebo.

*Abuse-Related Adverse Events*

An analysis of adverse events showed that each hydrocodone treatment condition reliably produced known opioid AEs such as nausea, vomiting, somnolence and pruritis (see Table 8, below). Hydrocodone powder produced the greatest degree of these opioid-related AEs, followed by crushed CEP-33237 and then intact CEP-33237. This order of opioid response is consistent with the results of the subjective measure analysis (see above).

**Table 8: Abuse-Related Adverse Events Following Oral Placebo, CEP-33237 (Intact and Crushed) and Hydrocodone Powder**

Measure	Placebo N = 43	45 mg powder hydrocodone N = 43	45 mg crushed CEP-33237 N = 44	45 mg intact CEP-33237 N = 43
Nausea	2 (5%)	12 (28%)	11 (25%)	7 (16%)
Vomiting	0	5 (12%)	3 (7%)	3 (7%)
Somnolence	1 (2%)	5 (12%)	3 (7%)	3 (7%)
Pruritus	1 (2%)	14 (33%)	15 (34%)	5 (12%)

**Intranasal Administration Human Abuse Potential Study with CEP-33237 (Study #C-10032)**

This is a single-dose, randomized, double-blind, quadruple-dummy, active- and placebo-controlled crossover study designed to assess the abuse potential of manipulated intranasal CEP-33237 in healthy, nondependent recreational opioid users. The study consists of a Screening Phase, the Main Study (Qualification Phase and Treatment Phase) and a Follow-Up Visit.

On July 24, 2014, the Sponsor informed Division of Anesthesia, Analgesia and Addiction Products (DAAAP) that they had completed the intranasal human abuse potential study, prior to submitting the protocol for review by FDA. Thus, CSS did not provide any feedback on the design of this study.

### **Subjects**

During the Main Study, 73 subjects (52 men and 21 women), 18 to 50 years of age (inclusive), who were nondependent, recreational opioid users were enrolled into Qualification Phase. There were 34 subjects who completed the Treatment Phase.

### **Inclusion and Exclusion Criteria**

The Inclusion and Exclusion criteria are standard for human abuse potential studies. Of particular note for this study:

#### *The Inclusion criteria include:*

- The subject is not physically dependent on opioids as demonstrated by successful completion of a Naloxone Challenge (see below).
- The subject has a history of recreational opioid use to achieve a “high” at least 10 times in the last year and at least on 1 occasion within the 12 weeks before screening.
- The subject has experience with intranasal use of opioids on at least 3 occasions in the year prior to screening.
- A subject who abuses multiple drugs should express a preference for opioids.

#### *The Exclusion criteria include:*

- The subject currently or has habitually consumed, within the past 2 years, more than 28 units of alcohol per week for male subjects or 21 units of alcohol per week for female subjects, or has a history or current diagnosis of substance dependence as assessed using by the DSM-IV-TR.
- The subject has participated in, is currently participating in or is seeking treatment for substance-related disorders (excluding nicotine).
- The subject has any clinically important condition of the intranasal cavity

### **Naloxone Challenge Test**

All subjects passed the Naloxone Challenge Test at least 12 hours prior to the administration of study drug in the Qualification Phase and in the Treatment Phase (if subjects left the facility after the Qualification Phase), using the Clinical Opiate Withdrawal Scale (COWS).

A total of up to 0.8 mg naloxone HCl was administered. An initial dose of 0.2 mg naloxone HCl was administered as an intravenous (IV) bolus, followed by another IV bolus dose of 0.6 mg naloxone HCl for subjects who displayed no signs of withdrawal after the initial dose (COWS score of <5). Vital signs were recorded at 5 minutes, and at 0.25, 0.5, 1, 1.5, and 2 hours following administration of naloxone.

### **Main Study:**

Subjects must pass the following criteria in the Qualification Phase to be eligible to enter the Treatment Phase:

- The subject must have a peak score (Emax) in response to hydrocodone API of at least 15 points greater than that of placebo on the Drug Liking VAS and the Overall Drug Liking VAS, with a minimum score of 65 points with hydrocodone API for both measures, within 3 hours after study drug administration (for Drug Liking VAS).
- The subject must have an acceptable placebo response (between 40 and 60, inclusive, for Drug Liking VAS and Overall Drug Liking VAS) and acceptable hydrocodone bitartrate API response on all other measures (as judged by the investigator and/or designee).
- Able to tolerate the 45 mg intranasal hydrocodone active pharmaceutical ingredient (API) dose, as assessed by the lack of emesis within 2 hours following dosing, ability to insufflate the entire volume of manipulated treatments (without sneezing or attempting to blow their noses within 1 hour of administration), and as otherwise judged by the investigator or designee.
- General behavior suggests that the subject could successfully complete the study, as judged by the research site staff.

On the bipolar Drug Liking VAS Emax, placebo responses were appropriate (mean = 50; range = 49.8 to 50.0), as were responses to hydrocodone (mean = 85.3; range = 67-100) for those subjects who were allowed to participate in the Treatment Phase.

## **Study Drug Doses**

Subjects were required to abstain from food for at least 8 hours prior to dosing during the Qualification and Treatment Periods and for at least 4 hours post-dose.

### ***Main Study***

#### ***Qualification Phase (single blinded)***

The following treatments were administered intranasally:

- 45 mg hydrocodone bitartrate powder blended with 45 mg lactose
- 90 mg lactose

The 45 mg dose of hydrocodone is the same as that used in the Treatment Phase.

There was a washout period of at least 48 hours in between treatments.

#### ***Treatment Phase (double-blind)***

### ***Study Drugs***

During the Treatment Phase, the following 5 treatments were tested:

- 45 mg manipulated intranasal CEP-33237
- 45 mg intranasal hydrocodone API
- 45 mg intact oral CEP-33237
- 45 mg manipulated intranasal Zohydro (ER single entity hydrocodone)
- placebo

Notably, the 45 mg dose of hydrocodone tested in the Treatment Phase is the mid-range dosage strength of CEP-33237 that will be marketed (range of 15 to 90 mg). This is the same dose that was tested in the oral human abuse potential study (Study #1085, see above). Thus, this intranasal study not only does not test the highest proposed therapeutic dose of hydrocodone (90 mg), but it does not test suprathreshold doses of hydrocodone. The Sponsor justifies not using higher doses for the intranasal study, given that the weight of the 60 mg tablets (1150 mg vs 575 mg for a 45-mg tablet) may have been prohibitive for intranasal administration for some subjects and may have resulted in a proportion of subjects being unable to complete insufflation. CSS was not consulted regarding the design of this study at any time prior to its initiation or completion.

Subjects will receive each of the treatments once. There was a minimum 7 day washout period between each administration of study drug.

Notably, the Zohydro condition was conducted with the original formulation of the drug product, as approved in October 2013, which contained hydrocodone without

acetaminophen or other OTC analgesics. The present intranasal study began in May 2014, and was completed in July 2014. Thus, the completion of the study occurred some six months before the approval of the reformulated Zohydro extended-release drug product in February 2015. Therefore, manipulation of the Zohydro condition was with the original non-abuse deterrent extended-release formulation.

#### *Oral Administration*

Subjects ingested the oral tablet of 45 mg CEP-33237 with 240 ml of noncarbonated room temperature water. Oral administration of the oral treatment occurred before insufflation of the intranasal treatment.

#### *Intranasal Administration*

Each subject will receive ~575 mg of intranasal material to insufflate. Subjects were required to intranasally administer the study drugs within 5 minutes of oral administration of the oral treatments.

Intranasal treatments were administered sequentially from 3 containers with straws preinserted to facilitate administration. To ensure blinding, given the difference in weights and particle size distribution between:

- CEP-33237 (~575 mg for a single 45-mg tablet)
- the API (~90 mg when 45 mg hydrocodone blended 50/50 with 45 mg lactose)
- Zohydro (~248 mg total weight for 45 mg hydrocodone from one 30-mg capsule plus one 15-mg capsule)

Table 9 (below) delineates the 5 treatments as presented to subjects.

**Table 9: Summary of Treatment Phase Study Conditions (Includes Amount of Hydrocodone (HC) in Parenthesis)**

Treatment Conditions	<u>Intranasal Treatments</u> (Each treatment = <b>45 mg dose of hydrocodone</b> from the specified product administered, contained in a <b>total volume of 575 mg of material</b> from 3 containers)			<u>Oral Treatments</u>
	Container 1	Container 2	Container 3	
<b>A (intranasal CEP-33237) (575 mg wt)</b>  (45 mg <u>total</u> HC)	90 mg of manipulated 45-mg CEP-33237 tablet  (7 mg HC)	158 mg of manipulated 45-mg CEP-33237 tablet  (12.4 mg HC)	327 mg of manipulated 45-mg CEP-33237 tablet  (25.6 mg HC)	1 intact CEP-33237 <b>placebo</b> tablet  (NONE)
<b>B (intranasal hydrocodone API) (45 mg total HC)</b>	45 mg <b>hydrocodone bitartrate API</b> plus ~45 mg lactose  (45 mg HC)	158 mg crushed sugar spheres <b>placebo</b>  (NONE)	327 mg lactose <b>placebo</b>  (NONE)	1 intact CEP-33237 <b>placebo</b> tablet  (NONE)
<b>C (oral CEP-33237) (45 mg total HC)</b>	90 mg crushed sugar spheres <b>placebo</b>  (NONE)	158 mg lactose <b>placebo</b>  (NONE)	327 mg crushed sugar spheres <b>placebo</b>  (NONE)	1 intact 45-mg CEP-33237 tablet  (45 mg HC)
<b>D (placebo) (NO HC)</b>	90 mg manipulated CEP-33237 <b>placebo</b> tablet  (NONE)	158 mg manipulated CEP-33237 <b>placebo</b> tablet  (NONE)	327 mg manipulated CEP-33237 <b>placebo</b> tablet  (NONE)	1 intact CEP-33237 <b>placebo</b> tablet  (NONE)
<b>E (intranasal hydrocodone ER capsules; Zohydro 248 mg wt) (45 mg total HC)</b>	90 mg of manipulated <b>Zohydro</b>  (16 mg HC)	158 mg of manipulated <b>Zohydro</b>  (29 mg HC)	327 mg lactose <b>placebo</b>  (NONE)	1 intact CEP-33237 <b>placebo</b> tablet  (NONE)

The intranasal treatments were administered sequentially in 3 containers.

Container 1 was always administered first so that administration of the primary active control would not be compromised in subjects who have difficulty managing the higher volume of containers 2 and 3.

Subjects were instructed to use one nostril to administer container 1 and the other nostril to administer containers 2 and 3. If the contents of container 3 could not be administered

in the same nostril, the subject was allowed to return to the first nostril to complete administration.

Intranasal administration was performed over a tray or piece of paper. The containers were inspected following intranasal administration by the subject. If any material remained in the bottle, the subject was asked to re-attempt administration. If any material inadvertently dropped (i.e., from the container, straw or subject's nose) during administration, it was collected, returned to the container and the subject was asked to re-attempt administration. If administration failed following the second attempt or if the subject refused to re-attempt administration, the remaining drug was carefully collected and returned to the container. The container was weighed before and after administration.

Subjects were not allowed to blow their nose for at least 1 hour post-dose. Any events of sneezing within 1 hour post-dose were recorded. Drug administration was performed under blue lighting to further mask any visual differences in study drugs/placebos, in case any drug inadvertently fell onto the tray/paper during dosing.

### *Blinding*

To ensure blinding, 3 different placebos were used; one to match CEP-33237 (manipulated CEP-33237 placebo tablet), one to match hydrocodone API (lactose) and one to match Zohydro (manipulated sugar spheres).

To ensure complete blinding of intranasal CEP-33237, placebo comprised 3 containers of manipulated CEP-33237 placebo tablet.

To ensure blinding of hydrocodone API and Zohydro, a combination of crushed sugar spheres and lactose placebo were administered in these periods, as well as the oral CEP-33237 period.

Since manipulated CEP-33237 placebo could affect the absorption of hydrocodone API and Zohydro and/or induce nasal irritation, it was administered in only one condition.

### *Hydrocodone Treatments*

The 4 active treatments in this study were administered at an equivalent hydrocodone bitartrate dose of 45 mg. The 45-mg dose is within the planned therapeutic dose range for CEP-33237 for two reasons:

- 1) This dose was administered orally (crushed and intact) in a previous human abuse potential study of nondependent recreational opioid users.
- 2) The weight of the 60-mg CEP-33237 tablets (1150 mg) is much greater than that of the 45-mg tablet (575 mg). Thus, use of the 60 mg tablet may be prohibitive for intranasal administration for some subjects.

Because hydrocodone is primarily available as low-dose combination products with acetaminophen or other active ingredients, hydrocodone bitartrate API was used as the primary active control. Due to the small volume and potential for material loss, hydrocodone bitartrate API was blended 50/50 with lactose for intranasal administration. Lactose is an excipient that is commonly used in opioid tablet formulations and was not expected to affect the absorption of hydrocodone.

Another extended-release hydrocodone product (Zohydro), which recently became commercially available, was also manipulated and used as a comparator. The Sponsor asserts that “because the abuse-deterrent characteristics of Zohydro are not fully known, this comparison was considered secondary.” Notably, Zohydro ER does not have an abuse-deterrent label claim.

Oral administration of intact CEP-33237 has also been included to provide a reference to help determine the clinical relevance of the reduced abuse potential observed with the manipulated CEP-33237. This study also provides pharmacokinetic data for an intra-subject comparison of the manipulated intranasal CEP-33237 relative to the intended route.

#### *Manipulation of Formulations*

The intranasal CEP-33237, intranasal placebo tablet, Zohydro, and the sugar spheres (Zohydro placebo) were comminuted with a rotary blade mill (Maxi-Matic Elite Mixer) to produce a fine powder suitable for nasal insufflation. The Sponsor states that selection of the Maxi-Matic Elite Mixer was based on results of the *in vitro* physical manipulation. Particle size distribution was a primary consideration for the intranasal liking study to ensure the selected method produced materials with a particle size appropriate for insufflation. The Sponsor states that their design goals for the manipulation procedure for intranasal dosing included 3 general considerations:

- “Physical properties: Milling results in a sufficiently fine particle size suitable for insufflation for both extended release products. However, inherent differences between the extended release formulations necessarily result in different particle size distribution (PSD) after manipulation. Milling Zohydro for just 10 seconds (pulsed) results in proportionally more particles finer than 300 µm than milling CEP-33237 for 30 seconds (pulsed). Zohydro (b) (4) are highly fracturable and are easily powdered with minimal manipulation. CEP-33237 tablets contain polymeric coated granule (b) (4) designed to exhibit elasticity and resist comminution. The use of matching placebos was employed for blinding purposes in part because closely matching the PSD of manipulated CEP-33237 to manipulated Zohydro was not feasible.

- “Drug release: The milling procedures for CEP-33237 and Zohydro challenge the extended release mechanisms of the formulations and are intended to generate high release of the opioid. Two *in vitro* tests were employed to assess the drug released after manipulation: simulated nasal insufflation to assess drug extracted into simulated nasal

fluid, and simulated ingestion conditions to assess release in the gastrointestinal tract (as may occur when nasally insufflated material is eventually cleared from the nasal passages by swallowing).

- “Clinical dose preparation: The milling procedure is a practical manipulation technique that maximizes opioid release reproducibly in a clinical setting. The technique is straightforward and not highly operator-dependent. It minimizes the loss of material during manipulation and transfer to the dose container, minimizes potential for cross contamination in the pharmacy, and minimizes the potential for pharmacy personnel exposure. The Sponsor considers the proposed method to manipulate CEP-33237 and Zohydro for nasal insufflation appropriate to provide a high rate of release that can be executed consistently and safely within the clinical trial setting.”

#### *Pharmacodynamic Variables*

All subjective endpoints were assessed at baseline, 0.25, 0.75, 1.25, 1.75, 2.5, 4, 6, 7, 8, 9, 10, 12, 24 hours after drug administration -- except for VAS for Overall Drug Liking, Take Drug Again, and Price Value Assessment, which were assessed at 24 hours (as well as 8 hours in the Qualification Phase). During the Treatment Phase, additional measurements were taken for the subjective measures at 36 and 48 hours after drug administration (except for VAS for Overall Drug Liking, Take Drug Again, and Price Value Assessment, which was also assessed only at 12 and 24 hours).

Questions from the ARCI were completed prior to study drug administration and at 1, 3, 6 and 24 hours. Ease of Snorting VAS was evaluated immediately after drug administration was completed. Pupil diameter measurements were completed prior to study drug administration and at 0.25, 0.5, 1, 1.5, 2, 4, 6, 8 and 24 hours after study drug administration in each period.

#### Primary Measure:

Drug Liking VAS (Emax)

#### Secondary Measures:

##### *Balance of effects:*

- Drug Liking VAS (Emax, Emin and TA\_AUE)
- Overall Drug Liking VAS (Emax, Emin; end-of-day and next day scores)
- Take Drug Again VAS (Emax; end-of-day and next day scores)
- Price Value Assessment (end-of-day and next day scores)

##### *Positive effects:*

- Good Effects VAS (Emax and TA\_AUE)
- ARCI MBG scale (Emax and TA\_AUE)

*Negative effects:*

- Bad Effects VAS (Emax and TA\_AUE)
- Nausea VAS (Emax and TA\_AUE)
- ARCI LSD scale (Emax and TA\_AUE)

*Sedative effects:*

- Alert/Drowsiness VAS (Emax and TA\_AUE)
- ARCI PCAG scale (Emax and TA\_AUE)

*Other drug effects:*

- Any Effects VAS (Emax and TA\_AUE)
- Ease of Snorting VAS (Emax and TA\_AUE)

*Objective Measures:*

- Pupillometry

*Safety Variables*

- Adverse events
- Clinical laboratory parameters
- Vital signs measurements
- ECG and physical examination findings
- SpO<sub>2</sub> monitoring
- Concomitant medication usage.

Blood samples were obtained for measurement of plasma concentrations of hydrocodone and hydromorphone prior to study drug administration (i.e., within approximately 60 minutes) and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 7, 8, 9, 10, 12, 24, 36, and 48 hours after the start of administration of the study drug.

## **Results**

### **Pharmacokinetics of Hydrocodone Conditions**

As shown in the Table 10 below, identical amounts of hydrocodone administered intranasally produced different pharmacokinetic responses, based on the formulation. Each of the intranasal formulations had 97-98% insufflation across subjects. The greatest C<sub>max</sub> value (80 ng/ml) was from crushed Zohydro. The next highest C<sub>max</sub> of 71 ng/ml was produced by hydrocodone powder (API; 45 mg). The lowest C<sub>max</sub> from the insufflated hydrocodone was 57 ng/ml, which was produced by crushed CEP-33237 (45 mg). All of the insufflated hydrocodone conditions produced plasma levels that were within similar ranges to each other. The oral hydrocodone condition (intact) produced the lowest C<sub>max</sub> value (25 ng/ml).

**Table 10: Drug Plasma Levels of Intranasal Placebo, API hydrocodone, Zohydro and CEP-33237 (IN and Oral) Based on Drug Amount Utilized**

Measure	Placebo N = 34	45 mg IN API N = 34	45 mg IN Zohydro N = 34	45 mg IN CEP-33237 N = 34	45 mg ORAL CEP-33237 N = 34
Percent Dose Insufflated	98% placebo	97% IN hydrocodone	98% IN hydrocodone	97% IN hydrocodone	100% ORAL hydrocodone
Cmax (ng/ml)	--	71 ± 31	80 ± 29	57 ± 15	25 ± 7
AUC (0-inf) (ng*hr/ml)	--	579 ± 163	639 ± 179	572 ± 150	568 ± 172

**Subjective Responses**

The subjective responses produced by the three treatment conditions reflect the plasma levels of hydrocodone produced by these conditions, as shown in the pharmacokinetic data above.

The order of plasma hydrocodone produced by each of these conditions was IN Zohydro > IN hydrocodone powder (API; immediate release) > IN crushed CEP-33237 > ORAL intact CEP-33237, which also reflects the order of subjective measures response, shown in the Table 11 below.

**Table 11: Effects of Intranasal Placebo, API hydrocodone, Zohydro and CEP-33237 (IN and Oral) on Subjective Measures (VAS and ARCI)**

Measure	Placebo N = 34	45 mg IN API N = 34	45 mg IN Zohydro N = 34	45 mg IN CEP-33237 N = 34	45 mg ORAL CEP-33237 N = 34
Drug Liking VAS bipolar	59 ± 2	80 ± 2	83 ± 2	73 ± 2	57 ± 2
Overall Drug Liking VAS bipolar	58 ± 2	77 ± 3	80 ± 3	69 ± 3	58 ± 3
Take Drug Again VAS	56 ± 12	76 ± 15	79 ± 17	68 ± 20	56 ± 14
PVAQ VAS (\$0.25-50.00)	3 ± 6	11 ± 8	13 ± 10	9 ± 8	3 ± 7
Good Drug Effects VAS	16 ± 23	59 ± 28	68 ± 24	44 ± 27	13 ± 23
ARCI-MGB Euphoria (0-16)	3.9 ± 3.4	7.1 ± 4.3	6.8 ± 4.2	6.3 ± 4.6	3.0 ± 2.5
Bad Drug Effects VAS	5 ± 10	15 ± 18	19 ± 24	23 ± 28	8 ± 14
Nausea VAS	4 ± 8	15 ± 22	16 ± 23	15 ± 23	6 ± 14
ARCI LSD Dysphoria (0-14)	4.2 ± 1.9	6.2 ± 2.5	6.3 ± 2.6	5.8 ± 2.6	3.8 ± 1.3
Any Drug Effect VAS	16 ± 22	61 ± 26	70 ± 23	48 ± 28	14 ± 20
Drowsy/Alert VAS bipolar	40 ± 15	27 ± 14	25 ± 14	33 ± 13	42 ± 12
ARCI PCAG Sedation	4.7 ± 2.7	7.9 ± 2.7	8.5 ± 3.1	7.5 ± 3.2	4.3 ± 2.5
Ease of Snorting VAS	32 ± 24	41 ± 25	36 ± 27	42 ± 27	29 ± 22
Burning VAS	1 ± 1	1 ± 1	2 ± 1	1 ± 1	1 ± 1
Need to Blow Nose VAS	1.6 ± 1.2	1.9 ± 1.1	2.0 ± 1.2	1.9 ± 1.2	1.4 ± 1.2
Runny Nose VAS	1.2 ± 1.0	1.7 ± 1.1	1.8 ± 1.1	1.1 ± 1.1	1.3 ± 1.2
Nasal Congestion (0-5)	1.9 ± 1.1	1.5 ± 1.1	1.7 ± 1.3	1.8 ± 1.3	1.3 ± 1.2
Facial Pain VAS	0.8 ± 1.1	1.0 ± 1.0	1.2 ± 1.2	1.1 ± 1.2	0.5 ± 1.0
Pupil Diameter (mm)	5.5 ± 0.8	3.3 ± 0.7	3.0 ± 0.5	3.4 ± 0.6	4.0 ± 0.8

### Statistical Analysis of Subjective Measures

The primary measure of Drug Liking was evaluated for statistically significant differences between CEP-33237, placebo and oxycodone by both the FDA Office of Biostatistics as well as by the Sponsor. However, a statistical evaluation of the secondary measures was only conducted by the Sponsor.

#### Drug Liking VAS (bipolar):

- Both positive control conditions, intranasal 45 mg hydrocodone API and intranasal 45 mg Zohydro, produced significantly higher Emax scores on Drug Liking compared to placebo ( $P < 0.0001$  for both). These two conditions were not statistically different from one another. These data show that intranasal hydrocodone in these two forms was significantly liked by subjects, which validates the study.
- Intranasal CEP-33237 (45 mg) produced Emax scores on Drug Liking that were significantly greater than placebo ( $P < 0.0001$ ). This response was statistically significantly lower than the responses to the API and to Zohydro ( $P < 0.004$ ), but only by 10 points or less.
- Oral CEP-33237 (45 mg) did not produce an Emax score on Drug Liking that was significantly different than placebo ( $P = 0.22$ ). This is likely due to the fact that Cmax levels of hydrocodone following oral administration was 1/3 to 1/2 that produced by intranasal administration of hydrocodone. Thus, while 45 mg of CEP-33237 in oral form was not liked by subjects, the same dose of CEP-33237 was liked when utilized intranasally.

#### Overall Drug Liking VAS:

- Both positive control conditions, intranasal 45 mg hydrocodone API and intranasal 45 mg Zohydro, produced significantly higher Emax scores on Overall Drug Liking compared to placebo ( $P < 0.0001$  for both). These two conditions were not statistically different from one another. These data show that intranasal hydrocodone in these two forms was significantly liked by subjects, which validates the study.
- Intranasal CEP-33237 (45 mg) produced Emax scores on Drug Liking that were significantly greater than placebo ( $P < 0.0014$ ). This response was statistically significantly lower than the response to the API and to Zohydro ( $P < 0.004$ ).
- Oral CEP-33237 (45 mg) did not produce an Emax score on Drug Liking that was significantly different than placebo ( $P = 0.84$ ). As noted above, this is likely due to the fact that Cmax levels of hydrocodone following oral administration was 1/3 to 1/2 that produced by intranasal administration of hydrocodone. Thus, while 45 mg of CEP-33237 in oral form was not liked by subjects, the same dose of CEP-33237 was liked when utilized intranasally.

Take Drug Again VAS:

- All three intranasal hydrocodone conditions (API, Zohydro and CEP-33237) produced a statistically significant increase in desire to Take Drug Again compared to placebo ( $P < 0.001$ ). However, intranasal CEP-33237 produced a statistically lower score than API or Zohydro ( $P < 0.005$ ). Oral CEP-33237 was numerically indistinguishable from placebo but was not assessed statistically by the Sponsor. However, oral CEP-33237 was significantly lower on Take Drug Again compared to intranasal CEP-33237 ( $P < 0.001$ ).

PVAQ (Price Value Assessment Questionnaire):

- All three intranasal hydrocodone conditions (API, Zohydro and CEP-33237) produced a statistically significant increase in the subjective monetary value of the drug compared to placebo ( $P < 0.0001$ ). There was no statistical difference between API and Zohydro. However, intranasal CEP-33237 produced a statistically lower score than API or Zohydro ( $P < 0.03-0.0002$ ). Oral CEP-33237 was numerically indistinguishable from placebo but was not assessed statistically by the Sponsor. However, oral CEP-33237 produced a statistically significantly lower monetary value compared to intranasal CEP-33237 ( $P < 0.001$ ).

Good Drug Effects VAS:

- All three intranasal hydrocodone conditions (API, Zohydro and CEP-33237) produced a statistically significant increase in the Good Drug Effects compared to placebo ( $P < 0.0001$ ). There was no statistical difference between API and Zohydro ( $P > 0.05$ ). However, intranasal CEP-33237 produced a statistically lower score than API or Zohydro ( $P < 0.0001$ ). Oral CEP-33237 was numerically similar to placebo but was not assessed statistically by the Sponsor. However, oral CEP-33237 produced a statistically significantly lower Good Drug Effects score compared to intranasal CEP-33237 ( $P < 0.001$ ).

ARCI – MBG (Euphoria):

- All three intranasal hydrocodone conditions (API, Zohydro and CEP-33237) produced a statistically significant increase in the Good Drug Effects compared to placebo ( $P < 0.0006$ ). There was no statistical difference between API, Zohydro or intranasal CEP-33237 ( $P > 0.05$ ). Oral CEP-33237 was numerically similar to placebo but was not assessed statistically by the Sponsor. However, oral CEP-33237 produced a statistically significantly lower MBG score compared to intranasal CEP-33237 ( $P < 0.0001$ ).

Bad Effects VAS:

- All three intranasal hydrocodone conditions (API, Zohydro and intranasal CEP-33237) produced a statistically significant increase in the Bad Drug Effects compared to placebo ( $P < 0.0001$ ). There was no statistical difference between API and either Zohydro or intranasal CEP-33237. However, intranasal CEP-33237 produced a statistically lower score than API ( $P < 0.0001$ ). Oral CEP-33237 was numerically similar to placebo but was not assessed statistically by the

Sponsor. However, oral CEP-33237 produced a statistically significantly lower Bad Drug Effects score compared to intranasal CEP-33237 ( $P<0.0001$ ).

#### Nausea VAS

- All three intranasal hydrocodone conditions (API, Zohydro and CEP-33237) produced a statistically significant increase in the Nausea compared to placebo ( $P<0.01$ ). There was no statistical difference between API, Zohydro or intranasal CEP-33237. Oral CEP-33237 was numerically similar to placebo, but was not assessed statistically by the Sponsor. However, oral CEP-33237 produced a statistically significantly lower Nausea score compared to intranasal CEP-33237 ( $P<0.0002$ ).

#### Any Drug Effects VAS:

- All three intranasal hydrocodone conditions (API, Zohydro and CEP-33237) produced a statistically significant increase in the Any Drug Effects compared to placebo ( $P<0.001$ ). There was no statistical difference between API and Zohydro. However, intranasal CEP-33237 produced a statistically lower score than API or Zohydro ( $P<0.001$ ). Oral CEP-33237 was numerically similar to placebo but was not assessed statistically by the Sponsor. However, oral CEP-33237 produced a statistically significantly lower Any Drug Effects score compared to intranasal CEP-33237 ( $P<0.001$ ).

#### Alertness/Drowsiness VAS:

- All three intranasal hydrocodone conditions (API, Zohydro and intranasal CEP-33237) produced a statistically significant increase in the Drowsiness compared to placebo ( $P<0.005$ ). There was no statistical difference between API and either Zohydro or intranasal CEP-33237 in Drowsiness. However, intranasal CEP-33237 produced greater Drowsiness compared to Zohydro ( $P<0.006$ ). Oral CEP-33237 was numerically similar to placebo but was not assessed statistically by the Sponsor. However, oral CEP-33237 produced a statistically significantly lower Drowsiness score compared to intranasal CEP-33237 ( $P<0.002$ ).

#### ARCI – PCAG (Sedation):

- All three intranasal hydrocodone conditions (API, Zohydro and intranasal CEP-33237) produced a statistically significant increase in the Sedation compared to placebo ( $P<0.0001$ ). There was no statistical difference between API and either Zohydro or intranasal CEP-33237 in Sedation. However, intranasal CEP-33237 produced greater Sedation compared to Zohydro ( $P<0.04$ ). Oral CEP-33237 was numerically similar to placebo but was not assessed statistically by the Sponsor. However, oral CEP-33237 produced a statistically significantly lower Sedation score compared to intranasal CEP-33237 ( $P<0.0001$ ).

#### Pupil Diameter

- All three intranasal hydrocodone conditions (API, Zohydro and intranasal CEP-33237) produced a statistically significant decrease in the pupil diameter compared to placebo ( $P<0.01$ ). Zohydro produced the largest miosis, which was

statistically significantly different than API or intranasal CEP-33237. Oral CEP-33237 was numerically similar to placebo but was not assessed statistically by the Sponsor. However, oral CEP-33237 produced a statistically significantly less miosis compared to intranasal CEP-33237 ( $P < 0.001$ ).

### ***Conclusions about Subjective Measures in Response to Hydrocodone Conditions***

- The intranasal human abuse potential study was validated by both API and Zohydro producing a statistically significant increase on the primary measure of Drug Liking compared to placebo.
- For all of the positive subjective measures (Overall Drug Liking, Take Drug Again, Drug Value, Good Drug Effects and Euphoria), the intranasal drug conditions (API, Zohydro and CEP-33237) produced increases that were statistically significantly greater than placebo. In contrast, oral CEP-33237 was typically indistinguishable statistically from placebo. The order of response on the positive subjective measures was typically: API = Zohydro > IN CEP-33237 > Oral CEP-33237  $\geq$  placebo.
- For the negative and sedative subjective measures (Bad Drug Effects, Nausea, Sedation and Drowsiness), the intranasal drug conditions (API, Zohydro and CEP-33237) produced increases that were statistically significantly greater than placebo. In contrast, oral CEP-33237 was typically indistinguishable statistically from placebo. The order of response was typically: API = Zohydro = IN CEP-33237 > Oral CEP-33237 = placebo.
- Scores on all subjective scales (as described above) paralleled peak plasma concentrations ( $C_{max}$  values) of hydrocodone produced by each drug condition, suggesting a close correlation between drug levels and drug response. The order of  $C_{max}$  and AUC hydrocodone levels were typically: API = Zohydro = IN CEP-33237 > Oral CEP-33237 = placebo.

Thus, intranasal use of crushed CEP-33237 produced a clear abuse potential signal that was greater than that produced by oral CEP-33237 and placebo but less than that produced by hydrocodone powder or crushed hydrocodone as formulated in Zohydro.

### ***Abuse-Related Adverse Events***

Similar to the response on subjective measures described above, the likelihood of the occurrence of adverse events during the Treatment Phase was correlated with peak plasma concentrations ( $C_{max}$  values) of hydrocodone produced by each drug condition. Intranasal API and Zohydro produced the greatest plasma concentrations of hydrocodone and subsequently produced the largest degree of AEs. Oral CEP-33237 produced the lowest hydrocodone plasma values, which was 1/3 to 1/2 that of the other conditions – and produced the lowest degree of AEs (similar to that of placebo). Intranasal CEP-33237 produced both intermediate plasma levels of hydrocodone as well as intermediate

reporting of AEs. The most common treatment related adverse events (those occurring with an incidence of more than 10% of subjects) were as follows:

- Intranasal hydrocodone API produced a high degree of nausea (18%) and pruritis (18%)
- Intranasal Zohydro produced pruritis (24%), vomiting (24%), nausea (17%), and euphoric mood (12%)
- Intranasal CEP-33237 produced nausea (24%), headache (17%), vomiting (17%), and pruritis (14%)

No adverse events occurred in more than 10% of subjects following administration of placebo or oral intact CEP-33237.

In general, during Phase C of the study, the types of AEs were similar overall following administration of intranasal hydrocodone API, intranasal finely milled CEP-33237, intranasal finely milled Zohydro ER, and oral intact CEP-33237 and consistent with opioid pharmacology (see Table 12, below). However, the overall incidence of AEs was highest in subjects following administration of intranasal Zohydro ER, similar between intranasal hydrocodone API and intranasal CEP-33237, and lowest following administration of placebo and oral intact CEP-33237.

**Table 12: Adverse Events Following Administration of Intranasal Placebo, API hydrocodone, Zohydro and CEP-33237 (IN and Oral)**

Measure	Placebo N = 34	45 mg IN API N = 34	45 mg IN Zohydro N = 34	45 mg IN CEP-33237 N = 34	45 mg ORAL CEP-33237 N = 34
Nausea	2 (5%)	7 (18%)	7 (17%)	10 (24%)	2 (5%)
Vomiting	1 (3%)	4 (10%)	10 (24%)	7 (17%)	1 (3%)
Euphoria	2 (5%)	1 (3%)	5 (12%)	3 (7%)	0
Pruritus	0	7 (18%)	10 (24%)	3 (7%)	1 (3%)

**D. Physical Dependence Evaluation (Study #3103)**

This was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, randomized withdrawal study to assess the efficacy and safety of CEP-33237 in patients with moderate to severe chronic low back pain who require continuous opioid treatment for an extended period of time. During the study, an evaluation of withdrawal signs and symptoms was conducted during periods of drug reduction.

Patients were initially titrated in a Run-Up phase for 6 weeks to a dose of CEP-33237 that produced adequate analgesia for each individual. The initial dose of CEP-33237 for opioid-naïve patients was 15 mg and for opioid-experience patients was a dose of CEP-33237 that was equivalent to the 50% of the opioid dose they had been taking prior to the study. After the initial exposure, patients were titrated up to doses of CEP-33237 that produced adequate analgesia, ranging from 30 to 90 mg every 12 hours as needed. Rescue medication of 10 mg of hydrocodone/650 mg of acetaminophen per day was allowed.

At the conclusion of the Run-Up phase, patients were then randomized to receive either CEP-33237 (at the dose that provided adequate analgesia) (n = 191) or placebo (n = 180) for 12 weeks during the Treatment Phase. During the first two weeks, all patients had their drug dose tapered to reduce the risk of withdrawal responses in patients who would receive placebo. In the first week, patients received half of the dose of CEP-33237 administered during the Run-Up phase. In the second week, they received 15 mg/day of CEP-33237. From Weeks 3-12, patients in the CEP-33237 group were titrated back up to the twice-daily dose of CEP-33237 that provided adequate analgesia during the Run-Up phase, while patients in the placebo group received placebo. Notably, rescue medication of 60 mg of hydrocodone/3900 mg of acetaminophen per day was allowed during the Treatment Phase.

During all phases of the study, the Clinical Opiate Withdrawal Scale (COWS) and the Subjective Opiate Withdrawal Scale (SOWS) were used to evaluate withdrawal responses.

The Sponsor claims that the COWS and SOWS data demonstrate that CEP-33237 was not associated with withdrawal signs and symptoms. However, the design of this study was not sufficiently standardized in order to evaluate this issue.

The primary design flaw with the study is that patients were allowed up to 60 mg/day of immediate-release hydrocodone as rescue medication. This negates the ability to determine whether CEP-33237 was responsible for any observed withdrawal responses during the study. Additionally, such a high daily dose of IR hydrocodone might have prevented the appearance of withdrawal during periods of CEP-33237 discontinuation. This design element by itself invalidates the study as a means of evaluating physical dependence associated with CEP-33237.

However, other design elements also prevent this study from being utilized to determine the nature of a CEP-33237-associated withdrawal syndrome, such as:

- The doses that patients received were individualized to their specific analgesic needs. Doses could change throughout the study, based on changing responsivity and medical advice. Thus, doses were not inherently stable enough to determine if there was a dose-response relationship with any withdrawal signs or symptoms.

- Patients could be either opioid-naïve or opioid-experienced prior to participation in the Run-Up phase. This might play a role in the ability of an individual patient to tolerate or respond to opioid treatment and subsequent drug discontinuation.
- The COWS and SOWS withdrawal data are provided in both individual and summarized forms, but are not associated with any information about the dose of CEP-33237 that patients were taking during the study or, more specifically, when drug discontinuation occurred.

### **Evaluation of CEP-33237 Diversion During Clinical Studies**

#### *Summary for Study #3079 and #3080*

In both studies, study drug loss and diversion were recorded. The overall rate of study drug loss was < 9% for Study #3079, and 11% for Study #3080. Most occurrences for study drug loss with either CEP-33237 or rescue medication was for 10 or fewer tablets. The overall rate of possible diversion of study drug was 1% in the 12-week study (Study #3079) and 2% in the 12-month study (Study #3080).

However, the Sponsor notes that more patients reported diversion of rescue medication than CEP-33237 tablets in Study #3079 (3 rescue; 1 CEP-33237) and in Study #3080 (4 rescue; 3 CEP-33237; 1 patient had both stolen).

#### *Summary for Study #3103 and Study #3104*

In both studies, study drug loss and diversion were recorded.

The overall rate of study drug loss was approximately 3% in Study #3103 with CEP-33237 being lost by more patients than either rescue medication or placebo. There was no study drug loss reported in Study #3104.

The overall rate of diversion of study drug was < 2% in the 12-week study (Study #3103) and <1% in the 6-month study (Study #3104). In Study #3103, 5 patients diverted CEP-33237, 4 patients diverted rescue medication (hydrocodone/ acetaminophen IR tablets), and 2 patients diverted both medications. In Study #3104, one patient diverted both CEP-33237 and rescue medication.

Appendix 1- CMC Review as finalized on August 18, 2015

**CMC Review for NDA 207975 – Abuse Deterrence studies**  
(Category 1 Laboratory Manipulation and Extraction Studies)

REVIEW NO.: 1

DATE OF REVIEW: June 30, 2015.

PROPRIETARY NAME: **Vantrela ER™ Tablets**

ALTERNATE NAMES / CODES USED: CEP-33237 (ALO-02)

GENERIC NAME: Hydrocodone Bitartrate Extended Release Tablets.

SPONSOR: Teva Branded Pharmaceutical Products R&D, Inc

DOSAGE STRENGTH(S): 15 mg, 30 mg, 45 mg, 60 mg and 90 mg.

PRIMARY CMC / QUALITY REVIEWER: Christopher Hough, Ph. D;

IN VITRO ABUSE-DETERRENT STUDIES REVIEWER:

Venkateswara Pavuluri, Ph. D., R. Ph.

Branch Chief, ONDP Division II, Branch IV: Julia Pinto, Ph. D;

Quality Assessment Lead: Ciby, Abraham, Ph. D;

**Summary:**

According to the sponsor, Vantrela ER™ Tablets (Hydrocodone bitartrate extended-release tablets) can deter abuse when subjected to physical manipulations. The sponsor performs the following category 1 laboratory-based in vitro manipulation and extraction studies:

- I. Physical manipulation tool assessment using a variety of household tools, i.e. cutting, crushing, grinding of tablets. Planned physical manipulations were also performed on tablets subjected to heating and frozen conditions prior to manipulation. In vitro dissolution studies using simulated gastric fluid were conducted on manipulated drug products to compare the effectiveness of various manipulation tools.
- II. Simple chemical manipulations include extraction of crushed or ground tablets into solutions representing common household products, e.g. water, aqueous solutions of pH 2 and 8, 20 % and 40 % ethanol for direct oral ingestion.
- III. Extractions using various organic solvents e.g. methanol, isopropyl alcohol, acetone, ethyl acetate etc. for isolation of solid drug substance
- IV. Multiple-step extractions carried out on physically manipulated tablets to assess the extraction efficiency and purity of isolated drug substance using acid/base, polar, non-polar and aromatic organic solvents, under various experimental conditions.

Following overall conclusions were based on review of study results for the above category 1 laboratory-based in vitro manipulation and extraction studies, comparing with either the pure drug substance or one of the two marketed products (Zohydro<sup>(R)</sup> ER tablets and immediate release combination product Vicoprofen<sup>®</sup> tablets).

The proposed drug product, Vantrela ER™ Tablets (Hydrocodone bitartrate extended release tablets) is

1. More resistant to abuse by inhalation /insufflation (simulated nasal fluid extraction studies) and injection (small volume aqueous extraction studies) when compared to Zohydro ER.
2. Less susceptible to large volume extractions using aqueous media of varying pH when compared to immediate release Vicoprofen<sup>®</sup>.
3. Susceptible to simple solvent and complex liquid/liquid extractions comparable to Zohydro ER, more so upon physical manipulation, for separation of drug substance and/or preparation of concoctions by methodical abusers.
4. Able to reduce the susceptibility of extended release properties to an extent comparable to Zohydro<sup>®</sup> ER, when subjected to physical manipulation followed by simulated oral ingestion and dose dumping studies in presence of alcohol up to 40 % v/v, retaining extended-release properties to some extent.

Overall, the drug product under review has superior abuse-deterrence properties when compared to immediate release combination product Vicoprofen<sup>®</sup> tablets, and has comparable or better resistance to manipulation than Zohydro<sup>®</sup> ER, depending on the mode of abuse. Vantrela ER<sup>™</sup> tablets demonstrated better resistance for abuse by inhalation and injection routes, but data submitted by sponsor is not sufficient to establish any significant abuse-deterrence by oral route or its superiority over approved drug product with Hydrocodone Bitartrate as single ingredient in extended-release form, Zohydro<sup>®</sup> ER. Thus the superiority of Vantrela ER<sup>™</sup> tablets over Zohydro<sup>®</sup> ER capsules for abuse-deterrence by oral route of administration or solvent extraction following physical manipulation, can't be established at this time.

## Review of Category 1 Laboratory based Abuse Deterrence studies

### Introduction

The scope of this review is for the evaluation of category 1 laboratory-based *in vitro* experiments, consisting of physical and chemical manipulation of the tablets. The review includes a brief discussion on i) physico-chemical properties of hydrocodone bitartrate and functional excipients used in the formulation to confer extended-release properties and resistance to manipulation/abuse of the drug product and ii) properties of intact and manipulated drug product(s) pertinent to abuse-deterrence testing protocols and test reports included by the sponsor. Suitability of analytical methods and dissolution media used for demonstrating the resistance of intact or manipulated drug product to dose dumping (abuse-deterrence) is reviewed by the CMC drug product reviewer and the Biopharmaceutics reviewer. Comparative evaluation on the relevance /adequacy of the physical and chemical manipulations, and simulation methods used by sponsor to determine the abuse-deterrence to those commonly used by abusers are evaluated by Controlled Substance Staff (CSS).

### Overview of in vitro Abuse-deterrent studies conducted by Sponsor

Several premarket studies were conducted by the sponsor under categories 1, 2 and 3 of the FDA's Draft Guidance for Industry 'Abuse-Deterrent Opioids - Evaluation and Labeling'. The category 1 abuse-deterrent studies are based on in vitro characterization of Hydrocodone Bitartrate extracted from Vantrela™ ER tablets by using various manipulations /tampering techniques, in comparison with two marketed products. The two marketed products selected for comparison are Zohydro® ER (hydrocodone) 50 mg capsules, and Vicoprofen® IR tablets, 7.5 mg / 200 mg hydrocodone/ ibuprofen.

A list of all executed in vitro manipulation protocols, originally submitted by sponsor to the IND 105587 application, with Type B pre-NDA meeting materials (15 September 2011, in sequence 0047) and additional in vitro characterization studies as requested by the Agency (FDA) at Type C (23 January 2014) and Type B pre-NDA (23 July 2014) meetings were consolidate in a table and submitted under section 3.2.P.2.

Study Type	Brief Description	Products Studied <sup>a</sup>
Simulated Oral Ingestion	In vitro dissolution (USP 2, 50 rpm, 37°C) in simulated gastric fluid to simulate ingestion, 500 mL or 900 mL. Heated (150°C) and frozen (-20°C) CEP-33237 were also included.	CEP-33237 ZOHYDRO ER Vicoprofen Hydrocodone Bitartrate drug substance
Particle Size Distribution	Particle size distributions of manipulated materials were characterized by sieve analysis with six screens of mesh sizes ranging from 106 µm to 850 µm. Heated (150°C) and frozen (-20°C) CEP-33237 were also included.	CEP-33237 ZOHYDRO ER
Simulated Nasal Insufflation	Extraction into simulated nasal fluid at 37°C, 10 mL. Heated (150°C) and frozen (-20°C) CEP-33237 were also included.	CEP-33237 ZOHYDRO ER Vicoprofen Hydrocodone Bitartrate drug substance

Simulated Intravenous Extraction	Extraction for simulated intravenous (IV) injection, with physical assessment of the feasibility of IV abuse by syringeability and injectability tests (functional tests for viscosity). Per FDA's request, IV extraction experiments included both intact and comminuted tablets and employed multiple pH media (water, pH 6.3 and pH 10.3 buffers), 5 or 10 mL extraction volume.	CEP-33237 ZOHYDRO ER Hydrocodone Bitartrate drug substance
Simple Aqueous Extractions for Ingestion	Simple chemical extractions into 30 mL of solutions that could be directly ingested after extraction, represented by water, pH 2 and pH 8 buffers, 20% ethanol and 40% ethanol solution. Temperatures from ambient to 100°C were explored.	CEP-33237 ZOHYDRO ER Vicoprofen Hydrocodone Bitartrate drug substance
Simple Organic Solvent Extractions	Simple chemical extractions into common organic solvents, represented by methanol, isopropanol, acetone, ethyl acetate, and methylene chloride. After removal of the solvent, the isolated solid residues were characterized for hydrocodone content and purity.	CEP-33237 ZOHYDRO ER Hydrocodone Bitartrate drug substance
Multiple-Step Extractions	Multiple-step, acid/base liquid/liquid extractions to simulate tampering that may be performed by the most sophisticated abusers to attempt isolation of the opioid free base from the excipients. The residual solids obtained were characterized for hydrocodone content and purity.	CEP-33237 ZOHYDRO ER Hydrocodone Bitartrate drug substance

a Note that that CEP-33237 and applicable comparators were studied under the conditions indicated in the referenced summary tables (column 4 above)

Results of category 1 in vitro studies for demonstrating abuse-deterrence of the new Hydrocodone Bitartrate extended release tablets, (Vantrela™ ER) in comparison with the two marketed products, along with details of manipulation equipment selection experiments (multiple (b) (4) protocols and results of the in-vitro manipulation studies) were also included in section 3.2.P.2.2. The titles for various major studies submitted by sponsor are as follows:

- In vitro abuse potential comprehensive high level summary
- Teva Study Report: Tools Selection for Physical Manipulations
- Teva Study Report: Simulated Ingestion Studies
- Teva Study Report: Particle Size Distribution
- Teva Study Report: Simulated Nasal Fluid Extraction Studies
- Teva Study Report: Simulated Intravenous Manipulation and Small Volume Extraction Studies
- Teva Study Report: Larger Volume Extractions

An overall summary of the study results from the Category 1 in vitro manipulation studies was included in section 1.11.4 as a document titled "Abuse Deterrence Assessment". The in vitro studies designed for challenging the controlled release and abuse-deterrent properties of Vantrela™ ER tablets were separated in to sub-sections. These are a) Physical manipulations, b) Simulated oral ingestion (in vitro dissolution) c) Simulated nasal insufflation (in vitro dissolution in simulated nasal fluid) studies, d) Simulated intravenous injection, accompanied by assessments

on injectability and syringability, e) Large volume extractions, using various aqueous media and single organic solvents and f) Multi-step liquid/liquid chemical extractions.

**Physicochemical Properties of Hydrocodone Bitartrate and Functional Excipients**

Solubility of Hydrocodone Bitartrate (HCBT): Soluble in water; slightly soluble in alcohol; insoluble in ether and in chloroform. (Source: USP/NF accessed online Dt. 4/10/2015). Sparingly soluble in methanol, slightly soluble in acetone and insoluble in hexane (Source: <http://www.swgdrug.org/Monographs/HYDROCODONE.pdf> accessed on 4/28/2015).

Solubility and other relevant properties of functional excipient(s): Information derived from Handbook of Pharmaceutical Excipients, eBook accessed online Dt. 4/3/2015



(b) (4)

**Composition and Properties of the Drug Product**

All five dose strengths of Hydrocodone Bitartrate extended-release tablets, 15 mg, 30 mg, 45 mg, 60 mg and 90 mg were prepared (b) (4)

(b) (4). However each dose was differentiated by the (b) (4). The proposed composition of extended-release tablets is intended to provide release of drug over an extended period of time while limiting dose dumping when tablets are physically manipulated or ingested with alcohol, and to prevent rapid release of drug when the manipulated dosage form (powder) is ingested or administered via nasal insufflation or subjected to small volume extraction in preparations for intravenous injection.

**Table 2: Quantitative Composition of Hydrocodone Bitartrate Extended Release Tablets 15 mg, 30 mg, 45 mg, 60 mg and 90 mg**

Component	Reference to standard	Function	mg /tablet				
			15 mg tablet	30 mg tablet	45 mg tablet	60 mg tablet	90 mg tablet
Hydrocodone bitartrate (b) (4)	USP	Active Ingredient	15.00	30.00	45.00	60.00	90.00
Lactose monohydrate (b) (4)	NF	(b) (4)	(b) (4)				

Ethyl cellulose (b) (4)	NF	(b) (4)				
Hypermellose (b) (4)	USP					
Glyceryl behenate	NF					
Magnesium stearate, (b) (4)	NF					
(b) (4) (Varies for each strength)	various					
<b>Total weight / Tablet</b>		575	575	575	1150	1150

The sponsor developed the drug product utilizing a combination of release controlling materials to obtain desired extended release profiles suitable for twice daily dosing regimen under normal conditions and to resist misuse or abuse by physical or chemical manipulation. According to sponsor's submission, (b) (4) formulation technology was used in development of the Hydrocodone bitartrate extended-release tablets. Following are the three major processing steps involved in manufacturing of the drug product

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According to the sponsor, (b) (4) are critical for reducing the susceptibility of the drug product to physical manipulations and dose dumping in presence of ethanol that may occur during accidental misuse and intentional manipulation.

**Reviewer Comment on Small volume Extractions** Considering the physico-chemical properties of and functional excipients used together with the manufacturing process described above, the drug product is likely to release hydrocodone bitartrate over an extended period and resist rapid extraction into small volume of aqueous media, either from intact or manipulated tablets. The coating of Hydrocodone (b) (4) granules with a (b) (4) polymer, (b) (4) prevents rapid release of hydrocodone from (b) (4) granules and the tablets. (b) (4) resists rapid extraction of hydrocodone in to small volumes of aqueous media from physically manipulated drug product, due to (b) (4). Thus the proposed composition and properties of the drug product

may resist small volume extractions using water or other aqueous media, i.e. simulating abuse by insufflation and injection (syringeability and injectability studies) of proposed drug product.

***Reviewer Comment on large volume and Solvent Extractions:*** Hydrocodone bitartrate is soluble in water and slightly soluble in alcohol. (b) (4)

(b) (4)

may not confer any barrier (b) (4) and thus may not be effective in preventing drug release from manipulated drug product. Thus hydrocodone bitartrate may be extracted from physically manipulated drug product by methodical abusers, by following a series of extraction and isolation steps as described below.

- a) Extraction of physically manipulated drug with pure ethanol (95%, 190 proof) under hot conditions, facilitating dissolution of hydrocodone, (b) (4) and fraction of (b) (4).
- b) Separation of suspended (b) (4) from the hot alcohol extract by filtration.
- c) Separation of (b) (4) from the hot alcohol extract, by precipitation with gradual addition of hot water maintained at temperatures just above 60°C.
- d) Separation of (b) (4) by phase separation and/or solidification, upon cooling the mixture, leaving the drug in hydro alcoholic solution which is suitable for oral consumption (abuse).

Following sponsor's statements also supports the above assumption.

*Start of sponsor material*

“Unlike some abuse deterrent products with physical barriers, the CEP-33237 tablet itself is not exceptionally hard and is not intended to be physically difficult to manipulate. As previously described, hydrocodone bitartrate is contained within coated (b) (4) granules, and the coated (b) (4) granules are (b) (4) gel-forming polymer in the tablet matrix. The (b) (4) polymers in the (b) (4) granule control drug release and provide mechanical resistance to limit damage to the (b) (4) granule when a tablet is manipulated. The drug release rate from manipulated tablets is expected to increase as a function of physical damage to the coated (b) (4).”

*“Simple and multiple-step chemical extractions may be used to extract the majority of a dose for methodical abusers willing to invest time to defeat the release controlling mechanism prior to each use. However, doing so required significant time and effort and these techniques did not result in the extraction of a pure opioid drug substance.”*

*End of sponsor material*

### **Evaluation of Physical Manipulation Tools and in vitro Characterization Studies**

Physical manipulation experiments were conducted on Hydrocodone extended-release tablets stored at ambient, heated, and frozen conditions to simulate common forms of manipulation of opioid medications. Resultant powders were characterized by particle size distribution, in vitro dissolution in simulated gastric fluid, extraction into simulated nasal fluid, and small volume extraction for simulated intravenous injection. Assessment of the feasibility of abuse by intravenous injection was simulated by syringeability and injectability tests, and assay of the

small volume extracts for content of drug substance when feasible. Different controls were used for comparison during each type of in vitro study conducted on the drug product:

- Hydrocodone bitartrate drug substance for all extraction experiment
- VICOPROFEN<sup>®</sup> (AbbVie) tablets (Immediate-release, containing 7.5 mg hydrocodone bitartrate and 200 mg ibuprofen) for simulated oral ingestion, simulated insufflation, and simple chemical extraction (pH 2 and 8 buffers) tests after manipulation (two Vicoprofen<sup>®</sup> tablets were used simultaneously to represent a 15 mg hydrocodone dose).
- Zohydro ER tablets were used for additional studies requested by FDA.

The HPLC method is same as the method used for quantitation of the released drug during in vitro dissolution studies from finished drug product. The results presented are mean values for six replicates (with a few exceptions) for study product and three replicated for reference products; and are expressed both as percent of extracted from one dose unit and absolute mass of drug extracted. Much of the in vitro manipulation data for the 15-, 30-, and 45-mg strengths was obtained on development lots containing coated (b) (4) granule (b) (4), while all data for the 60-mg and 90-mg tablets were obtained on tablets with a (b) (4) coated (b) (4), representing the to-be-marketed formulation.

**Physical Manipulations – Feasibility Assessment:** Initial manipulation tool selection and feasibility assessment was performed by (b) (4) (for CIMA Labs) for physical manipulation of tablets from among the several household and pharmacy tools that could potentially be employed for manipulation. The selected manipulation tools include hammer, mortar and pestle, coffee mill and PediPaws as representative of the linear crushing, grinding, rotary cutting, and rotary abrasion mechanisms respectively. The physically manipulated drug product, Vantrela<sup>™</sup> tablets and the comparator Vicoprofen<sup>®</sup> immediate release were used for laboratory based characterization studies and in vitro abuse-deterrence assessment.

**Particle size distribution:** PSD was measured after manipulation using various tools. Coffee mill manipulation had resulted in more large particles (> 850 µm) and fewer fine particles (< 106 µm) than after tablet manipulation using Powder crusher (15 seconds) and EZYDose crusher. The resulting manipulated drug products were subjected to in vitro drug release study to evaluate the abuse-deterrent properties of drug product upon tampering with various tools, using simulated Gastric fluid without enzymes, or 0.1 N HCl. No direct correlations were found between PSD and drug release rate across the tools tested.

#### **Simulated Oral Ingestion Studies:**

**Effect Manipulation Tool on Drug Release:** In vitro dissolution studies on manipulated tablets resulted in release of drug ranging from 32% to 53% at 120 minutes compared to 11% drug released from intact Vantrela<sup>™</sup> tablets. The cumulative drug release from split tablets was stated to be comparable to intact tablets during initial time points with a gradual increase towards the end of the six hour study. Manipulation by rotary abrasion method (simulating intended abuse) resulted in highest extraction efficiencies among the other manipulation tools used, e.g. 80% release (rotary abrasion tool) compared to the ~20% release from intact and split tablets (accidental / unintended misuse) at 120 minutes for 15 mg dose strength. Among the various dose strengths subjected to manipulation by rotary abrasion, about 74% cumulative drug release was observed in 60 minutes for the 15-mg strength and 39% cumulative drug release in 60 minutes for the 90-mg strength. Vicoprofen<sup>®</sup> drug release values were ≥ 92% within 15 minutes for every tool used.

***The effect of temperature extremes on formulated tablets:*** This was investigated by freezing tablets at about –20°C for 24 hours or heating them to 150°C for 30 minutes before manipulation. While freezing has no impact on the release rate of hydrocodone relative to tablets maintained at room temperature, it was reported that heating of tablets before manipulation resulted in changes in release rate of hydrocodone in some cases, i.e. the release rate for 60 and 90 mg strengths increased upon pre-heating to 150°C for 30 minutes.

***Comparison of Manipulated Vantrela™ tablets with Manipulated Zohydro ER:*** Zohydro® ER capsule, 50 mg containing coated beads of Hydrocodone Bitartrate became commercially available after completion of initially comparative studies with Vicoprofen® tablets. Zohydro® ER did not exhibit comparable resistance to that of Vantrela™ tablets, when subjected to simulated oral ingestion (drug release) studies after manipulation with three different tools. More than 70 % extraction observed for Zohydro® ER after 15 minutes compared to the < 10 % extraction from Vantrela™ tablets.

***Reviewer Evaluation:*** The selected tools represent the mechanisms of crushing, grinding, or chewing of tablets mimicking abusers or patients inadvertently manipulating to make a tablet easier to swallow or to titrate dose. Grinding and abrading/shaving mechanisms affected the formulated tablets differently than direct blunt force or milling mechanisms while grating / abrasion has the highest impact on drug release when compare to intact tablets. Based on the in vitro drug release profiles presented, the crushed Vantrela™ tablets are low compared to Vicoprofen® tablets and Zohydro® ER capsules. Manipulated Zohydro® ER capsules exhibited faster drug release compared to manipulated Vantrela™ tablets. No comparative in vitro dissolution data on intact Vantrela™ tablets to Zohydro® ER capsules was evaluated as part of this review.

***In Vitro Alcohol Interaction Studies:*** The in vitro dissolution profiles of clinical batches were initially evaluated by sponsor with 40% v/v alcohol to verify whether the tablets maintain comparable in vitro release profiles in the presence of ethanol as in the absence of ethanol, and that there is no dose dumping. The 15 mg strength demonstrated the greatest susceptibility to the 40% v/v alcohol challenge, with about 50 percent of drug released in four hours. An interaction study was conducted to evaluate the in vitro release profile of a batch of 15 mg tablets (Lot C62020) in the presence of 0%, 5%, 10%, 20%, and 40% v/v alcohol.

***Reviewer Evaluation:*** This conclusion of sponsor is based on data from the in vitro dissolution profiles of drug product obtained using medium containing different alcohol concentrations below 40% v/v. Additional studies using dissolution medium with different alcohol concentrations above 40% v/v are to be performed by sponsor to justify that alcohol has no dose dumping effect.

***IR response:*** Information request sent to sponsor for additional information on studies using alcohol above 40 %v/v and up to 95 % v/v. Sponsor states that though the Agency requested additional extraction experiments in 20% ethanol and 75% ethanol (on July 18, 2014 Pre-NDA Preliminary Reviewer Comments, page 7), during the July 23, 2014 Pre-NDA (Type-B) meeting the Agency acknowledged that only the 20% ethanol experiments were necessary, to serve as a reference point relative to other products (Meeting Minutes, Type B pre- NDA meeting, IND 105587, p. 11), apart from the studies conducted using 0 % and 40 % v/v ethanol. Sponsor claims that extraction results in (b) (4) are relevant substitutes for the data requested and admits that extractions using concentrations of ethanol above 40% v/v and up to 95% v/v will generate results progressively approaching those from pure organic solvents.

**Reviewer comment on IR response:** We disagree with sponsor on use of [REDACTED] (b) (4) [REDACTED] as substitutes for the extraction studies using ethanol above 40 % v/v and up to 95 % v/v. Information requested was to evaluate the oral abuse potential, by defeating the extended release properties, when subjected to physical manipulations in presence of ethanol. Abusers are more likely to use ethanol with little or no water to extract the drug from the intact or manipulated tablet, for direct oral ingestion after diluting with water, but not the other two solvents as claimed by sponsor.

**Studies Simulating Abuse by Nasal Insufflation:** Abuse potential by nasal insufflation was also assessed by sponsor through extraction of hydrocodone bitartrate from manipulated Vantrela™ tablets, along with controls, drug substance and two comparator products, (Vicoprofen® tablets and Zohydro® ER) in the nasal environment. The quantity of dissolved hydrocodone in 10 mL of simulated nasal fluid at 10 and 30 minutes was measured. The amount of hydrocodone extracted during a 30 minute interval in simulated nasal fluid was highest for Vantrela™ tablets 15 mg strength, i.e. 46% or 7.0 mg among the different strengths, while 91 % (6.9 mg) was recovered from Vicoprofen® tablets under similar extraction condition and ≥ 82% for manipulated Zohydro ER (50 mg) after 10 minutes of extraction.

**Reviewer Evaluation:** Based on the in vitro drug release profiles presented, the liability of Vantrela™ tablets for abuse by nasal insufflation appears low.

**In Vitro Studies simulating Abuse by Intravenous Injection:** Abuse potential by intravenous injection was assessed by small volume extraction studies (5 mL) on intact and manipulated dosage forms using water or other aqueous media of different pH as extraction media with and without agitation. Both syringability and injectability of the extracts were assessed as suggested in FDA's Draft Guidance for Industry 'Abuse-Deterrent Opioids - Evaluation and Labeling'. It was reported that gel-forming excipients rendered small volume extraction mixtures visually unappealing and increased the difficulty of filtering and syringing samples from manipulated tablets for intravenous injection.

**Reviewer Evaluation:** Based on the in vitro drug release profiles presented and because of the gelling of sample, the liability of Vantrela™ tablets for abuse by intravenous injection appears low.

**Simple and Complex Drug Extraction studies:** Several extraction studies were designed by the sponsor to liberate the drug substance or separate the drug as solid residue from manipulated tablet. Larger volume extractions range from simple aqueous extractions to complex organic solvent extractions. Simple aqueous extractions were carried out using a fixed volume of 30 ml solutions of pH range from 2 to 8, along with 20% ethanol and 40% ethanol, with change of extraction times, temperatures, and/or agitation. It was reported that extraction efficiencies increased with temperature, agitation, extraction time, and ethanol content in the solvent and were higher in general with use of the rotary abrasion tool relative to other tools. The most aggressive conditions used for extraction has more than 80% drug extracted within 30 minutes. The pH of extraction medium had little to no impact on the drug release properties of manipulated tablets.

Organic solvents used by sponsor for simple extraction include isopropanol, methylene chloride, and ethyl acetate. The drug was fully extracted within 30 minutes in methanol while only 40% to 50% was extracted in ethyl acetate in 30 minutes because of the limited solubility of Hydrocodone Bitartrate. Extraction efficiencies of the drug from manipulated Vantrela™ Tablets

(coffee mill) using acetone, isopropanol and methylene chloride relatively high while purity of the residue was reported to be low when compared to Zohydro® ER Capsules. Among the three solvents isopropyl alcohol has the highest extraction efficiency, above 80 % in 30 minutes. Sponsor also performed complex extractions involving multiple-step, acid/base, liquid/liquid extractions, simulating manipulation that may be performed by the most sophisticated abusers to isolate the opioid free base from the excipients. Solvents used include methylene chloride, hexanes, or toluene. Among the solvents used for multiple-step liquid/liquid extraction by sponsor, methylene chloride was found to be the most efficient solvent, with drug extraction efficiencies in the range of 49 -84 %, with the highest efficiency in 15 mg manipulated tablets using coffee mill. The purities of the isolated materials from manipulated Vantrela™ tablets were generally higher than those obtained from the simple organic extractions.

*Reviewer Evaluation:* Organic solvent selected represent a wide range of polarities and the tampering methods used for physical manipulations are deemed adequate. However manipulations using aqueous solutions and organic solvent need to be expanded to include alcohol content above 40% v/v and up to 95 % v/v (190 proof, grain alcohol).

Sponsor was advised, through an information request sent on June 29, 2015, to provide additional information to the agency on category 1 in vitro studies comparing the test product and Zohydro® ER capsules under identical in vitro test conditions as described below. Sponsor's responses were noted above, in the review

1. Simple extractions using aqueous media containing alcohol in concentrations above 40% v/v, i.e. 60 % v/v/, 80 % v/v and pure ethanol (95% or 190 proof alcohol).
2. Complex multi-step extractions performed using any combinations of solvents deemed relevant by sponsor or by following the method described here
  - e) Extract physically manipulated drug with pure ethanol (95%, 190 proof) under hot conditions, facilitating dissolution of hydrocodone, (b) (4) and fraction of (b) (4).
  - f) Suspended (b) (4) may be separated from the hot alcohol extract by filtration.
  - g) Separate (b) (4) from the hot alcohol extract, by precipitation with gradual addition of hot water maintained at temperatures just above 60°C.
  - h) Also separated (b) (4) by phase separation and/or solidification, upon cooling the mixture, leaving the drug in hydro alcoholic solution which is suitable for oral consumption (abuse).

#### **IR Responses:**

1. Extractions using concentrations of ethanol above 40% v/v and up to 95% v/v will generate results progressively approaching those from pure organic solvents. The extraction results in (b) (4) are relevant substitutes for the data requested. Teva believes that requested experiments at ethanol levels between 40% and 95% v/v are not necessary to characterize the drug product.
2. The sequence of steps proposed by the Agency is designed to achieve high purity of drug by removing the (b) (4) polymers as well as the (b) (4) from the dissolution media. The material obtained at the end of the proposed procedure, if successful, would be a solution of hydrocodone bitartrate in a relatively large volume of ethanol/water of unknown ratio. This solution could be ingested by the abuser. Alternatively, the ethanol and water could be evaporated and the remaining pure drug reconstituted for injection. Both of these procedures represent considerable effort on the

part of an abuser for a marginal potential improvement in yield and purity. Teva has demonstrated that the formulation can be defeated using relatively sophisticated chemical extractions, and believes the requested experiments are not necessary to characterize the drug product.

**Reviewer Comment on IR Response:**

1. Same as under In Vitro Alcohol Interaction Studies above.
2. Teva agrees that the formulation can be defeated using relatively sophisticated chemical extractions and purification methods for isolation of the drug substance.

**Overall Evaluation / Conclusions:**

1. The rotary abrasion tool yielded the highest fraction of fine particles (< 106 µm), 45% w/w among the manipulation tools used.
2. Manipulation with a rotary abrasion tool results in more rapid drug release than any of the other tools in the comprehensive in vitro manipulation studies.

Manipulation Tool (CEP-33237 tablet lot no.)	> 850 µm	600-850	425-600	300-425	180-300	106-180	< 106
Hammer (C73181)	1.2	8.6	17.3	15.3	10.7	7.9	39.1
Mortar and Pestle (C73181)	1.5	9.2	19.1	18.2	14.8	11.2	26.1
Coffee Mill (C73181)	1.0	7.7	19.9	18.8	15.8	10.9	25.9
Rotary Tool (C73181)	10.7	7.1	8.8	8.7	9.0	10.7	45.0
Silent Knight (C93274)	3.6	10.5	23.7	19.4	13.2	6.1	23.6
Maxi-Matic Mixer (C93274)	1.5	3.3	19.1	17.1	12.1	8.2	38.6

3. The gel-forming excipients render small volume extraction difficult for filtering and syringing samples from manipulated tablets for intravenous injection.
4. Intact or manipulated tablets clearly resist extraction of hydrocodone in biologically-relevant volumes of simulated nasal fluid when compared to Vicoprofen (IR) and to ZOHYDRO (ER).
5. Extraction of hydrocodone from manipulated tablets into aqueous solutions intended for ingestion varies as a function of the extraction medium, the temperature and the agitation condition.
6. Hydrocodone bitartrate can be readily extracted from comminuted CEP-33237 tablets as well as manipulated Zohydro ER comparator. Solubility limitations in various organic solvents can be overcome with larger volumes of solvent. The purity of the extracted residues after solvent removal varies with the solvents used and comparable or better than Zohydro ER comparator.
7. Hydrocodone bitartrate can be extracted in high yields using liquid/liquid extraction procedures with the appropriate organic solvents. The purity of isolated materials varies with the type and volume of solvent used, apart from the skills and willingness of chronic abusers

Thus, the overall abuse-deterrent properties of Vantrela™ tablet are comparable to Zohydro® ER capsules and superior to the IR combination product Vicoprofen® tablets for abuse by intranasal (insufflation) and intravenous (injection) routes. The information provided by sponsor is not sufficient to establish the superiority of Vantrela™ tablet over Zohydro® ER capsules, when administered by oral route or for isolation of drug substance by using liquid/liquid extraction methods.

Venkateswara R. Pavuluri -  
A (Affiliate)

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0.9.2342.19200300.100.1.1=0011799946, cn=Venkateswara R.  
Pavuluri -A (Affiliate)  
Date: 2015.08.18 18:56:14 -04'00'

Julia C. Pinto -A

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Date: 2015.08.18 19:15:34 -04'00'

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KATHERINE R BONSON  
09/28/2015

SILVIA N CALDERON  
09/28/2015

MICHAEL KLEIN  
09/28/2015

**MEMORANDUM**

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

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**CLINICAL INSPECTION SUMMARY (CIS)**

DATE: September 11, 2015

TO: Kim Compton, Regulatory Project Manager  
Robert Levin, M.D., Medical Officer  
John Feeney, M.D., Team Leader  
Division of Analgesia, Anesthesia, and Addiction Products

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

THROUGH: Janice Pohlman, M.D., M.P.H., Team Leader  
Susan Thompson, M.D., Team Leader, for  
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

APPLICATIONS: NDA 207975

APPLICANT: Teva Branded Pharmaceutical Products Research and Development, Inc.

DRUG: Hydrocodone Bitartrate Extended-Release Tablets (Vantrela® ER)

NME: No

INDICATION: Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment, for which alternative treatment options are inadequate

REVIEW CLASSIFICATION: Standard

DARRTS CONSULTATION DATE: March 20, 2015

INSPECTION SUMMARY GOAL DATE: September 11, 2015

REGULATORY ACTION GOAL DATE: October 9, 2015

PDUFA DUE DATE: October 23, 2015

## I. BACKGROUND

In this NDA 207975, Teva Branded Pharmaceutical Products Research and Development, Inc. (**Teva**) references Vicoprofen<sup>®</sup> (previously approved under NDA 20716) in seeking 505(b)(2) approval of Vantrela<sup>®</sup> (trade name pending), a hydrocodone formulation engineered for extended abuse-deterrent analgesia. Teva's proposed indication for Vantrela<sup>®</sup> reads "management of severe pain requiring continuous long-term opioid use, for which alternative treatment options are inadequate."

Currently in the United States (**US**), extended-release (**ER**) opioids with abuse-deterrence (**AD**) features are available only as two oxycodone formulations. Hydrocodone bitartrate (**HB**) is a semi-synthetic opioid alternative to oxycodone currently available in the US only as immediate-release (**IR**) formulations, typically in combination with other analgesics and without AD features. Vantrela<sup>®</sup> was developed as a single-agent granule formulation of extended-release HB (**ERHB**) using polymer excipients of varying alcohol/water solubility to achieve the following advantages: oxycodone alternative, single-agent flexibility, extended analgesia, and AD (crushing and/or alcohol extraction).

Teva sponsored 23 new studies (under IND 105587) in developing Vantrela<sup>®</sup>, 19 pharmacology and four clinical studies. Of the four clinical studies, two were blinded and two were open-label (safety studies). In support of this NDA review, Study C33237/31 03 was identified as the core efficacy study to be audited at good clinical practice (**GCP**) inspections of three clinical investigator (**CI**) sites. In the following outline of Study C33237/31 03, Vantrela<sup>®</sup> is referred to as CEP-33237 (investigational product name) or as ERHB (generic).

### **Study C33237/3103**

*A 12-Week, Randomized, Double-Blind, Placebo-Controlled, Randomized-Withdrawal Study to Evaluate the Efficacy and Safety of Hydrocodone Bitartrate Extended-Release Tablets (CEP-33237) at 30 to 90 mg Every 12 Hours for Relief of Moderate to Severe Pain in Patients With Chronic Low Back Pain Who Require Opioid Treatment for an Extended Period of Time*

This double-blind, placebo-controlled, randomized-withdrawal study was conducted between March 2013 and February 2014 at 78 US CI sites in 623 subjects with moderate/severe chronic low back pain (**CLBP**) requiring around-the-clock (**ATC**) use of an opioid analgesic. The primary study objective was to evaluate Vantrela<sup>®</sup> relative to placebo at doses of 30-90 mg every 12 hours (**Q12h**) in alleviating moderate to severe CLBP, as assessed by worst pain intensity (**WPI**) score on 11-point numerical rating scale (**NRS-11**).

The study consisted of four periods (20 weeks maximum duration): (1) screening Visit 1; (2) open-label dose titration Visits 2-6, up to six weeks; (3) randomization and double-blind treatment Visits 7-11, up to 12 weeks; and (4) final evaluation Visit 12. Using an e-diary, subjects completed NRS-11 daily from the start of the open-label dose titration phase through the end of the study. Subjects completing all 12 visits were eligible for Study C33237/31 04, a six-month open-label extension study.

### **Subject Selection**

Adults of age 18-80 years with moderate/severe CLBP for at least the last three months and taking oxycodone/equivalent for at least the last 14 days, either opioid-naive (< 10 mg) or experienced (≥ 10 mg)

#### *Exclusion Criteria*

- Taking > 135 mg/day of oxycodone (or equivalent) within 14 days
- Physical/chiropractic therapy, biofeedback, acupuncture, or herbal remedy within two weeks
- Any non-pharmacologic intervention for pain within two weeks
- Primary pain unrelated to CLBP, including radicular or neuropathic pain
- Cardiopulmonary disease that significantly increases the risk of treatment with opioids
- Participation in any previous study by the sponsor with HBER

- Suicidal history; on-study surgery; pregnancy, lactation, or unacceptable contraception
- Unexplained positive urine drug screen (**UDS**)
- Receipt of mono-amine oxidase inhibitor (**MAOI**) within 14 days before the first dose of study drug
- Alcohol or other substance abuse (except for nicotine) within five years
- Any condition that may compromise subject safety and/or study conduct
- Active or settled litigation and/or disability claim within the five years related to CLBP
- Receiving workman's compensation in relation to CLBP
- Abnormal physical examination and/or clinical laboratory tests
- Seropositive for human immunodeficiency virus (**HIV**)
- Any condition that may interfere with following the study protocol, including data collection
- Considered by CI to be unsuitable for any reason, including planned surgery or active malignancy

### **Treatment Groups and Regimen**

#### *Open-label dose titration*

- Stable oral regimen of 30-90 mg Q12h (self-administered)
- Initial dose of either 15 mg (opioid-naive) or half of screening dose equivalent (opioid-experienced)
- Next higher dose (30, 45, 60, or 90 mg) for inadequate pain relief without unacceptable AEs

#### *Randomized blinded treatment*

- Double-blinded randomization (if stable pain relief at end of open-label dose titration) in equal ratio to: (1) continued Vantrela<sup>®</sup>, or (2) matching placebo
- Stable pain relief: API score  $\leq 4$  and WPI score  $\leq 6$  on NRS-11 over 24 hours for four of seven consecutive days, on same study medication dose and without unacceptable adverse events (**AEs**)
- Randomization using Interactive Response Technology (**IRT**), stratified by study center and opioid-status (naive or experienced)
- Subjects randomized to placebo, first two weeks: double-blinded dummy dose taper, step-wise tapering schedule based on ERHB dose at end of open-label titration

#### *Rescue medication (open-label or blinded treatment)*

- Hydrocodone/acetaminophen 5/325 mg, one or two tablets every four to six hours (**Q4-6h**) as needed, not to exceed 10/650 mg per day
- Other analgesics including nonsteroidal anti-inflammatory drugs (**NSAIDs**) were not permitted, except for non-pain indications (e.g., cardiovascular prophylaxis or fever) at stable doses

### **Major Endpoints and Analyses**

- Primary endpoint: Change from randomization to blinded treatment Week 12 in weekly average of daily WPI scores, subject self-reporting using NRS-11 and electronic diary (**e-diary**)
- Change from randomization to blinded treatment Week 12 in weekly average of daily API scores, subject self-reporting using NRS-11 and e-diary; rescue medication use
- Clinical AEs, including all deaths, serious AEs (**SAEs**), and discontinuation-related AEs (**DAEs**) leading to discontinuation from study
- Time to study medication discontinuation (lack of efficacy); change in Roland-Morris Disability Questionnaire (**RMDQ**) score from randomization to final on-treatment visit; rescue medication use
- Proportion of subjects with: (1)  $\geq 30\%$  API score increase from randomization baseline to final on-treatment visit, and (2) API score  $\geq 5$  at final on-treatment visit

- Clinical AEs, physical examination findings including vital signs, laboratory testing results, electrocardiogram (ECG) findings, and concomitant medication use
- Changes in pure tone audiometry (as adjudicated by audiologist) from titration baseline to: (1) Visit 7 (randomization), (2) final on-treatment visit, and (3) final study visit (Week 12 or early termination)
- Subjective Opiate Withdrawal Scale (SOWS) scores, calculated from e-diary data, daily during first four weeks of blinded treatment through final on-treatment Visit 11
- Clinical Opiate Withdrawal Scale (COWS) scores at blinded treatment Weeks 1, 2, and 4 through final on-treatment Visit 11

### Major Sponsor-Reported Outcomes

- ERHB at doses of 30-90 mg Q12h was effective (relative to placebo) in alleviating CLBP, as measured using weekly average of daily WPI scores ( $p < 0.001$ ).
- Efficacy results from a major secondary analysis using API were consistent with those of the primary analysis using WPI ( $p < 0.001$ ).
- Opioid withdrawal by SOWS/COWS appeared comparable for the two groups. Seven placebo versus 11 ERHB subjects withdrew after an AE.
- SAEs included: respiratory arrest (overdose), chest pain, dyspnea, and pancreatitis. There were no deaths in the study. The observed safety profile was consistent with that known for hydrocodone and new safety concerns were not identified.

## II. INSPECTIONS

In auditing Study C32337/3103 in support of this NDA review, three CI sites were selected for GCP inspection based on their large contribution to the overall study efficacy outcome. Site 10390 was selected also as an outlier for subject discontinuation (relatively low rate of 10%), potentially important in interpreting the data from this CI site. No special concerns were identified at NDA review about study conduct, including protocol violations, AEs, and CI conflicts of interest.

	Clinical Investigator	Study C32337/3103 Enrollment	Inspection Outcome
1	Joseph S. Gimbel, M.D. Arizona Research Center 2525 West Greenway Road Phoenix, Arizona 85023	Site 10366: 48 subjects	June 3-9, 2015 Pending, preliminary NAI
2	Jeffrey A. Potts, M.D. Great Lakes Research Group 200 South Wenona Bay City, Michigan 48706	Site 10388: 25 subjects	June 16-24, 2015 VAI
3	Francisco L. Badar III, M.D. Skyline Research 18115 Valley View Avenue Cerritos, California 90703	Site 10390: 21 subjects	June 10-17, 2015 Pending, preliminary NAI

NAI = no action indicated (no significant violations); VAI = voluntary action indicated (minor violations)  
Pending = preliminary results based on communication with field investigator

**1. Joseph S. Gimbel, M.D.**

## a. What was inspected:

- Records review: local institutional review board (**IRB**) oversight and sponsor monitoring, CI financial disclosure, drug accountability and disposition, and subject records
- Subject records: subject screening and eligibility, informed consent, treatment compliance, and data verification
- Data verification: randomization, major efficacy endpoints, AEs, protocol deviations, subject discontinuations, and concomitant medication use

## b. General observations and comments:

Study C33237/3103, Site 10366: 51 subjects were screened, 48 were enrolled (3 screen failures), 29 were randomized (19 titration failures), and 21 completed the study (8 early terminations). The major reasons for not completing the study (8 subjects) were AEs and protocol non-compliance (discontinuation by CI and/or sponsor). Case records were reviewed for all enrolled subjects, including detailed review for 12 randomized subjects.

No significant deficiencies were observed and a Form FDA 483 was not issued. Study conduct appeared adequate, including informed consent, AE monitoring and reporting, and drug accountability. IRB oversight and sponsor monitoring appeared acceptable. Source records were well maintained. All audited endpoint data were verifiable among source records, case report forms (**CRFs**), and NDA data listings.

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

Note: The findings noted above are based on preliminary communication with the field investigator.

**2. Jeffrey A. Potts, M.D.**

## a. What was inspected:

- Records review: local IRB oversight and sponsor monitoring, CI financial disclosure, drug accountability and disposition, and subject records
- Subject records: subject screening and eligibility, informed consent, treatment compliance, and data verification
- Data verification: randomization, major efficacy endpoints, AEs, protocol deviations, subject discontinuations, and concomitant medication use

## b. General observations and comments:

Study C33237/3103, Site 10388: 35 subjects were screened, 25 were enrolled (10 screen failures), nine were randomized (16 titration failures), and eight completed the study (one early termination). Case records were reviewed for all enrolled subjects, including detailed review for 12 subjects (including all nine randomized subjects). The following deficiencies were observed, cited on Form FDA 483 (single item) or verbally discussed:

*Form FDA 483*

Of the nine subjects randomized at this CI site, three (Subjects 20, 28, and 33) may have been incorrectly stratified with respect to their previous opioid exposure, as opioid-experienced when actually opioid-naive (inadequate documentation of exposure history), and the potential imbalance in subject enrollment across the two opioid exposure strata was not rigorously minimized as intended in the study protocol.

*Verbal discussion*

- Opioid exposure (opioid naive/experienced): Stratification was not always rigorous in that sponsor guidance was not consistently requested to resolve cases with inadequate opioid use history according to the stratification criteria specified in the study protocol.
- Subjects 01-06: Unclear history of prior investigational treatment was not always adequately evaluated, resolved, and/or documented to comply with subject eligibility criteria as specified in the study protocol.
- Subjects 20 and 25: The use of concomitant medications for muscle spasm and/or pain (Skelaxin®, Celexa®, and Flexeril®) was not always adequately evaluated (by history and/or medical records review) and/or reported to the sponsor on CRF.
- Subject 25: Unclear history of radiating leg pain was evaluated and diagnosed by the CI as tendinitis (study-eligible) and not nerve compression (exclusion criterion), but this evaluation was not adequately documented to support subject eligibility as specified in the study protocol.
- Subject 02: Treatment assignment was unblinded after completion of study participation (no impact on study results) at receipt of accidentally unblinded urine drug testing results. No corrective action was taken (needed), other than reporting the unblinding as a protocol violation.

These observed deficiencies appear minor, isolated, and/or otherwise unlikely to be significant to the study outcome. Overall, study conduct at this CI site appeared adequate, including informed consent, AE monitoring and reporting, and drug accountability. IRB oversight and sponsor monitoring appeared acceptable. Source records were well maintained. All audited endpoint data were verifiable among source records, CRFs, and NDA data listings.

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

**3. Francisco L. Badar III, M.D.**

- a. What was inspected:

- Records review: local IRB oversight and sponsor monitoring, CI financial disclosure, drug accountability and disposition, and subject records
- Subject records: subject screening and eligibility, informed consent, treatment compliance, and data verification
- Data verification: randomization, major efficacy endpoints, AEs, protocol deviations, subject discontinuations, and concomitant medication use

- b. General observations and comments:

Study C33237/3103, Site 10390: 23 subjects were screened, 21 were enrolled and randomized, and 19 completed the study. Case records were reviewed for all subjects, including detailed review for 12 subjects completing study.

No significant deficiencies were observed and a Form FDA 483 was not issued. Verbal discussion with the CI was limited to the adequacy of IRB reporting/oversight (no impact on data reliability). Study conduct appeared adequate, including informed consent, AE monitoring, protocol deviations reporting, drug accountability, and sponsor oversight of study conduct. Source records were well maintained. All audited data were verifiable among source records, CRFs, and NDA data listings.

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

Note: The findings noted above are based on preliminary communication with the field investigator.

### III. OVERALL ASSESSMENT AND RECOMMENDATIONS

Teva submitted this NDA 207975 as a 505(b)(2) application with Vicoprofen® as the reference listed drug in seeking approval of Vantrela®, a new hydrocodone formulation engineered for extended abuse-deterrent analgesia of severe pain requiring continuous long-term use of an opioid analgesic.

- In support of this NDA review, Study C32337/3103 was audited as the core efficacy study at GCP inspections of three CI sites with large subject enrollment.
- Study C32337/3103 was a double-blind, placebo-controlled, randomized withdrawal study conducted between 2013 and 2014 at 78 US CI sites in 623 subjects with CLBP. Open-label dose titration preceded randomization and double-blinded treatment with either Vantrela® or placebo. Pain intensity was recorded daily from the start of open-label period through end of study.
- At the three inspected CI sites combined (4% of 78 sites), 94 subjects were enrolled (15% of 623 total study enrollment), of whom case records for all subjects were reviewed, including detailed review for 36 subjects (38% of 94 subject to detailed review).

No significant deficiencies were observed at all CI sites. Observed GCP deficiencies were limited to minor isolated findings unlikely to be significant to the study outcome, typically discussed with the CI or cited on Form FDA 483 (inspector discretion). Study conduct appeared adequate, including IRB and sponsor oversight of study conduct. All audited data were verifiable among source records, CRFs, and NDA data listings. The data from the three CI sites appear reliable as reported in the NDA.

Note: For two CI sites (see Section II), the EIR has not been received from the field office and the final inspection outcome remains pending. Upon receipt and review of the EIR, an addendum to this CIS will be forwarded to the review division if the final outcome changes from that reported in this CIS. Close-out correspondence (with each CI, copied to review division) otherwise indicates EIR review completion without new significant findings and inspection outcome finalization as reported in this CIS.

{See appended electronic signature page}

John Lee, M.D.  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

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For:

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

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JONG HOON LEE  
09/10/2015

JANICE K POHLMAN  
09/11/2015

SUSAN D THOMPSON  
09/11/2015

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### **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\*\*\***

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**Date of This Review:** March 12, 2015

**Requesting Office or Division:** Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

**Application Type and Number:** NDA 207975

**Product Name and Strength:** Vantrela ER (hydrocodone bitartrate extended-release tablets), 15 mg, 30 mg, 45 mg, 60 mg, 90 mg

**Product Type:** Single ingredient

**Rx or OTC:** Rx

**Applicant/Sponsor Name:** Teva Branded Pharmaceutical Products R and D, Inc.

**Submission Date:** December 23, 2014

**OSE RCM #:** 2014-2515

**DMEPA Primary Reviewer:** Millie Brahmhatt, PharmD, BCPS

**DMEPA Acting Team Leader:** Vicky Borders-Hemphill, PharmD

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## 1 REASON FOR REVIEW

Teva Branded Pharmaceutical Products R and D, Inc. submitted NDA 207975 for Vantrela ER (hydrocodone bitartrate extended-release tablets). Vantrela ER is a schedule II extended-release formulation of hydrocodone bitartrate with abuse deterrent properties. Thus, the Division of Anesthesia, Analgesia, and Addition Products (DAAAP) requested we review the proposed container labels and prescribing information for areas of vulnerability that could lead to 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.

<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B
Previous DMEPA Reviews	C
ISMP Newsletters	D
Labels and Labeling	E
Full Prescribing Information	F

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed container labels and prescribing information to identify deficiencies that may lead to medication errors and other areas for improvement.

### Prescribing Information

Our review of the *Dosage and Administration* section in the Full Prescribing Information identified areas of improvement to increase clarity of important information. We identified that the frequency of administration is missing from the dosing information in sections 2.5 *Patients with Hepatic Impairment* and 2.6 *Patients with Renal Impairment*. Thus, we provide recommendations to mitigate dosing confusion and promote safe use of this product in Section 4.1.

### Container Labels

Our review of the container labels identified areas of improvement to increase clarity and prominence of important information. Additionally, according to the prescribing information, Vantrela ER tablets must be swallowed intact and are not amenable to cutting, breaking,

chewing, crushing, or dissolving due to the risk of rapid release and absorption of a potentially fatal dose of hydrocodone. We recommend adding the statement, “Swallow tablets whole. Do not cut, break, chew, crush, or dissolve” to the principal display panel of the container labels to mitigate the risk of wrong technique errors. Thus, we make recommendations to mitigate confusion and promote safe use of this product in Section 4.2.

#### **4 CONCLUSION & RECOMMENDATIONS**

We conclude the Sponsor can improve the proposed labels and labeling to increase clarity and prominence of important information to promote safe use of this product.

If you have further questions or need clarifications, please contact Vaishali Jarral, OSE Project Manager, at 301-796-4248.

##### **4.1 RECOMMENDATIONS FOR THE DIVISION**

We have revised the *Dosage and Administration* section of the Full Prescribing Information (See Appendix F) and have provided a detailed summary below for review and consideration by DAAAP.

###### **A. Full Prescribing Information**

1. We note the frequency of administration is missing from the dose information in sections *2.5 Patients with Hepatic Impairment* and *2.6 Patients with Renal Impairment*. We recommend adding the frequency of administration to these sections to mitigate dosing confusion.

##### **4.2 RECOMMENDATIONS FOR TEVA BRANDED PHARMACEUTICAL PRODUCTS R AND D, INC.**

We recommend the Sponsor implement the following prior to approval of this NDA:

###### **A. Container Labels (all strengths)**

1. Add the statement, “Swallow tablets whole. Do not cut, break, chew, crush, or dissolve.” to the principal display panel to mitigate the risk of wrong technique errors. Add this statement above the statement, “Dispense the accompanying Medication Guide to each patient.” Decrease the size of the statement, “Dispense the accompanying Medication Guide to each patient” and remove the “Teva” logo from the principal display panel to accommodate the addition of the statement.
2. Increase the size of the strength statement. Decrease the size, remove the blue colored background, and change the font color to black for the net quantity statement. As currently presented, the strength does not appear more prominent than the net quantity statement. From post marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net

quantity statement is located in close proximity and prominence to the strength statement.<sup>1</sup>

3. Remove the (b) (4) the modifier “ER.” Use the same font size and color for the modifier “ER” as the rest of the proprietary name. The modifier “ER” is an important indicator of the extended-release dosage form and as currently presented, it appears smaller and in a different color than the rest of the proprietary name, which could lead to medication errors if it is over looked.<sup>2</sup>
4. Revise the presentation of the proprietary name from all lower case letters “tradenamE” to title case “Tradename” to improve readability. We recommend using title case because words written in all lower case letters are less legible than words written in title case.<sup>3</sup>
5. Ensure lot number is present on the immediate container per 21 CFR 201.10(i)(1).
6. Ensure expiration date is present on the immediate container per 21 CFR 201.17.
7. Revise the middle four digits of the NDC numbers to ensure that they are not sequential among the different strengths. Traditionally, healthcare providers use the middle four digits to check the correct product, strength, and formulation. The similarity of the NDC numbers has led to selecting and dispensing of the wrong strength and wrong drug. Therefore, assignment of sequential numbers for the middle digits is not an effective differentiating feature (e.g., 6666, 6667, and 6668).<sup>4</sup>

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<sup>1</sup> Food and Drug Administration. *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, April 2013. Available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

<sup>2</sup> Food and Drug Administration. *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, April 2013. Available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

<sup>3</sup> Food and Drug Administration. *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, April 2013. Available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

<sup>4</sup> Food and Drug Administration. *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, April 2013. Available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Vantrela ER (hydrocodone bitartrate extended-release tablets), that Teva Branded Pharmaceutical Products R and D, Inc. submitted on December 23, 2014.

<b>Initial Approval Date</b>	Not applicable
<b>Active Ingredient</b>	hydrocodone bitartrate
<b>Indication</b>	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate
<b>Route of Administration</b>	oral
<b>Dosage Form</b>	oral tablet, extended-release
<b>Strength</b>	15 mg, 30 mg, 45 mg, 60 mg, 90 mg
<b>Dose and Frequency</b>	Dosing interval is every 12 hours with a maximum daily dose of 180 mg per day
<b>How Supplied/ Container Closure</b>	Bottles containing 100 tablets with child-resistant closure
<b>Storage</b>	20°C to 25°C (68°F to 77°F) [See USP Controlled Room Temperature]

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

#### B.1 Methods

Active surveillance of the FDA Adverse Event Reporting System (FAERS) did not identify any cases that described errors possibly associated with the label and labeling.

#### B.2 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

## APPENDIX C. PREVIOUS DMEPA REVIEWS

### C.1 Methods

We searched the L:drive on March 6, 2015 using the term “hydromorphone” to identify label and labeling reviews previously performed by DMEPA.

### C.2 Results

Our search identified four previous reviews, and we confirmed that our previous recommendations were implemented or considered.

<b>OSE RCM #</b>	<b>Review Date</b>	<b>Summary of Recommendations</b>
2014-2273 <sup>5</sup>	December 18, 2014	This review evaluated the revised container labels, carton labeling, and prescribing information in response to supplement 003 for an abuse deterrent formulation of Zohydro ER. We determined the plan to introduce the new abuse deterrent formulation to the market acceptable. We did not have revisions or comments to the label or prescribing information.
2014-872-1 <sup>6</sup>	October 22, 2014	This memo evaluated the revised container labels for Hysingla ER to determine if they are acceptable from a medication error perspective. We found the revised labels and labeling acceptable.
2014-872 <sup>7</sup>	July 18, 2014	This review evaluated container labels, carton labeling, and prescribing information for Hysingla ER for potential confusion that could lead to medication errors. We provided recommendations to improve the prominence of important information and to clarify the net quantity statement.
2012-1171 <sup>8</sup>	October 5, 2012	This review evaluated the proposed container label

<sup>5</sup> Schlick J. Label and Labeling Review for Zohydro ER (hydrocodone bitartrate) extended-release capsules (NDA 202880/S-003). 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); 2014 DEC 18. 10 p. OSE RCM No.: 2014-2273.

<sup>6</sup> Schlick J. Memorandum Review of Revised Label and Labeling for Hysingla ER (hydrocodone bitartrate) extended-release tablets (NDA 206627). 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); 2014 OCT 22. 4 p. OSE RCM No.: 2014-872-1.

<sup>7</sup> Schlick J. Label and Labeling Review for Hysingla ER (hydrocodone bitartrate) extended-release tablets (NDA 206627). 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); 2014 JUL 18. 8 p. OSE RCM No.: 2014-872.

<sup>8</sup> Baugh D. Label, Labeling, and Packaging Review for Zohydro ER (hydrocodone bitartrate) extended-release capsules (NDA 202880). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and

		and insert labeling for Zohydro ER (NDA 202880) for areas of vulnerability that could lead to medication errors. We determined that the strengths are not well differentiated and the labels can be improved to increase the readability and prominence of important information to promote the safe use of the product and mitigate any confusion. In addition, the proposed opioid conversion table in the insert labeling is confusing and lacks clarity.
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**APPENDIX D. ISMP NEWSLETTERS**

**D.1 Methods**

We searched the Institute for Safe Medication Practices (ISMP) newsletters on March 9, 2015 using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care, Community, and Nursing
Search Strategy and Terms	Boolean Query: hydrocodone AND extended release

**D.2 Results**

Our search did not identify any newsletter articles describing errors associated with the labels or labeling of hydrocodone extended release products.

**APPENDIX E. LABELS AND LABELING**

**E.1 List of Labels and Labeling Reviewed**

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>9</sup> along with postmarket medication error data, we reviewed the following Vantrela ER (hydrocodone bitartrate extended-release tablets) labels and labeling submitted by Teva Branded Pharmaceutical Products R and D, Inc. on December 23, 2014.

- Container label
- Medication Guide

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Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2012 OCT 05. 29 p. OSE RCM No.: 2012-1171.

<sup>9</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MILLIE C BRAHMBHATT  
03/12/2015

BRENDA V BORDERS-HEMPHILL  
03/12/2015

**RPM FILING REVIEW**  
(Including Memo of Filing Meeting)

Application Information	
NDA # 207975	
Proprietary Name: Vantrela ER Established/Proper Name: Hydrocodone bitartrate Dosage Form: extended-release tablets Strengths: 15, 30, 45, 60, and 90 mg	
Applicant: Teva Branded Pharmaceutical Products R&D Agent for Applicant (if applicable): N/A	
Date of Application: 12/23/14 Date of Receipt: 12/23/14 Date clock started after UN: N/A	
PDUFA/BsUFA Goal Date: 10/23/15	Action Goal Date (if different): TBD
Filing Date: 2/21/15	Date of Filing Meeting: 2/5/15
Chemical Classification (original NDAs only) : <input type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input checked="" type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch	
Proposed indication(s)/Proposed change(s): the management of Pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate	
Type of Original NDA: AND (if applicable)	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a>	

Review Classification:		<input checked="" type="checkbox"/> Standard
<i>The application will be a priority review if:</i>		<input type="checkbox"/> Priority
<ul style="list-style-type: none"> <li>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</li> <li>The product is a Qualified Infectious Disease Product (QIDP)</li> <li>A Tropical Disease Priority Review Voucher was submitted</li> <li>A Pediatric Rare Disease Priority Review Voucher was submitted</li> </ul>		<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<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)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input checked="" 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 checked="" 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 (FDCA Section 505B) <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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List referenced IND Number(s): 105587

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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the 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>	<input checked="" type="checkbox"/>	<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,	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a>  <i>If no, ask the document room staff to make the appropriate entries.</i>				
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u>  <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>	Payment for this application ( <i>check daily email from <a href="mailto:UserFeeAR@fda.hhs.gov">UserFeeAR@fda.hhs.gov</a>:</i> ):  <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>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>	Payment of other user fees:  <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u>  <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf</a>	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i>  <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
<b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application a 505(b)(2) NDA? ( <i>Check the 356h form, cover letter, and annotated labeling</i> ). <b>If yes, answer the bulleted questions below:</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

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)].												
<ul style="list-style-type: none"> <li>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</li> </ul> <p><i>If you answered yes to any of the above bulleted 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 for advice.</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>										
<ul style="list-style-type: none"> <li>Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</li> </ul> <p><i>Check the Electronic Orange Book at: <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></i></p> <p><b>If yes, please list below:</b></p> <table border="1"> <tr> <td>Application No.</td> <td>Drug Name</td> <td>Exclusivity Code</td> <td>Exclusivity Expiration</td> </tr> <tr> <td>202880</td> <td>Zohydro</td> <td>NP</td> <td>10/25/16</td> </tr> </table> <p><i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, 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>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	202880	Zohydro	NP	10/25/16	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration									
202880	Zohydro	NP	10/25/16									
<b>Exclusivity</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>								
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at: <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a></i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>										
<b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>									
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>												
<b>NDAs/NDA efficacy supplements only:</b> Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>									
<b>If yes, # years requested:</b> 3												
<i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>												
<b>NDAs only:</b> Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>									
<b>If yes, did the applicant:</b> (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>									

<p>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>				
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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><b>If mixed (paper/electronic) submission</b>, which parts of the application are submitted in electronic format?</p>				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>If electronic submission</b>, does it follow the eCTD guidance?<sup>1</sup>  <b>If not</b>, explain (e.g., waiver granted).</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<p><b>Index</b>: Does the submission contain an accurate comprehensive index?</p>	<input checked="" type="checkbox"/>	<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 checked="" type="checkbox"/> legible  <input checked="" type="checkbox"/> English (or translated into English)  <input checked="" type="checkbox"/> pagination  <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p><b>If no</b>, explain.</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Forms and Certifications				
<p><i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included. <b>Forms</b> include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?</p> <p><i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<p>Are all establishments and their registration numbers listed</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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

on the form/attached to the form?				
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
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, both 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&amp;C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>For paper submissions only:</b> Is a Field Copy Certification (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>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>

<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>  <u>For non-NMEs:</u> Date of consult sent to Controlled Substance Staff: 1/21/15	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<u>PREA</u>  Does the application trigger PREA?  <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting<sup>2</sup></i>  <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)?</b>  <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?</b>  <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<u>BPCA:</u>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Invited to

2

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

3

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

<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				Filing/Planning mtg, review team assigned
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input 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)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the PI submitted in PLR format? <sup>4</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Invited to Filing/Planning mtg and reviewer assigned
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	DRISK Rvwtr assigned and invited to Filing/Planning mtg
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	DMEPA Rvwtr assigned and invited to Filing/Planning mtg
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>

4

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

Version: 12/09/2014

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Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	PLLR consult issued
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b> 7/14/10 and 10/20/10 (CMC only) <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> 9/15/11 (1 <sup>st</sup> ) and 7/23/14 (2 <sup>nd</sup> ) <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b> <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** 2/5/15

**BACKGROUND:**

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Kim Compton (Matt Sullivan to cover filing mtg)	N
	CPMS/TL:	Matt Sullivan	Y
Cross-Discipline Team Leader (CDTL)	John Feeney		Y
Division Director/Deputy	Sharon Hertz		Y
Office Director/Deputy	Curt Rosebraugh/Mary Parks		N
Clinical	Reviewer:	Robert Levin	
	TL:	John Feeney	
Clinical Pharmacology	Reviewer:	Srikanth Nallani	
	TL:	Yun Xu	
Biostatistics	Reviewer:	Yan Zhou	
	TL:	Freda Cooner	

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Beth Bolan	
	TL:	Dan Mellon	
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Chris Hough	
	TL:	Ciby Abraham	
Biopharmaceutics	Reviewer:	Fang Wu	
	TL:	John Duan	
Quality Microbiology	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton/container labels))	Reviewer:	Millie Brahmhatt	
	TL:	Vicky Borders Hemphill	
OSE/DRISK (REMS)	Reviewer:	Danny Gonzalez	
	TL:	Kim Lehrfeld	
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	John Lee	
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	Kit Bonson	
	TL:	Silvia Calderon	
Other reviewers/disciplines	Reviewer:		
	TL:		
Other attendees			

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>• 505(b)(2) filing issues: <ul style="list-style-type: none"> <li>○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?</li> </ul> </li> </ul> <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <ul style="list-style-type: none"> <li>• <b>Relative BA Studies</b> <ul style="list-style-type: none"> <li>– C33237/1071: Relative BA study comparing 45 mg hydrocodone ER tablet with 45 mg IR (reference drug: Norco by Watson)</li> <li>– C33237/1090: Relative BA, food-effect study</li> </ul> </li> </ul> <p>Treatment Arms</p> <ul style="list-style-type: none"> <li>• 2 x 45 mg HC ER tablets (fasted)</li> <li>• 2 x 7.5/200 mg Vicoprofen (fasted)</li> <li>• 2 x 45 mg HC ER tablets (fed)</li> <li>• 2 x placebo tablets (fasted)</li> </ul>
<ul style="list-style-type: none"> <li>• Per reviewers, are all parts in English or English translation?</li> </ul>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>

<p><b>If no, explain:</b></p>	
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments
<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason:
<ul style="list-style-type: none"> <li>If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CONTROLLED SUBSTANCE STAFF</b></p> <ul style="list-style-type: none"> <li>Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></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

<b>CLINICAL MICROBIOLOGY</b>	<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
<b>Comments:</b>	
<b>CLINICAL PHARMACOLOGY</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>Comments:</b>	
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b>BIOSTATISTICS</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>Comments:</b>	
<b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>Comments:</b>	

<b>IMMUNOGENICITY (protein/peptide products only)</b>	<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
<b>Comments:</b>	
<b>PRODUCT QUALITY (CMC)</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>Comments:</b>	
<b>New Molecular Entity (NDAs only)</b>	
<ul style="list-style-type: none"> <li>Is the product an NME?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b><u>Environmental Assessment</u></b>	
<ul style="list-style-type: none"> <li>Categorical exclusion for environmental assessment (EA) requested?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b><u>Quality Microbiology</u></b></p> <ul style="list-style-type: none"> <li>Was the Microbiology Team consulted for validation of sterilization?</li> </ul> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>Establishment(s) ready for inspection?</li> <li>Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?</li> </ul> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b><u>CMC Labeling Review</u></b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</b></p> <ul style="list-style-type: none"> <li>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?</li> <li>If so, were the late submission components all submitted within 30 days?</li> </ul>	<p><input checked="" type="checkbox"/> N/A</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>

<ul style="list-style-type: none"> <li>• What late submission components, if any, arrived after 30 days?</li> </ul>	
<ul style="list-style-type: none"> <li>• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</li> </ul>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li> </ul>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li> </ul>	<input type="checkbox"/> YES <input type="checkbox"/> NO

**REGULATORY PROJECT MANAGEMENT**

**Signatory Authority:** Sharon Hertz

**Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in “the Program” PDUFA V): TBS around 5/23/15 if NDA is filed

**21<sup>st</sup> Century Review Milestones (see attached)** (listing review milestones in this document is optional):

**Comments:**

**REGULATORY CONCLUSIONS/DEFICIENCIES**

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter.</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>

<b>ACTIONS ITEMS</b>	
<input checked="" type="checkbox"/>	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, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone 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"/>	351(k) BLA/supplement: If filed, send filing notification letter on day 60
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (see CST for choices)</li> <li>• notify OMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	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 applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRAAs completed: September 2014

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KIMBERLY A COMPTON  
02/20/2015

## Controlled Substance Staff (CSS) Filing Checklist for NDA

**NDA Number:** 207,975

**Applicant:** Teva, Inc.

**Date:** February 19, 2015

**Drug Name:** Vantrela (CEP-

**IND Number:** 105,587

33237 = hydrocodone bitartrate  
single entity (ER, abuse deterrent)

Checklist	Yes	No	NA	Comment
What is the regulatory history of this application?				2/21/12 – Biostat consult on design of the oral human abuse potential study; 5/2/12 – CSS consult on design of oral human abuse study; 6/11/14 – CSS consult on design of product manipulation studies; 8/4/14 – CSS consult on design of intranasal human abuse study; 9/4/14 – Biostat consult on design of intranasal human abuse potential study; 2/11/15 – CSS consult to Biostat for review of two human abuse potential studies submitted in NDA.
<b>Abuse potential assessment is required if any of the following are true for a drug<sup>12</sup>:</b>				
It affects the CNS	x			
It is chemically or pharmacologically similar to other drugs with known abuse potential	x			Opioid agonist
It produces psychoactive effects such as sedation, euphoria, and mood changes	x			Classic opioid responses
<b>Is the drug a new molecular entity?</b>		x		
<b>Is this a new or novel drug formulation?<sup>3</sup></b>	x			Proposed abuse deterrent
<b>Content of NDA abuse potential section:<sup>4</sup></b>				
<i>Module 1: Administrative Information and Prescribing Information</i> 1.11.4 Multiple Module Information Amendment contains:				
<ul style="list-style-type: none"> <li>A summary, interpretation, and discussion of abuse potential data provided in the NDA.</li> </ul>	x			A 135 page abuse summary was submitted, mostly focused on abuse deterrent claim (Section 1.11.4)

1 21 CFR 314.50(d)(5)(vii): If the drug has a potential for abuse, a description and analysis of studies or information related to abuse of the drug, including a proposal for scheduling under the Controlled Substances Act. A description of any studies related to overdose is also required, including information on dialysis, antidotes, or other treatments, if known.

2 21USC811(f) Abuse potential: If, at the time a new-drug application is submitted to the Secretary for any drug having a stimulant, depressant, or hallucinogenic effect on the central nervous system, it appears that such drug has an abuse potential, such information shall be forwarded by the Secretary to the Attorney General.

## Controlled Substance Staff (CSS) Filing Checklist for NDA

Checklist	Yes	No	NA	Comment
• A link to a table of contents that provides additional links to all studies (non-clinical and clinical) and references related to the assessment of abuse potential.	x			
• A proposal and rationale for placement, or not, of a drug into a particular Schedule of the CSA	x			Schedule II, consistent with other hydrocodone placement
<i>Module 2: Summaries</i> 2.4 Nonclinical Overview - includes a brief statement outlining the nonclinical studies performed to assess abuse potential.	x			<i>In vitro</i> abuse deterrent studies were conducted (Section 3.2.P.2) – CMC will take the lead in reviewing
<i>Module 3: Quality</i>				
3.2.P.1 Description and Composition of the Drug Product - extraction of the drug substance (solvents, pH, or mechanical manipulation).	x			Category 1 abuse deterrent studies conducted
Is there an assessment of extractability/formulation release characteristics of intact and manipulated product?	x			Pharmacy manual conveyed to CMC group 2/9/15
3.2.P.2 Description and Composition of the Drug Product - describes the development of any components of the drug product that were included to address accidental or intentional misuse.				
Is this an extended release or abuse-deterrent formulation?	x			Both ER and AD
<i>Module 4: Nonclinical Study Reports</i>				
4.2.1 Pharmacology		x		Known already
4.2.1.1 Primary Pharmacodynamics - binding profile		x		Known already
Are in vitro receptor binding studies included?		x		Known already
Are functional assays included?		x		Known already
<b>Animal Behavioral and Dependence Pharmacology</b>				
Was a self administration study conducted?		x		Known already
Was a conditioned place preference study conducted?		x		Known already
Was a drug discrimination study conducted?		x		Known already
Was a physical dependence study conducted?		x		Known already
<i>Module 5: Clinical Study Reports</i>				
<b>5.3.5.4 Other Study Reports</b>				
<b>Human abuse potential study:</b>				
Was a human abuse potential study conducted?	x			Intact/crushed formulation studies (Section 5.3.5.4)
Are all the primary data included in the NDA?	x			
Is a Statistics consult necessary?	x			Consult sent 2/11/15, Stats confirmed filability 2/19/15
Preparation of study drug treatments	x			Pharmacy manual located
<b>Other Clinical trials:</b>				
Are all abuse/misuse Case Report Forms submitted?	x			
<b>Labeling</b>				
Section 9.0 text proposed?	x			
<b>Postmarketing activities [PMRs, PMCs, REMS]</b>				
<b>Scheduling activities</b>				
Is the drug already scheduled?	x			Schedule II

## Controlled Substance Staff (CSS) Filing Checklist for NDA

### Is NDA FILEABLE from a CSS perspective?

Yes, the Sponsor provided appropriate preclinical and clinical abuse-related data for review.

CSS Reviewer: Katherine Bonson, Ph.D. Date: Feb. 19, 2015

CSS Team Leader: Silvia Calderon, Ph.D. Date: Feb 19, 2015

CSS Director: Michael Klein, Ph.D. Date: Feb. 19, 2015

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KATHERINE R BONSON  
02/19/2015

SILVIA N CALDERON  
02/19/2015

MICHAEL KLEIN  
02/19/2015