

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205677Orig1s000**

**OTHER REVIEW(S)**

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

<b>Product Title<sup>1</sup></b>	<b>HETLIOZ™ (tasimelteon) capsules, for oral use</b>
Applicant	Vanda Pharmaceuticals Inc.
Application/Supplement Number	NDA 205677
Type of Application	Original
Indication(s)	treatment of Non-24-Hour Sleep-Wake Disorder (Non-24)
Office/Division	ODE I/DNP
Division Project Manager	Cathy Michaloski
Date FDA Received Application	May 31, 2014
Goal Date	January 31, 2014
Date PI Received by SEALD	January 29, 2014
SEALD Review Date	January 30, 2014
SEALD Labeling Reviewer	Elizabeth Donohoe
Acting SEALD Division Director	Sandra Kweder

<sup>1</sup> Product Title that appears in draft agreed-upon prescribing information (PI)

This Study Endpoints and Labeling Development (SEALD) Director sign-off review of the end-of-cycle, prescribing information (PI) for important format items reveals **outstanding format deficiencies** that should be corrected before taking an approval action. After these outstanding format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The Selected Requirements of Prescribing Information (SRPI) is a checklist of 42 important format PI items based on labeling regulations [21 CFR 201.56(d) and 201.57] and guidances. The word “must” denotes that the item is a regulatory requirement, while the word “should” denotes that the item is based on guidance. Each SRPI item is assigned with one of the following three responses:

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

# Selected Requirements of Prescribing Information

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## Highlights

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

### HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

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

**Comment:**

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

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

➤ **For the Filing Period:**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of-Cycle Period:**

- Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

**Comment:**

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

**Comment:** *For improved readability, consider moving the horizontal line between TOC and FPI directly under the end of the TOC; also, since there is a lot of white space on the first page, consider moving FPI up so it begins on the first page.*

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

**Comment:**

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

**Comment:**

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format

## Selected Requirements of Prescribing Information

is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

**Comment:**

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

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

\* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

**Comment:**

### HIGHLIGHTS DETAILS

#### Highlights Heading

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

**Comment:**

#### Highlights Limitation Statement

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

**Comment:**

#### Product Title in Highlights

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

**Comment:**

#### Initial U.S. Approval in Highlights

- NO** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

**Comment:** *The year is missing and should state: 2014*

## Selected Requirements of Prescribing Information

### Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.  
*Comment:*
- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.  
*Comment:*
- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.  
*Comment:*
- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).  
*Comment:*

### Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.  
*Comment:*
- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.  
*Comment:*
- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).  
*Comment:*

### Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.  
*Comment: The eList does not include an EPC for this drug. If the proposed EPC is appropriate, please ask Paul Brown to update eLIST.*

### Dosage Forms and Strengths in Highlights

**N/A**

## Selected Requirements of Prescribing Information

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

Comment:

### Contraindications in Highlights

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

Comment:

### Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment: *The sponsor has included a website address "www.hetlioz.com"; according to the Labeling Review Tool, "for manufacturers with a Web site for voluntary reporting of AR, the Web address of the direct link to the site may be included. NOTE: ..... a general link to a company’s website does not meet the requirement to have AR reporting contact information in HL. It would not provide a structured process for reporting AR (e.g., telephone interview, a form, or instructions for reporting). Delete this information if it appears in HL." The website does not appear to be operating so it is not possible to verify if it would be a valid site for AR reporting; recommend deleting the website from the AR statement in HL.*

### Patient Counseling Information Statement in Highlights

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

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

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

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

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

### Revision Date in Highlights

- NO** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment: *The revision date is missing and should state: "01/2014". Also, the revision date should be fully right justified on the page and in line with the text.*

## Selected Requirements of Prescribing Information

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### Contents: Table of Contents (TOC)

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

- YES** 25. The TOC should be in a two-column format.  
*Comment:*
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.  
*Comment:*
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.  
*Comment:*
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.  
*Comment:*
- NO** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].  
*Comment:* In subsections 7.1, 7.2, 8.3, 8.4, 8.5, 12.1 and 13.1 some words in the subheadings are not capitalized and should be (e.g., in 7.1 and 7.2 the word "Inhibitors" should have the first letter capitalized; for the other subsections, see the listing in item #32 below for the correct case). These will also need to be corrected in the corresponding headings in FPI.
- NO** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.  
*Comment:* In the TOC, there is a "." after each section heading number; these are not present in the FPI and should be removed from TOC. Also, the subsection "8.7 Smokers" is in the FPI but missing from TOC.
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the full prescribing information are not listed.”  
*Comment:*

## Selected Requirements of Prescribing Information

### Full Prescribing Information (FPI)

#### FULL PRESCRIBING INFORMATION: GENERAL FORMAT

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

<b>BOXED WARNING</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>
<b>8.4 Pediatric Use</b>
<b>8.5 Geriatric Use</b>
<b>9 DRUG ABUSE AND DEPENDENCE</b>
<b>9.1 Controlled Substance</b>
<b>9.2 Abuse</b>
<b>9.3 Dependence</b>
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
<b>12.1 Mechanism of Action</b>
<b>12.2 Pharmacodynamics</b>
<b>12.3 Pharmacokinetics</b>
<b>12.4 Microbiology (by guidance)</b>
<b>12.5 Pharmacogenomics (by guidance)</b>
<b>13 NONCLINICAL TOXICOLOGY</b>
<b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b>
<b>13.2 Animal Toxicology and/or Pharmacology</b>
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

***Comment:***

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

## Selected Requirements of Prescribing Information

**Comment:** *The cross-reference in subsection 8.7 currently reads "see Clinical pharmacology (12.3)" and should read "see Clinical Pharmacology (12.3)".*

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

**Comment:**

### FULL PRESCRIBING INFORMATION DETAILS

#### FPI Heading

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

**Comment:**

#### BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

**Comment:**

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

**Comment:**

#### CONTRAINDICATIONS Section in the FPI

- YES** 38. If no Contraindications are known, this section must state "None."

**Comment:**

#### ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

**Comment:**

- N/A** 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

**Comment:**

#### PATIENT COUNSELING INFORMATION Section in the FPI

**N/A**

## Selected Requirements of Prescribing Information

41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

**Comment:**

- N/A**
42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

**Comment:**

# Selected Requirements of Prescribing Information

## Appendix A: Format of the Highlights and Table of Contents

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]  
Initial U.S. Approval: [year]

#### WARNING: [SUBJECT OF WARNING]

*See full prescribing information for complete boxed warning.*

- [text]
- [text]

#### RECENT MAJOR CHANGES

[section (X.X)] [m/year]  
[section (X.X)] [m/year]

#### INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for:

- [text]
- [text]

#### DOSAGE AND ADMINISTRATION

- [text]
- [text]

#### DOSAGE FORMS AND STRENGTHS

- [text]

#### CONTRAINDICATIONS

- [text]
- [text]

#### WARNINGS AND PRECAUTIONS

- [text]
- [text]

#### ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

#### DRUG INTERACTIONS

- [text]
- [text]

#### USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

### FULL PRESCRIBING INFORMATION: CONTENTS\*

WARNING: [SUBJECT OF WARNING]

#### 1 INDICATIONS AND USAGE

- 1.1 [text]
- 1.2 [text]

#### 2 DOSAGE AND ADMINISTRATION

- 2.1 [text]
- 2.2 [text]

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

- 5.1 [text]
- 5.2 [text]

#### 6 ADVERSE REACTIONS

- 6.1 [text]
- 6.2 [text]

#### 7 DRUG INTERACTIONS

- 7.1 [text]
- 7.2 [text]

#### 8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

#### 9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

#### 10 OVERDOSAGE

#### 11 DESCRIPTION

#### 12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology
- 12.5 Pharmacogenomics

#### 13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

#### 14 CLINICAL STUDIES

- 14.1 [text]
- 14.2 [text]

#### 15 REFERENCES

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 17 PATIENT COUNSELING INFORMATION

\*Sections or subsections omitted from the full prescribing information are not listed.

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/s/  
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ELIZABETH A DONOHOE  
01/30/2014

ERIC R BRODSKY  
01/30/2014

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

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

**Final Label Memorandum**

Date: January 29, 2014  
Acting Team Leader: Julie Neshiewat, PharmD, BCPS  
Division of Medication Error Prevention and Analysis  
Drug Name and Strengths: Hetlioz (Tasimelteon) Capsules, 20 mg  
Application Type/Number: NDA 205677  
Applicant: Vanda Pharmaceuticals  
OSE RCM #: 2013-1436

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

## **1 INTRODUCTION**

This memorandum evaluates the revised labels for Hetlioz (Tasimelteon) Capsules, NDA 205677, submitted on January 20, 2014 (Appendix A). DMEPA previously reviewed the proposed labels under OSE Review # 2013-1436 dated September 26, 2013 and December 31, 2013.

## **2 MATERIAL REVIEWED**

DMEPA reviewed the labels submitted on January 20, 2014. We compared the revised labels against the recommendations contained in OSE Review # 2013-1436 dated September 26, 2013 and December 31, 2013.

## **3 CONCLUSIONS AND RECOMMENDATIONS**

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

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

1 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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JULIE V NESHIEWAT  
01/29/2014

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

**Label and Braille Label Comprehension Study Review**

Date: December 31, 2013

Acting Team Leader: Julie Neshiewat, PharmD, BCPS  
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Tasimelteon Capsules, 20 mg

Application Type/Number: NDA 205677

Applicant: Vanda Pharmaceuticals

OSE RCM #: 2013-1436

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

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## 1 INTRODUCTION

This review evaluates the revised labels and Braille Label Comprehension Study for Tasimelteon Capsules, NDA 205677, for areas of vulnerability that could lead to medication errors in response to a request from the Division of Neurology Products (DNP).

### 1.1 PRODUCT INFORMATION

Tasimelteon is a New Molecular Entity (NME). The following product information is provided in the August 20, 2013 insert labeling submission.

- Active Ingredient: Tasimelteon
- Indication of Use: Treatment of non-24-hour disorder in the totally blind
- Route of Administration: Oral
- Dosage Form: Capsules
- Strength: 20 mg
- Dose and Frequency: 20 mg per day taken (b) (4) prior to bedtime, (b) (4) at the same time every night
- How Supplied: Bottles of 30 capsules
- Storage: Controlled room temperature
- Container and Closure System: High Density Polyethylene (HDPE) bottles with (b) (4) closures containing induction seals

## 2 METHODS AND MATERIALS REVIEWED

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>1</sup> along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted December 3, 2013 (Appendix A)
- Recommendations contained in OSE Review # 2013-1436 dated September 26, 2013 and recommendations sent via e-mail to the Applicant on November 13, 2013 (No image)
- Braille Label Comprehension Study submitted December 3, 2013 (No image)

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

### **3 MEDICATION ERROR RISK ASSESSMENT**

The sections below discuss our label risk assessment and the results of our review of the Braille Label Comprehension Study.

#### **3.1 REVISED LABELS**

Review of the revised labels show that the Applicant implemented DMEPA recommendations contained in OSE Review # 2013-1436 dated September 26, 2013 and recommendations sent via e-mail to the Applicant on November 13, 2013. However, the Review Division has indicated that a Medication Guide is not needed for this product (b) (4)

In addition, the Review Division has made revisions to the Dosage and Administration section of the insert labeling which affect the information presented on the container labels. The Usual Dosage statement on the container label should be revised for consistency with the revisions made to the Dosage and Administration section of the insert labeling.

#### **3.2 BRAILLE LABEL COMPREHENSION STUDY**

##### **Objective**

Intended patient population can understand the information in Braille presented on the label and distinguish it from other medication bottles

##### **Study Design**

- Part 1: 22 Totally Blind Braille Readers were asked to locate a bottle on the table in front of them and asked to read the first and second line of Braille
- Part 2: 22 Totally Blind non-Braille Readers were asked if they were able to distinguish between two bottles (one bottle label with Braille and one bottle label without Braille) placed in front of them

##### **Results**

- Part 1: 100% of participants identified at least 5 out of the 7 letters and 77% of participants correctly interpreted “20 mg”
- Part 2: 100% of participants identified a difference between the two bottles and correctly identified the bottle with the Braille label
- A majority of subjective feedback referenced poor printing quality of the Braille lettering
- (b) (4) did not appear more beneficial than the Braille lettering in distinguishing the Hetlioz medication bottle from a similar bottle with a non-Braille label

##### **Discussion**

The Applicant noted the 95% confidence interval of 59.8 to 94.8 misses the lower bound target of 60 for Braille readers to correctly read the name and strength of Hetlioz; however, given the other positive results of the study, the Applicant concludes the Hetlioz label is adequate for the target population to correctly identify their medication.

Since the strength was the main misinterpretation of Braille, we considered if the strength in Braille is needed given the proposed product is single strength. (b) (4)

To address subjective feedback received from the study, the Applicant proposes to (b) (4)

This proposal appears reasonable and we find the Braille Label Comprehension study acceptable. A certificate of translation will also be requested to ensure the proposed Braille is accurate.

#### 4 CONCLUSIONS

DMEPA concludes that the proposed labels can be improved to clarify information.

#### 5 RECOMMENDATIONS

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

##### A. Comments to the Applicant

##### 1. Container Label

- a. Since your proposed product will not have a Medication Guide, remove the statement (b) (4)
- b. For consistency with the Dosage and Administration section of the insert labeling, revise the statement (b) (4) to read similar to “Usual dosage: 20 mg per day taken before bedtime, (b) (4) at the same time every night. Hetlioz should be taken without food. See full prescribing information.”

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

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JULIE V NESHIEWAT  
12/31/2013

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

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

**Memorandum**

**Date:** December 24, 2013

**To:** Cathleen Michaloski, BSN, MPH  
Senior Regulatory Project Manager  
Division of Neurology Products (DNP)  
Office of Drug Evaluation (ODE)-I

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

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

**Subject:** **NDA 205677 HETLIOZ (tasimelteon) capsules**

**Background**

On July 29, 2013, DNP consulted OPDP to review the proposed package insert (PI), medication guide (MG), and carton and container labeling for the new molecular entity, HETLIOZ (tasimelteon) capsules.

OPDP reviewed the proposed substantially complete version of the PI provided by DNP on December 18, 2013, and the carton and container labeling submitted to the eDR on December 3, 2013. Our comments on the PI and carton and container are provided below. We note that the carton and container include text in Braille. In order for us to evaluate this content, we request that the sponsor submit a certificate of translation for this content.

According to communication from DNP on December 18, 2013, there will be no patient labeling, MG, or Patient Package Insert approved for this product. Therefore, OPDP defers review of the proposed MG. Reference is also made to the Review Deferral Memorandum by the Division of Medical Policy Programs (DMPP) on December 20, 2013.

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

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MELINDA W MCLAWHORN  
12/24/2013

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

**REVIEW DEFERRAL MEMORANDUM**

Date: December 20, 2013

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

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

From: Twanda Scales, BSN MSN/Ed.  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Subject: Review Deferred: Medication Guide (MG)

Drug Name (established name): tasimelteon

Dosage Form and Route: Capsules

Application Type/Number: 205677

Applicant: Vanda Pharmaceuticals, Inc. (Vanda)

## **1 INTRODUCTION**

On May 31, 2013, Vanda submitted for the Agency's review a New Drug Application (NDA) for tasimelteon indicated for non-24-Hour Disorder in the totally blind. On July 3, 2013, the DNP requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) for tasimelteon.

This memorandum documents the DMPP review deferral of the Applicant's proposed Medication Guide (MG) for tasimelteon.

## **2 CONCLUSIONS**

Per discussion with DNP, there will be no patient labeling, Medication Guide or Patient Package Insert, approved for this product. Therefore, DMPP defers comment on the Applicant's submitted patient labeling at this time.

Please notify us if you have any questions.

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TWANDA D SCALES  
12/20/2013

MELISSA I HULETT  
12/20/2013



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

**Date:** November 26, 2013

**To:** Eric Basting, M.D., Acting Director  
Division of Neurology Products

**Through:** Michael Klein, Ph.D., Director  
Silvia Calderon, Ph.D., Team Leader  
Controlled Substance Staff

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

**Subject:** Tasimelteon (Hetlioz)  
NDA 205,677  
Indication: Treatment for Non-24-Hour Sleep-Wake Disorder  
in blind individuals  
Dosage: 20 mg/day (oral)  
Sponsor: Vanda Pharmaceuticals, Inc.  
PDUFA Goal Date: July 27, 2014

**Materials reviewed:** NDA (5/31/13); Pharm/Tox review (Dr. Banks-Muckenfuss,  
DARRTS 10/30/13)

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## **1. Background**

This memorandum responds to a consult request by the Division of Neurology Products to evaluate the abuse potential of tasimelteon, based on receptor binding data, a self-administration study and a drug discrimination study in rats. Tasimelteon and its major metabolites have picomolar affinity at melatonin receptors (MT1 and MT2) but no significant affinity (> 10 micromolar) at other CNS relevant sites. This mechanism of action is identical to that of ramelteon, a drug approved to treat insomnia that is not scheduled under the Controlled Substances Act (CSA). The Sponsor has proposed that tasimelteon not be scheduled under the CSA, based on preclinical and clinical data in the NDA.

Tasimelteon (20 mg/day) is proposed for the treatment of Non-24-Hour Disorder in blind individuals with no light perception, a circadian rhythm disorder that occurs when individuals are unable to entrain (synchronize) their endogenous master body clock to the 24-hour day-night cycle. Tasimelteon was granted an orphan drug designation for this indication. Tasimelteon was previously investigated for other indications (insomnia, Circadian Rhythm Sleep Disorders, and Jet Lag Disorder due to eastward travel) but development for these indications was discontinued.

## **2. Conclusions:**

- 1) Tasimelteon and its major metabolites do not have affinity for any CNS sites other than melatonin sites in receptor binding studies. Melatonin sites are not associated with abuse potential.
- 2) The Sponsor did not conduct abuse-related general behavioral studies. However, the behavioral signs from toxicology studies in animals do not show abuse-related signals.
- 3) Tasimelteon was not self-administered and is therefore unlikely to have rewarding properties.
- 4) The drug discrimination study with tasimelteon is not valid because animals were tested prior to Tmax. However, given that tasimelteon is a melatonin agonist, it is unlikely that it would have generalized to midazolam, a GABA agonist used as the training drug in this study.
- 5) Tasimelteon did not produce any abuse-related adverse events in clinical studies.
- 6) Tasimelteon did not induce any signs or symptoms of withdrawal in patients with Non-24, following chronic drug administration and subsequent drug discontinuation. Thus, tasimelteon does not produce physical dependence.

7) A human abuse potential study was not conducted because there were no abuse-related signs in animal abuse-related studies and because of the similarity between tasimelteon and the unscheduled melatonin agonist, ramelteon.

### **3. Recommendation:**

Tasimelteon is not recommended for scheduling under the Controlled Substances Act because there are no signs that the drug produces abuse potential or physical dependence in animal and human studies submitted in the NDA.

### **4. Discussion:**

#### **4.1 Pharmacology of drug substance**

##### **4.1.1 *In vitro* studies**

##### **4.1.1.1 Receptor Binding Studies** (Study #52253, 52186, 1095880, AA82606, AA85237, AB04244, AB13313, AA98075, AB04243, and AB13314)

Receptor binding study reports were submitted for tasimelteon and five of its metabolites (M9, M11, M12, M13 and M14). The M8 metabolite was not evaluated because it is glucuronidated.

The receptor binding assays were comprehensive for 170 binding sites and included the following abuse-related CNS receptors: androgen, calcium channels, cannabinoid, dopamine, GABA, glutamate/NMDA, muscarinic, nicotinic, opioid, potassium channel, serotonin, sigma, sodium channel, and various transporters (dopamine, norepinephrine, serotonin, and GABA).

Binding of tasimelteon to the abuse-related CNS sites was low (< 10 micromolar). The only sites that showed high affinity for tasimelteon were two melatonin sites (MT1 and MT2), with respective  $K_i$  values of 0.3 nM and 0.07 nM.

Similarly, the tested metabolites of tasimelteon showed no significant affinity (< 10 micromolar) for any sites other than MT1 and MT2. The respective  $K_i$  values for each major metabolite at the MT1 and MT2 sites are as follows: M9 (1,180 nM and 72 nM), M11 (250 nM and 3 nM), M12 (136 nM and 11 nM), M13 (4 nM and 0.9 nM), M14 (103 nM and 4 nM).

##### **4.1.2 Safety Pharmacology Studies**

##### **4.1.2.1 General Behavioral Studies**

According to the pharmacology/toxicology review by Dr. Melissa Banks-Muckenfuss (placed in DARRTS on 10/30/13), the Sponsor did not conduct the standard battery of

safety pharmacology studies with tasimelteon, including any studies that evaluate CNS safety pharmacology. Thus, there are no preclinical data related to general behavior induced by tasimelteon, including those that would be part of the Irwin test.

In the preclinical toxicology studies conducted with tasimelteon, there were no behavioral signs in mice, rats, rabbits or monkeys at doses that produced plasma levels similar to those produced by proposed therapeutic doses in humans. In rats, behavioral signs were not present at doses that were similar to the dose ranges used in the abuse-related studies (self-administration and drug discrimination, see below). At very high doses tested for toxicological purposes, behavioral signs in rats included hypoactivity, ataxia, loss of righting reflex, tremors and ptosis. Given that tasimelteon is indicated for treatment of a sleeping disorder, these behaviors are to be expected and are not indicative of a sedative with abuse potential.

### **4.1.3 Abuse-Related Animal Studies**

#### **4.1.3.1 Self-Administration Study (Study # 8260771)**

**Study Title:** Potential Intravenous Self-Administration of Tasimelteon in Male Sprague-Dawley Rats Trained to Self-Administer Midazolam

#### **Methods:**

Male Sprague-Dawley rats (n = 10) were initially trained to press a lever to obtain food-reinforcement under a fixed-ratio 5 (FR5) schedule of reinforcement. Rats were then exposed to a training dose of 0.0125 mg/kg/inj midazolam (i.v.) during one-hour training sessions under an FR5 schedule. Three test doses of midazolam (0.005, 0.05 and 0.125 mg/kg/inj, i.v.) were also evaluated under an FR5 schedule to establish a dose-response curve. The midazolam training and test doses were based on scientific literature. Response to the training drug (midazolam) was considered stable when the number of injections maintained under midazolam was within 30% variability across three consecutive sessions or four out of five sessions. Response was also considered stable if the number of injections maintained under midazolam increased less than 10% over three sessions of daily availability.

The effect of tasimelteon was then evaluated by substituting vehicle, escalating doses of tasimelteon (0.625, 1.25 or 2.5 mg/kg/inj, i.v.), or 0.0125 mg/kg/inj midazolam (i.v.) for self-administration. Doses of tasimelteon were selected following a pharmacokinetic study (Study #8267772). The lowest dose of 0.625 mg/kg was expected to provide tasimelteon exposure similar to the C<sub>max</sub> in humans at the proposed 20 mg therapeutic dose, while the highest dose of 2.5 mg/kg provides exposure several times higher than the mean human C<sub>max</sub>. Similarly, at the 2.5 mg/kg dose level, the exposure to the tasimelteon metabolites in humans (M9, M12, M13, and M14) are expected to be similar to or higher than the mean human C<sub>max</sub>. The 1.25 mg/kg dose was then chosen as the intermediate dose.

## **Results:**

Midazolam produced an inverted U-shaped dose-response curve for self-administration. The highest number of injections was delivered when the dose of midazolam was 0.0125 mg/kg, with a mean injection number of 10 times per session. The dose of 0.005 mg/kg was injected an average of 6.5 times per session, while doses of 0.050 and 0.125 mg/kg were injected an average of 3-4 times per session. This rate is similar to that produced by vehicle for midazolam (4 times per session) and for tasimelteon (3 times per session).

In contrast to midazolam, tasimelteon was injected an average of 3-4 times per session for each of the three doses tested (0.625, 1.25 and 2.5 mg/kg).

Rats self-administering midazolam at a dose of 0.0125 mg/kg/inj (the training dose) produced significant increases in the number of injections when compared to injections of saline. In contrast, the mean number of injections for doses of 0.625, 1.25 or 2.5 mg/kg/inj tasimelteon was not significantly different relative to the mean number of saline injections self-administered.

## **Sponsor Conclusions:**

“The results of this study indicate that intravenous self-administration of tasimelteon at doses less than or equal to 2.5 mg/kg/inj did not function as a reinforcer similar to midazolam self-administered at a dose of 0.0125 mg/kg/inj. Additionally, the data indicate that rats positively responded to the effects of the maintenance dose of 0.0125 mg/kg/inj midazolam.”

## **CSS Conclusions:**

CSS concurs with the Sponsor conclusion that tasimelteon does not function as a reinforcer and produces self-administration levels that are indistinguishable from vehicle.

### **4.1.3.2 Drug Discrimination Study (Study # 8260770)**

**Study Title:** Drug Discrimination Testing in Midazolam Trained Male Sprague-Dawley Rats Administered Tasimelteon or Ramelteon (Study #8260770)

## **Methods:**

Male rats (n = 13) were trained to discriminate midazolam (3.0 mg/kg, p.o.) from water, initially under an FR1 schedule of reinforcement, increasing over time to FR10. Notably, in this study, any response on the incorrect lever reset the response requirement on the correct lever. The training dose of 3.0 mg/kg was selected on the basis of its use in published drug discrimination studies in rats. A 30 minute pretreatment time was used, but no justification was provided.

Once full generalization to the training drug dose (80% drug-appropriate lever activity) was achieved, rats were then tested with midazolam, as the positive control, at varying doses (1.0, 1.7, 3.0, and 10.0 mg/kg, p.o., 30 min pretreatment time) to confirm discriminative training. Vehicle sessions (sterile water) were interspersed during midazolam training to insure that rats would respond on the non-drug lever.

The test drug, tasimelteon, was tested in midazolam-trained rats at doses of 5.0, 11.2, 25 and 250 mg/kg (p.o., 30 min pretreatment time). The vehicle for tasimelteon was PEG-400.

A negative control, ramelteon, was also tested, at doses of 1, 3, 10 and 30 mg/kg (p.o., 30 min pretreatment time). Ramelteon is an unscheduled drug with an identical mechanism of action to tasimelteon that is also indicated for sleep disorders. The vehicle for ramelteon was methylcellulose in purified water.

Doses of midazolam, including the training dose, were selected based on experience with oral midazolam in drug discrimination paradigms. Tasimelteon doses of 5 and 25 mg/kg were selected with the intent to provide adequate plasma exposure of tasimelteon (up to 3 times the average maximum clinical exposure at the 20 mg dose tested in humans) and of the M9, M12, and M14 metabolites. The dose of 11.2 mg/kg tasimelteon was an approximate half-log between the 5 and 25 mg/kg doses. The addition of 250 mg/kg tasimelteon was selected with the intent to achieve similar exposure levels of the M13 metabolite in rats as those seen in humans. The doses for the comparator compound (ramelteon) were selected based on published information.

## **Results:**

Rats trained to discriminate midazolam from vehicle showed full generalization ( $\geq 80\%$ ) when challenged with the training dose of midazolam (3.0 mg/kg, 86%), but only partial generalization (20-80%) to the 1.7 and 10.0 mg/kg doses of midazolam (36% and 71%, respectively), and no generalization ( $\leq 20\%$ ) to the 1.0 mg/kg dose of midazolam (12%) or to vehicle (5%).

In contrast, tasimelteon did not produce generalization to midazolam at doses of 5.0, 11.2 or 25 mg/kg ( $< 2\%$  for each dose). At 250 mg/kg of tasimelteon, there was partial generalization to midazolam (50%). However, the Sponsor notes that this partial generalization was based on “two very lethargic rats lever pressing on the appropriate drug lever, but not meeting the FR10 criteria and had a dramatically reduced response rate.” A third animal tested at 250 mg/kg met criteria but had a 0% response on the midazolam lever. No further animal testing at this very high dose was conducted.

Similarly, ramelteon did not produce generalization to midazolam at 1.0, 3.0, 10 or 30 mg/kg ( $< 2\%$  for each dose).

### **Sponsor Conclusion:**

“These data indicate that tasimelteon and ramelteon did not produce a discriminative cue that generalized to the training dose of 3 mg/kg midazolam. This indicates that rats did not recognize the stimulus effects of orally administered tasimelteon or ramelteon as similar to the midazolam training cue. The ability to respond on the task, as indicated by response rates on the discrimination, was not compromised at the doses that were fully assessed and did not generalize to midazolam.”

### **CSS Conclusion:**

There are design flaws in the study protocol which make this study invalid:

#### **1) The challenge sessions with midazolam, tasimelteon and ramelteon may not have been conducted at Tmax.**

In this study, all drugs were administered orally, which is atypical for drug discrimination because it can produce uneven drug absorption. Although a 30 minute pretreatment time was selected for all drugs, no pharmacokinetic data were provided to verify that this time corresponded to Tmax for midazolam or ramelteon following oral administration. Pharmacokinetic data for tasimelteon following oral administration to rats (provided elsewhere in the NDA) show that the Tmax for males was 4-6 hours, while the Tmax for females was 30 minutes. Since this study used male rats only, the animals were not tested at the time of peak plasma levels for tasimelteon. Thus, it is not possible to conclude that tasimelteon did not generalize to midazolam.

#### **2) Ramelteon was not used as a training drug**

CSS had recommended the use of ramelteon as a control drug to determine whether tasimelteon generalized to ramelteon, since they both are melatonin agonists. However, the design of this study did not include a comparison of tasimelteon in rats trained to discriminate ramelteon from vehicle. Instead, ramelteon was only tested in midazolam-trained animals. Thus, there are no data showing whether tasimelteon produces interoceptive cues that are similar to those produced by ramelteon.

It is important to note that generalization between two drugs in a drug discrimination study is highly dependent on similarity between the pharmacological mechanism of action of the drugs. Thus, even though drugs may produce similar behavioral effects (e.g., sedation), if they do not have similar mechanisms of action, they are not likely to show generalization to each other. Therefore, it is very unlikely that tasimelteon (a melatonin agonist) would have produced full generalization to midazolam (a GABA agonist), even if the study had been conducted at Tmax, since their mechanisms of action are different. This strongly suggests that the lack of a valid drug discrimination study is not a deficit in terms of whether a complete abuse potential assessment has been conducted for tasimelteon.

## 4.2 Abuse-Related Clinical Studies

### 4.2.1 Abuse-Related Adverse Events in Clinical Studies

Based on the data provided in the NDA, a total of 1346 individuals were exposed to a minimum of one dose of tasimelteon. A total of 621 individuals were exposed to the proposed therapeutic dose of 20 mg/day, with 149 (24%) exposed for at least 12 weeks, 111 (18%) for at least 26 weeks, and 44 (7%) for at least 52 weeks. In addition, 555 subjects were exposed to at least one dose of tasimelteon at doses higher than 20 mg.

There were three primary adverse events (AEs) related to the central nervous system that occurred during tasimelteon administration. Headache was reported in 10-15% of subjects in tasimelteon groups, compared to 6-7% in placebo groups. Vivid or unusual dreams ranged from 3-8% with tasimelteon, compared to 1-4% for placebo. And somnolence (an AE related to the indication of a treatment for sleep disorder) was reported in 3-6% of tasimelteon-treated subjects, compared to 1-2% for placebo.

There were no abuse-related AEs reported following administration of tasimelteon or placebo. This is similar to the profile observed for ramelteon, the only other melatonin agonist that has been approved by FDA.

### 4.2.2 Human Physical Dependence Study (Study #VP-VEC-162-3203)

The Sponsor did not conduct a preclinical physical dependence study in animals. Instead, the Sponsor chose to conduct a human physical dependence study. At the EOP2 meeting in 2007, CSS conveyed to the Sponsor that the assessment of whether tasimelteon produces physical dependence in humans must include the following study design criteria:

- a) chronic administration of the drug to a clinical population
- b) a minimum of two-week observation period following drug discontinuation
- c) daily evaluation of behavioral signs and symptoms of withdrawal
- d) use of a benzodiazepine-withdrawal instrument to assess withdrawal
- e) prospective assessment of withdrawal

The study reviewed below fulfills these criteria.

**Title:** A randomized withdrawal study to demonstrate the maintenance of effect of 20 mg tasimelteon in the treatment of Non-24HSWD (Study #VP-VEC-162-3203)

#### **Methods:**

This was a multicenter, randomized withdrawal, placebo-controlled study designed to evaluate the long-term maintenance effect and safety of 20 mg of tasimelteon compared to placebo in patients with Non-24. All patients participated in a Pre-Randomization Phase, consisting of an open-label 20 mg tasimelteon run-in Phase for 6 weeks, followed

by an Estimation Phase for 6 weeks. Twenty patients whose data indicated entrainment to a 24-hour clock participated in a Randomized Withdrawal Phase, in which they received either placebo or 20 mg tasimelteon (n = 10/group) for 8 weeks.

During the Randomized Withdrawal Phase, patients continued to complete sleep diaries twice daily, and were contacted by telephone to collect information regarding AEs. All patients completed the Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ) on Days D0, D1, D2, D7, and D14. The BWSQ consists of 20 symptoms and each symptom was rated from 0 to 2. The maximum possible score was 40 with high scores indicating presence of symptoms. Each symptom score, the total score, and the change from Day D0 score were summarized by visit for each treatment group.

### **Results:**

During the withdrawal phase, there were few AEs. Those patients who continued to receive tasimelteon reported more AEs (n = 1-3 of 10 patients for liver enzyme increase, headache, somnolence/sleep disorder and twitching) compared to those who were switched to placebo and were undergoing tasimelteon discontinuation (n = 1-2 of 10 patients for unspecified AEs in categories of nervous system disorders, urinary disorders and psychiatric disorders).

There were no major treatment differences were observed in the BWSQ with scores ranging from 0 to 1 for the placebo group undergoing tasimelteon discontinuation and 0 to 9 for the tasimelteon group between Days 0 and 14.

### **Sponsor Conclusion:**

“With a maximum possible score of 40, the low scores indicated there were no withdrawal symptoms present in either treatment group.” Thus, the Sponsor concludes that tasimelteon does not produce physical dependence in humans.

### **CSS Conclusion:**

CSS concurs with the Sponsor that tasimelteon does not produce physical dependence in humans.

### **4.2.3 Human Abuse Potential Study**

At a meeting on October 28, 2011, CSS informed the Sponsor that, “A human abuse potential study with tasimelteon will be required if the nonclinical abuse-related studies (drug discrimination and self-administration) show positive signals. However, a human abuse potential study will not be needed if the nonclinical studies were to show that tasimelteon does not maintain self-administration, does not generalize to the proposed positive control benzodiazepine, but does generalize to ramelteon.” At that time, CSS

provided feedback to the Sponsor on a protocol for a human abuse potential study, in case preclinical data showed abuse-related signals.

**Sponsor Conclusion:**

The preclinical data do not show any abuse-related signals, so a human abuse potential study was not conducted or submitted in the NDA.

**CSS Conclusion:**

CSS concurs with the Sponsor that the receptor binding, drug discrimination, and self-administration studies do not show an abuse potential signal. Therefore, a human abuse potential study conducted with tasimelteon is not necessary.

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/s/  
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KATHERINE R BONSON  
11/26/2013

SILVIA N CALDERON  
11/26/2013

MICHAEL KLEIN  
11/26/2013

**M E M O R A N D U M**

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

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**CLINICAL INSPECTION SUMMARY**

DATE: November 4, 2013

TO: Cathleen Michaloski, Regulatory Health Project Manager  
Devanand Jillapalli, M.D. Clinical Reviewer  
Division of Neurology Drug Products

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

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

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

SUBJECT: Evaluation of Clinical Inspections

NDA: 205-677

APPLICANT: Vanda Pharmaceuticals Inc.

DRUG: Tasimelteon (VEC-162)

NME: No

THERAPEUTIC CLASSIFICATION: Priority review

INDICATION: Treatment of non 24 hour sleep-wake disorder in blind patients without light perception.

CONSULTATION REQUEST DATE: June 20, 2013  
DIVISION ACTION GOAL DATE: January 30, 2014  
INSPECTION SUMMARY GOAL DATE: N/A  
PDUFA DATE: January 30, 2014

## **I. BACKGROUND:**

Many biological processes, including melatonin and cortisol secretion, sleep–wake patterns, alertness, performance patterns, metabolism and cardiovascular processes have a circadian component. Circadian rhythms are regulated by an endogenous circadian pacemaker that in mammals resides in the suprachiasmatic nuclei (SCN) of the hypothalamus, which spontaneously generates circadian rhythms within a period of 24 hours, and in turn regulates biological functions controlled by the clock. Circadian rhythms are precisely synchronized (entrained) to the 24-hour day by exposure to environmental time cues, the strongest of which is the daily light-dark cycle, which is detected exclusively by the eyes. In the absence of light (most blind people), the primary environmental synchronizer is lost and the circadian rhythms will follow the non-24 hour-period of the endogenous circadian pacemaker.

Non-24 Hour Sleep-Wake Disorder (N24HSWD), occurs when individuals are unable to synchronize their endogenous circadian clock to the 24-hour light-dark cycle. The majority of reported cases of N24HSWD occur in blind people with conscious perception of light. The disorder is associated with significant clinical symptoms and increases risk of errors, accidents, and attention lapses which can be mistakenly diagnosed as insomnia, rather than as a result of a non-entrained circadian clock. For blind individuals, the sleeplessness and daytime fatigue that results from being blind non-entrained have profound impacts on their social and occupational lives and can be considered the most disabling aspects of their blindness. The ultimate goal in treating individuals with N24HSWD was to synchronize their circadian clock with the 24-hour day so that all of their physiology and behavior is aligned appropriately with the 24- hour social day. Two clinical trials were submitted in support of the application: Protocols VP-VEC-162-3201 and VP-VEC-162-3203.

**Protocols:** VP-VEC-162-3201 entitled “A Multicenter, Randomized, Double-Mask, Placebo-Controlled, Parallel Study to Investigate the Efficacy and Safety of 20 mg Tasimelteon Versus Placebo in Totally Blind Subjects with N24HSWD Followed by an OLE Phase” and

VP-VEC-162-3203 entitled “A Randomized, Withdrawal Study to Demonstrate the Maintenance of Effect of 20 mg Tasimelteon in the Treatment of N24HSWD’.

### **Investigational Drug**

Vanda Pharmaceuticals Inc. has developed a novel product to treat subjects who are totally blind and suffer from occasional sleeplessness associated with poor quality or quantity of sleep and excessive sleepiness resulting from a Non-24 hour Sleep-Wake Disorder who are unable to synchronize their endogenous circadian clock to the 24-hour light- dark cycle.

Tasimelteon, VEC-162, is a circadian regulator with specific and potent agonist activity at the MT1 and MT2 melatonin receptors located primarily at the SCN. The pharmacological properties of tasimelteon and preliminary experience, suggest that tasimelteon may be an effective therapy for patients suffering from N24HSWD. The applicant conducted a study to evaluate the efficacy and safety of 20 mg of tasimelteon versus placebo in blind patients with non-entrained circadian rhythms.

Although Tasimelteon is not an NME, it is currently being reviewed as part of an application to treat individuals with N24HSWD to synchronize their circadian clock and improve their physiology and behavior with the 24-hour day.

### **Protocol VP-VEC-162-3201**

The study was a multicenter, randomized, double-masked, placebo-controlled, parallel study designed to evaluate the efficacy and safety of 20 mg of tasimelteon versus placebo in patients suffering from Non-24HSWD. The study consisted of a pre-randomization phase known as a screening visit, followed by either a randomization phase or an open-label extension phase. Approximately 84 subjects were randomized in a ratio 1:1 to receive tasimelteon (20 mg/day) or placebo. Qualified subjects were administered one of the following 2 treatment groups:

- Tasimelteon 20 mg/day treatment group for 26 weeks
- Placebo 20 mg/day treatment group for 26 weeks

The primary objectives of this study were 1) to determine the efficacy of tasimelteon in patients with N24HSWD as measured by the proportion of entrainment, and 2) to determine the efficacy of tasimelteon in patients with N24HSWD as measured by the proportion of patients with a clinical response. Clinical response was defined as the coincident demonstration of:

- Entrainment of the 6-sulfatoxymelatonin (aMT6s) rhythms and
- A score of equal or greater than 3 on the Non-24 Clinical response Scale (N24CRS).

The secondary objectives of this study were: 1) to determine the efficacy of tasimelteon in patients with N24HSWD as measured by the proportion of responders with a combined sleep/wake response for nighttime sleep duration and daytime sleep duration defined as:

1. Increase of 90 minutes or greater in the lower quartile of nights of subjective nighttime total sleep time (LQ-nTST) and
2. Decrease of 90 minutes or greater in the upper quartile of the days of subjective daytime sleep duration (UQ-dTSD). I refer the field investigator to pages 19-20 of the protocol for additional objectives.

**Protocol VP-VEC-162-3203**

This study was a multicenter, randomized withdrawal, double-masked, placebo-controlled, parallel study. The study has three phases: the tasimelteon run-in-phase, the tau estimation phase, and the randomization withdrawal phase. Subjects who participated in study VP-VEC-162-3201 that meet the entry criteria for this study were eligible for the run-in phase. The run-in phase comprises of a screening visit where subjects' initial eligibility were evaluated. Subjects that meet the inclusion/exclusion criteria at screening were assigned to enter the run-in phase and will be dosed with 20 mg of tasimelteon daily for 6 weeks.

Male and females with Non-24 hour sleep-wake disorder that participated in study VP-VEC-162-3201 and responded to treatment as measured by entrainment of their melatonin circadian rhythms were included in this study.

The primary objectives of this study were: 1) to demonstrate the maintenance of effect of tasimelteon to entrain circadian rhythms in subjects with N24HSWD, and 2) to measure entrainment of urinary 6-sulfatoxymelatonin (aMT6s).

The secondary objectives of this study were: 1) to demonstrate the maintenance of effect of tesimelteon to entrain circadian rhythms in subjects with N24HSWD as assessed by urinary cortisol, and 2) to demonstrate the maintenance of effect of tasimelteon on subjective nighttime total sleep time in subjects with N24HSWD as assessed by the change from run-in phase in the average total sleep time (nTST).

Four domestic site inspections are being requested in support for this NDA which includes protocols VP-VEF-162-3201 and VP-VEC-162-3203.

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

District	Name of CI/Address/ and Site #	Protocol #s and # of Subjects	Inspection Dates	Final Classification
Baltimore	Helene Emsellem, M.D. Center of Sleep and Wake Disorder 5454 Wisconsin Ave, Suite 1725 Chevy Chase, MD 20815 Site #401	VP-VEF-162-320 8 subjects	7/26-29/13	NAI
New England	Steven Lockely, M.D. Division of Sleep Medicine Brighman and Women's Hospital 2211 Longwood Avenue Boston, MA 02115 Site #412	VP-VEF-162-3201 and 3203 P3201-7pts P3202-2pts	8/6-9/13	NAI
Philadelphia	P.David Laman, M.D. Consolidated Clinical Trials 4240 Greenburg Pike, Suite 103 Pittsburgh, PA 15025 Site #410	VP-VEF-162-3201 and 3203 P3201-4pts P3202-3pts	8/21-27/13	NAI

Los Angeles	Daniel Norman, M.D. St. John Sleep Disorder Center 1301 Twentieth Street, Suite 360 Santa Monica, CA 90404 Site #424	VP-VEF-162-3201 and 3203 P3201-6pts P3202-2pts	7/24-8/2/13	NAI
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Key to Classifications

NAI = No deviations

VAI = Deviation(s) from regulations

OAI = Significant deviations from regulations. Data unreliable.

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

1. **Helene Emsellem, M.D.**  
**Chevy Chase, MD 20815**

**a. What Was Inspected:** At this site, 28 subjects were screened, 20 subjects were reported as screen failures, eight subjects were randomized into the study, and three subjects completed the study. Two subjects were terminated early, one subject completed the Open-Label Phase (OLE), and two subjects discontinued the OLE. Review of the Informed Consent Documents, for all subjects records reviewed, verified that subjects signed informed consent forms prior to enrollment. One blind subject listened to an audio version of the informed consent document in the presence of a representative and signed the informed consent document.

The medical records/source documents for all subjects were reviewed. The data for primary/secondary endpoints could not be reviewed because the data for the primary efficacy endpoint of entrainment of the 6-sulfaoxymelatonin (aMT6s) present in the urine samples were not analyzed at the site in order to maintain the blind. However, the field investigator was able to confirm that the site physician ordered the collection of urine samples to send the laboratory for analyses. The site received confirmation of receiving the urine samples but not the results. The medical records/source documents for all subjects were reviewed including drug accountability records, vital signs, IRB files, laboratory results, inclusion/exclusion criteria, and use of concomitant medications, and adverse events reporting. Source documents for all subjects were compared to case report forms and data listings except for primary efficacy endpoints.

**b. General observations/commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Amsellem. Overall, the medical records reviewed were found to be in order, organized, and the data verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were limitations to the inspection only due to the fact that the primary efficacy endpoints were not available at the site.

**c. Assessment of Data Integrity:** The data in support of the clinical efficacy and safety at Dr. Emsellem’s site are considered reliable and acceptable in support of the application.

2. **Steven Lockley, M. D.**  
**Boston, MA 02115**

**a. What Was Inspected:** Protocol VP-VEC-162-3201: At this site, a total of 27 were screened, 20 subjects were reported as screen failures and the reasons were documented. Seven subjects were randomized into the study, and four subjects completed the study. Two subjects were enrolled into the Open-Label Phase of the study and both completed the study.

For protocol VP-VEC-162-3202: At this site, a total of four subjects were screened, four subjects randomized, and two subjects completed the study.

Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed consent forms prior to enrollment.

The medical records/source documents for the majority (9) of the subjects in both protocols were reviewed. The data for primary/secondary endpoints could not be reviewed because the data for the primary efficacy endpoint of entrainment of the 6-sulfaoxymelatonin (aMT6s) present in the urine samples were not analyzed at the site in order to maintain the blind. However, the field investigator was able to confirm the tau data only (the screening results) that the site physician ordered the collection of urine samples to send the laboratory for analyses. The site received confirmation of receiving the urine samples but not the results. The medical records/source documents for certain subjects were reviewed including drug accountability records, vital signs, IRB files, laboratory results, inclusion/exclusion criteria, and use of concomitant medications, and adverse events reporting. Source documents for all subjects were compared to case report forms and data listings except for primary efficacy endpoints.

**b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Lockley. The medical records reviewed were found to be in order, organized, and the data verifiable. There were limitations to the inspection only due to the fact that the primary efficacy endpoints were not available at the site.

**c. Assessment of Data Integrity:** The data generated at Dr. Lockley’s site in support of the clinical efficacy and safety are considered acceptable and may be used in support of the pending application.

**3. Paul.D Laman, Jr., M.D.  
Pittsburg, PA 15025**

**a. What Was Inspected:** Protocol VP-VEC-162-301: At this site, a total of 15 subjects were screened, seven subjects were reported as screen failures and the reasons were documented. Four subjects were randomized into the study, and all completed the study. Four subjects were not eligible for randomization, and three of the four subjects who were not eligible for randomization were enrolled in the Open-Label Phase of the study.

For protocol VP-VEC-162-3202: At this site, a total of six subjects were screened, three were reported as screen failures, and three subjects randomized and completed the study.

Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed consent forms prior to enrollment.

The medical records/source documents for a total of (11) subjects in both protocols were reviewed. The data for primary/secondary endpoints could not be reviewed because the data for the primary efficacy endpoint of entrainment of the 6-sulfaoxymelatonin (aMT6s) present in the urine samples were not analyzed at the site in order to maintain the blind. However, the field investigator was able to confirm the tau data only (the screening results) that the site physician ordered the collection of urine samples to send the laboratory for analyses. The site received confirmation of receiving the urine samples but not the results. The medical records/source documents for 11 subjects were reviewed including drug accountability records, vital signs, IRB files, laboratory results, inclusion/exclusion criteria, and use of concomitant medications, and adverse events reporting. Source documents for all subjects were compared to case report forms and data listings except for primary efficacy endpoints. There were no evidence of inaccuracy of the data captured. However, the field investigator discussed with the clinical investigator the failure to perform urine pregnancy test on Subject (b) (6) at Visits 2, 3 and 4 in error. Subsequent visits revealed negative pregnancy results. Subject (b) (6) had an abnormal EKG in which the clinical investigator decided the ECG changes were not considered as an adverse event. Thus, the impact of these errors was minor.

**b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Laman. The medical records reviewed were found to be in order, organized, and certain data were verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were known limitations to the inspection due to the fact that the primary efficacy endpoints were not available at the site for review.

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

**4. Daniel Norman, M.D.  
Santa Monica, CA 90404**

**a. What Was Inspected:** Protocol VP-VEC-162-301: At this site, a total of 18 subjects were screened, 11 subjects were reported as screen failures, seven subjects were randomized into the study, and one subject withdrew after randomization; five subjects were randomized into the study and all completed the study. One subject completed the Open-Label Phase of the study.

For protocol VP-VEC-162-3202: At this site, a total of four subjects were screened, one subject was reported as a screen failure, one subject withdrew consent, and two subjects were randomized and completed the study.

Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed consent forms prior to enrollment.

The medical records/source documents for a total of 10 subjects in both protocols were reviewed. The data for primary/secondary endpoints could not be reviewed because the data for the primary efficacy endpoint of entrainment of the 6-sulfaoxymelatonin (aMT6s) present in the urine samples were not analyzed at the site in order to maintain the blind. However, the field investigator was able to confirm the tau data only (the screening results) that the site physician ordered the collection of urine samples to send the laboratory for analyses. The site received confirmation of receiving the urine samples but not the results. The medical records/source documents for 10 subjects were reviewed including drug accountability records, vital signs, IRB files, laboratory results, inclusion/exclusion criteria, financial disclosure and use of concomitant medications, and adverse events reporting. Source documents for all subjects were compared to case report forms and data listings except for primary efficacy endpoints. There were no evidence of inaccuracy of the data captured. No FDA 483 was issued.

**b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Laman. The medical records reviewed were found to be in order, organized, and certain data were verifiable. There were no deaths and no evidence of under-reporting of adverse events. There were known limitations to the inspection due to the fact that the primary efficacy endpoints were not available during the inspection.

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

**III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS**

Four clinical investigator sites were inspected in support of this application. The inspections of Drs. Emsellem, Lockley, Laman and Norman revealed no regulatory violations, and the final classifications for these inspections are noted above as No Action Indicated (NAI).

Overall, the data submitted from these four sites are considered acceptable in support of the pending application.

*{See appended electronic signature page}*

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

CONCURRENCE:

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**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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ANTOINE N EL HAGE  
11/07/2013

SUSAN D THOMPSON  
11/07/2013

KASSA AYALEW  
11/07/2013

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

<b>NDA</b>	205677
<b>Generic Name</b>	Tasimelteon /VEC-162
<b>Sponsor</b>	Vanda Pharmaceuticals, Inc.
<b>Indication</b>	Non-24-Hour Disorder in the totally blind
<b>Dosage Form</b>	Capsules
<b>Drug Class</b>	Human Melatonin Receptor agonist
<b>Therapeutic Dosing Regimen</b>	20 mg/day
<b>Duration of Therapeutic Use</b>	Chronic
<b>Maximum Tolerated Dose</b>	300 mg/day
<b>Submission Number and Date</b>	SDN 000/31 May 2013
<b>Review Division</b>	DNP

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

### 1 SUMMARY

#### 1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effects of VEC-162 (doses of 20 mg and 300 mg) were detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean differences between VEC-162 and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the 2-sided 90% CI for the  $\Delta\Delta\text{QTcI}$  for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 3, indicating that assay sensitivity was established.

In this randomized, 4-period, multiple-dose, crossover study, 44 healthy subjects received VEC-162 20 mg, VEC-162 300 mg, placebo, and moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

**Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for VEC-162 (20 mg and 300 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)**

Treatment	Time (hour)	$\Delta\Delta\text{QTcI}$ (ms)	90% CI (ms)
VEC-162 20 mg	2	5.0	(1.8, 8.2)
VEC-162 300 mg	2	1.6	(-1.6, 4.7)
Moxifloxacin 400 mg*	2	15.7	(12.6, 18.9)

\* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is 11.4 ms

The suprathreshold dose (300 mg) produces mean  $C_{\text{max}}$  values 13-fold the mean  $C_{\text{max}}$  for the therapeutic dose (20 mg). These concentrations are above those for the predicted worst case scenario of tasimelteon in clinical practice when metabolic inhibitors (CYP1A2 and 2C9) are coadministered.

## 2 PROPOSED LABEL

*QT-IRT's proposed labeling language is a suggestion only. We defer final labeling decisions to the Division.*

(b) (4)

## 3 BACKGROUND

### 3.1 PRODUCT INFORMATION

Tasimelteon is a novel orally active circadian regulator that demonstrates high affinity and agonist activity for both the human melatonin MT1 and MT2 receptors and is being developed for the treatment of Non-24-Hour Disorder in the blind, other Circadian Rhythm Sleep Disorders (CRSD) and mood disorders including Major Depressive Disorder (MDD).

### 3.2 MARKET APPROVAL STATUS

Tasimelteon is not approved for marketing in any country.

### 3.3 PRECLINICAL INFORMATION

From IB, December 2012

Tasimelteon did not produce any statistically significant effects on action potential parameters in isolated rabbit cardiac Purkinje fibers except for a shortening of the APD90 100  $\mu$ M at 1 s and 0.5 s BCL. Tasimelteon at all three concentrations did not induce statistically significant ( $P < 0.05$ ) changes in resting membrane potential (RMP), action potential amplitude (APA) and the maximum rate of depolarization ( $V_{max}$ ) at two stimulus intervals.

Tasimelteon inhibited hERG current by (Mean  $\pm$  SEM;  $n = 3$ )  $14.0 \pm 2.2\%$  at 100  $\mu$ M versus  $0.7 \pm 0.4\%$  ( $n = 3$ ) in control. The hERG inhibition at 100  $\mu$ M was statistically significant ( $P < 0.05$ ) when compared to vehicle control values. Since higher soluble concentrations were not tested, the median inhibitory concentration of tasimelteon on hERG potassium current could not be determined.

*Reviewer's comments: Tasimelteon slightly blocks hERG currents with very low affinity (22% inhibition with 100  $\mu$ M).*

### 3.4 PREVIOUS CLINICAL EXPERIENCE

From ISS, eCTD 2.7.4

The current safety data available and incorporated into the Integrated Summary of Safety (ISS) includes data from fourteen Phase I studies, two Phase II studies, and six Phase III studies. Two Phase III open-label safety studies of totally blind adults with a diagnosis of Non-24 are ongoing.

In the overall safety database, there were 20 subjects with reported cardiac or cardiac-related adverse events that were treatment-emergent. Of these 20 subjects, 19/1346 (1.4%) occurred in tasimelteon-treated subjects and 1/306 (0.3%) occurred in placebo-treated subjects. As the total person days for the tasimelteon-treated group ( $N=1346$ , Mean Exposure = 44.6 days) is over 8 times greater than the total person days for the placebo-treated group ( $N=306$ , Mean Exposure = 22.9 days) (ISS Table 1.0.3.2), the difference in the incidence of events between treatment groups is mitigated.

**Table 2: Study Groups in the Tasimelteon Integrated Summary of Safety**

Study Group	Population Studied	Purpose of Group	Tasimelteon N	Placebo N
1	All subjects in all studies	Overall safety database	1,346	306
2	Subjects with insomnia or Non-24	Placebo-controlled phases in repeated dosing efficacy studies	429	203
2.1	Subjects with insomnia or Non-24, non-elderly studies	Non-elderly, placebo-controlled phases in efficacy studies	259	146
3	Subjects with Non-24	Target indication, placebo-controlled	52	52
4	Subjects with Non-24	Target indication, all safety data in exposed subjects	183	N/A
5	Clinical Pharmacology and Healthy Volunteers	All studies not included in Groups 2-4	776	131

Source: ISS Table 1.0.1, ISS Table 2.0.1, ISS Table 2.1.1, ISS Table 3.0.1, ISS Table 4.0.1, ISS Table 5.0.1

*Reviewer's comments: No deaths were reported during these studies. No clinically relevant ECG changes were reported.*

### 3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of VEC-162's clinical pharmacology.

## 4 SPONSOR'S SUBMISSION

### 4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 54,776. The sponsor submitted the study report VP-VEC-162-1103 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

### 4.2 TQT STUDY

#### 4.2.1 Title

A Double-Blind Randomized Cross-Over Trial to Define the ECG Effects of VEC-162 Using a Clinical and a Supratherapeutic Dose Compared to Placebo and Moxifloxacin (a Positive Control) in Healthy Men and Women: a Thorough ECG Trial

#### 4.2.2 Protocol Number

VP-VEC-162-1103

#### 4.2.3 Study Dates

Date first subject enrolled: 22 June 2007

Date last subject completed: 16 June 2007

#### 4.2.4 Objectives

**Primary objective:** To characterize the effect of 20 mg/day and 300 mg/day of VEC-162 on QT intervals in healthy volunteers.

**Secondary objective:** To assess the pharmacokinetic-pharmacodynamic (PK/PD) relationship between plasma concentrations of VEC-162 and its effect, if any, on electrocardiogram (ECG) parameters.

##### 4.2.4.1 Design

This was a 4-period, randomized, double-blind (except for the use of moxifloxacin), multiple-dose, crossover study in healthy men and women. Each treatment period consisted of three dosing days and four washout days.

##### 4.2.4.2 Controls

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

##### 4.2.4.3 Blinding

Moxifloxacin was administered as a positive control in an open-label manner.

#### 4.2.5 Treatment Regimen

##### 4.2.5.1 Treatment Arms

Subjects took the following study treatments in a random order:

- VEC-162, 20 mg orally once a day for three days
- VEC-162, 300 mg orally once a day for three days
- Moxifloxacin, 400 mg orally on Day 3 (placebo on Days 1 and 2)
- Placebo for three days

##### 4.2.5.2 Sponsor's Justification for Doses

The selection and timing of the doses were chosen to meet FDA guidance standards for a thorough ECG trial. The clinical dose of VEC-162 is 20 mg/day. The half-life of VEC-162 is less than three hours, and no accumulation is expected with once-daily dosing. Consequently, steady-state is the same as a single dose and is achieved with the first dose. Three days of dosing was considered sufficient "steady-state" exposure to meet the objectives of this study. The 300-mg suprathreshold dose of VEC-162 mimics the exposure in healthy volunteers that might occur in the target population under the worst of circumstances, including effects related to the use of concomitant drugs and hepatic impairment. The 400-mg dose of moxifloxacin increases the QT interval in a reliable fashion, and thereby provides a measure of the "assay sensitivity" of the trial.

*Reviewer's Comment: Sponsor's dose selection appeared reasonable.*

##### 4.2.5.3 Instructions with Regard to Meals

Subjects fasted for 10 hours before dosing (Baseline and Day 3), and remained fasting until four hours after dosing (except for water).

*Reviewer's Comment: The sponsor's instruction on drug administration with regard to food is reasonable because  $C_{max}$  decreases with a high fat meal.*

##### 4.2.5.4 ECG and PK Assessments

ECG data were collected and assessed at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 18, 23.5 hours after Day 3 tasimelteon dose. The  $T_{max}$  of tasimelteon is 0.5-2.5 hours and the terminal half-life of tasimelteon is about 1.3 hours.

*Reviewer's Comment: The reviewer agrees with the timing of ECGs because it covers the period of tasimelteon peak exposure and potential delays over 24 hours.*

#### **4.2.5.5 Baseline**

The sponsor used the time-match of the individual QTc values on Day -1 as baseline.

#### **4.2.6 ECG Collection**

Intensive 12-Lead Holter monitoring will be used to obtain digital ECGs. Standard 12-Lead ECGs will be obtained while subjects are recumbent.

#### **4.2.7 Sponsor's Results**

##### **4.2.7.1 Study Subjects**

A total of 44 subjects (22 female, 22 male) were enrolled and forty-two subjects (95.5%) completed the study. Mean age was 30 years (18, 44) , BMI 25 Kg/m<sup>2</sup> (20, 30).

Two subjects discontinued from the study for personal reasons. All 44 subjects were included in the ECG analysis, PK, and safety populations.

##### **4.2.7.2 Statistical Analyses**

###### **4.2.7.2.1 Primary Analysis**

The primary endpoint was time-matched baseline-adjusted mean differences between VEC-162 (20 mg and 300 mg) and placebo in QTcI. The sponsor used an analysis of covariance model with gender and treatment group as factors and the results are presented in Table 3. This model included gender, time, treatment, and time-by-treatment interaction as fixed effect terms, and baseline as covariate. The upper limits of the 2-sided 90% CI for VEC-162 (20 mg and 300 mg) were below 10 ms.

**Table 3: Sponsor Results  $\Delta\Delta$ QTcI for VEC-162 20 mg, VEC-162 300 mg and Moxifloxacin 400 mg**

Time (h)	VEC-162 20 mg		VEC-162 300 mg		Moxifloxacin 400 mg	
	Estimate <sup>a</sup>	Upper bound <sup>b</sup>	Estimate <sup>a</sup>	Upper bound <sup>b</sup>	Estimate <sup>a</sup>	Upper bound <sup>b</sup>
0.5	3.2	5.9	0.1	2.8	11.2	15.6
1	1.8	4.6	-0.2	2.5	13.6	18.1
2	5.1	7.9	2.1	4.9	16.0	20.4
3	1.8	4.6	-1.9	0.9	9.8	14.2
4	1.7	4.4	-0.5	2.2	13.0	17.4
5	0.7	3.5	-0.5	2.1	8.3	12.7
6	0.8	3.6	-0.1	2.6	9.3	13.7
8	0.1	2.9	0.3	3.1	6.7	11.2
10	2.3	5.0	1.0	3.7	10.2	14.6
12	0.0	2.7	1.0	3.7	9.7	14.1
14	-0.3	2.4	-1.0	1.7	5.4	9.9
18	-2.1	0.6	-0.9	1.8	7.6	12.0
23.5	-0.2	2.6	-3.4	-0.6	6.1	10.6

a Mixed-model ANOVA is fit for placebo-corrected change from Baseline and includes terms for treatment, gender, time, and a time by treatment interaction.

Upper bound = upper 1-sided 95% ANOVA model based confidence limit. (Moxifloxacin is Bonferroni-corrected.) *P*-value for gender effect (gender main effect and treatment by gender IA) is 0.0079. Treatment\*gender IA = 0.1196.

Source: *Clinical Study Report No., Table 9, Pg 63/652*

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

#### **4.2.7.2.2 Assay Sensitivity**

The sponsor used the same mixed model to analyze the  $\Delta$ QTcI effect for moxifloxacin. The analysis results were presented in Table 3. However, the sponsor did not provide lower bound result. From our independent analysis, the largest unadjusted lower bound 2-sided 90% is 12.6 was greater than 5 ms. Thus, assay sensitivity in this thorough QTcI study was established.

#### **4.2.7.2.3 Categorical Analysis**

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

#### **4.2.7.3 Safety Analysis**

No deaths or SAEs were reported. There were no clinically relevant ECG abnormalities reported, no abnormal T-waves were reported.

#### **4.2.7.4 Clinical Pharmacology**

##### **4.2.7.4.1 Pharmacokinetic Analysis**

The PK results of VEC-162 are presented in Table 4.  $C_{max}$  and AUC values in the thorough QT study were 12.8-fold and 26.7-fold, respectively, higher following administration of 300 mg compared with 20 mg drug, the intended clinical dose.

**Table 4: Mean Pharmacokinetic Parameters for VEC-162 by Treatment**

Pharmacokinetic parameter (units)	VEC-162 20 mg (N = 43)		TRK-820 300 mg (N = 43)	
	n		n	
AUC <sub>0-t</sub> (ng·h/mL)	43	396.4 (182.3)	43	10609.8 (5780.2)
AUC <sub>0-tau</sub> (ng·h/mL)	43	396.8 (182.3)	43	10609.8 (5780.2)
AUC <sub>0-inf</sub> (ng·h/mL)	30	438.5 (177.0)	43	10641.4 (5841.7)
$C_{max}$ (ng/mL)	43	194.6 (82.7)	43	2491.5 (1058.3)
$T_{max}$ (h) <sup>a</sup>	43	0.58 (0.58, 1.08)	43	1.08 (0.58, 3.08)
$T_{1/2}$ (h)	30	2.34 (1.48)	43	2.68 (0.85)
CL/F (L/h)	43	64.4 (37.1)	43	39.9 (28.0)
V <sub>d</sub> /F (L)	30	172.2 (121.6)	43	162.3 (151.9)

Source: Sponsor's Study Report Page 65.

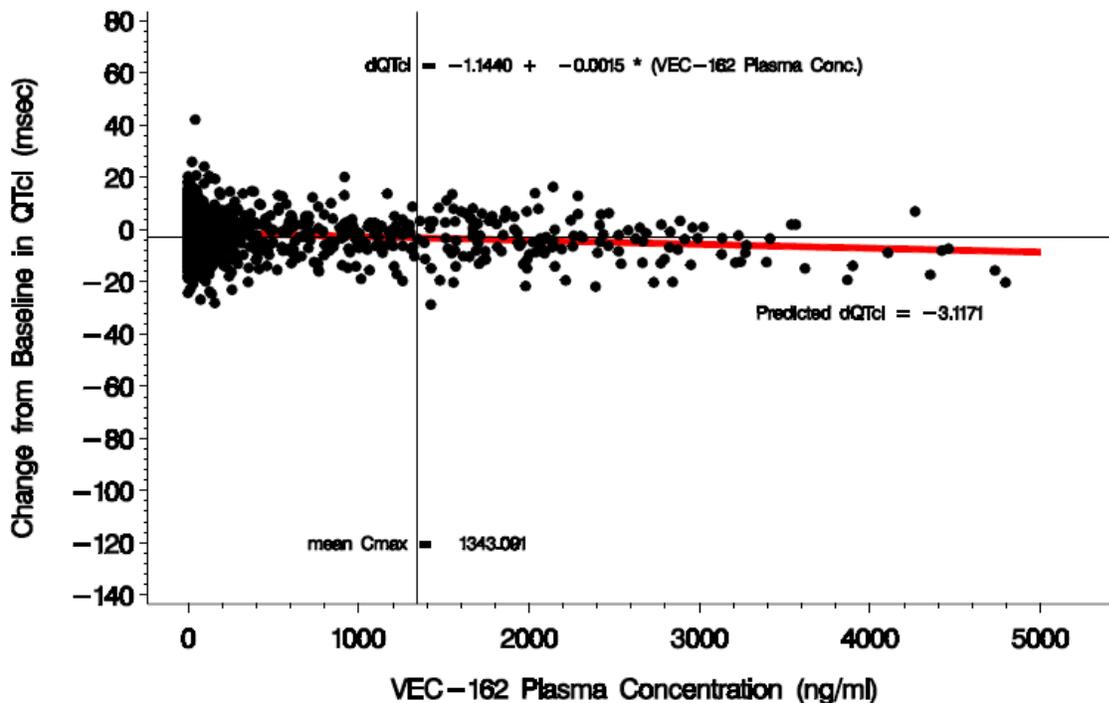
<sup>a</sup> Median (minimum, maximum)

Source: Study Report, Table 11, Page 65.

#### 4.2.7.4.2 Exposure-Response Analysis

The relationship between QTcI duration and plasma concentration from paired samples obtained in both VEC-162 dose groups is presented in Figure 1.

**Figure 1 QTcI Change from Baseline and Placebo versus VEC-162 Concentration**



Source: Study Report, Figure 2, Page 66.

The PK/PD model results show the slopes of the relationships for plasma concentration and the predicted QTc change at  $C_{max}$ . The slopes for QTcI and QTcF were negative ( $-0.0015$  for both), as were the predicted QTc changes at  $C_{max}$  ( $-3.1171$  and  $-3.0999$ , respectively). These data do not support any effect of VEC-162 on cardiac repolarization.

## 5 REVIEWERS' ASSESSMENT

### 5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

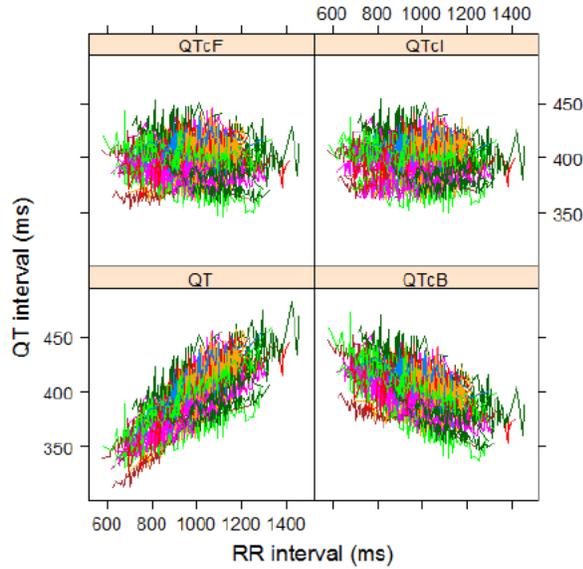
We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 5, it appears that QTcI is better than QTcF and QTcB. To be consistent with the sponsor's analyses, we choose to present QTcI results.

**Table 5: Average of Sum of Squared Slopes for Different QT-RR Correction Methods**

Treatment Group	Correction Method					
	QTcB		QTcF		QTcI	
	N	MSSS	N	MSSS	N	MSSS
20 mg VEC-162	43	0.0040	43	0.0019	43	0.0013
300 mg VEC-	44	0.0040	44	0.0009	44	0.0009
Moxifloxacin 400 mg	42	0.0037	42	0.0012	42	0.0008
Placebo	43	0.0046	43	0.0012	43	0.0007
All	44	0.0034	44	0.0011	44	0.0004

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

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



## 5.2 STATISTICAL ASSESSMENTS

### 5.2.1 QTc Analysis

#### 5.2.1.1 The Primary Analysis for the Study Drug

The statistical reviewer used mixed model to analyze the  $\Delta$ QTcI effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 6. The largest upper bounds of the 2-sided 90% CI for the mean differences between VEC-162 20 mg and placebo, and between VEC-162 300 mg and placebo are 8.2 ms and 4.7 ms, respectively.

**Table 6: Analysis Results of  $\Delta$ QTcI and  $\Delta\Delta$ QTcI for VEC-162 20 mg, VEC-162 300 mg and Moxifloxacin 400 mg**

Time (h)	Placebo	20 mg VEC-162 3 days				300 mg VEC-162 3 days				Moxifloxacin 400 mg on Day 3				
	$\Delta$ QTcI	$\Delta$ QTcI		$\Delta\Delta$ QTcI		$\Delta$ QTcI		$\Delta\Delta$ QTcI		$\Delta$ QTcI		$\Delta\Delta$ QTcI		
	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	Adj. 90% CI
0.5	-5.9	86	-3.1	2.8	(0.0, 5.6)	87	-6.3	-0.4	(-3.2, 2.4)	84	5.1	11.0	(8.2, 13.8)	(7.2, 14.9)
1	-5.5	86	-4.2	1.2	(-1.7, 4.1)	87	-6.0	-0.6	(-3.4, 2.3)	84	8.0	13.5	(10.6, 16.4)	(9.5, 17.4)
2	-6.3	83	-1.3	5.0	(1.8, 8.2)	86	-4.7	1.6	(-1.6, 4.7)	84	9.4	15.7	(12.6, 18.9)	(11.4, 20.1)
3	-0.3	85	1.4	1.6	(-1.2, 4.5)	87	-2.2	-1.9	(-4.7, 0.9)	84	9.9	10.2	(7.3, 13.0)	(6.3, 14.1)
4	-1.3	85	0.2	1.4	(-1.6, 4.5)	87	-2.2	-0.9	(-4.0, 2.1)	84	11.3	12.6	(9.5, 15.6)	(8.4, 16.8)
5	-0.7	86	-0.4	0.3	(-2.2, 2.9)	87	-1.6	-0.9	(-3.4, 1.6)	84	7.3	8.0	(5.5, 10.6)	(4.6, 11.5)
6	-0.6	85	-0.6	0.1	(-2.6, 2.7)	87	-1.1	-0.5	(-3.1, 2.2)	84	8.2	8.8	(6.2, 11.5)	(5.2, 12.4)
8	-0.0	85	0.5	0.5	(-2.3, 3.3)	85	0.3	0.3	(-2.5, 3.1)	84	7.1	7.1	(4.3, 9.9)	(3.3, 10.9)
10	-0.9	85	0.8	1.7	(-1.5, 4.8)	87	-0.5	0.4	(-2.8, 3.5)	84	8.8	9.7	(6.6, 12.9)	(5.4, 14.1)
12	-1.1	86	-1.1	0.0	(-2.8, 2.8)	86	-0.8	0.3	(-2.5, 3.1)	83	8.5	9.6	(6.7, 12.4)	(5.7, 13.5)
14	-0.2	86	-1.1	-0.9	(-3.9, 2.1)	87	-1.4	-1.2	(-4.2, 1.8)	84	5.4	5.6	(2.6, 8.6)	(1.4, 9.7)
18	-1.4	86	-4.0	-2.6	(-5.5, 0.4)	85	-3.1	-1.7	(-4.7, 1.3)	84	5.8	7.2	(4.2, 10.1)	(3.1, 11.2)

	Placebo	20 mg VEC-162 3 days				300 mg VEC-162 3 days				Moxifloxacin 400 mg on Day 3				
	$\Delta$ QTcI	$\Delta$ QTcI		$\Delta\Delta$ QTcI		$\Delta$ QTcI		$\Delta\Delta$ QTcI		$\Delta$ QTcI		$\Delta\Delta$ QTcI		
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	Adj. 90% CI
23.5	-0.3	84	-1.2	-0.9	(-3.8, 2.0)	86	-3.7	-3.3	(-6.2, -0.4)	83	5.2	5.5	(2.6, 8.4)	(1.5, 9.5)

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

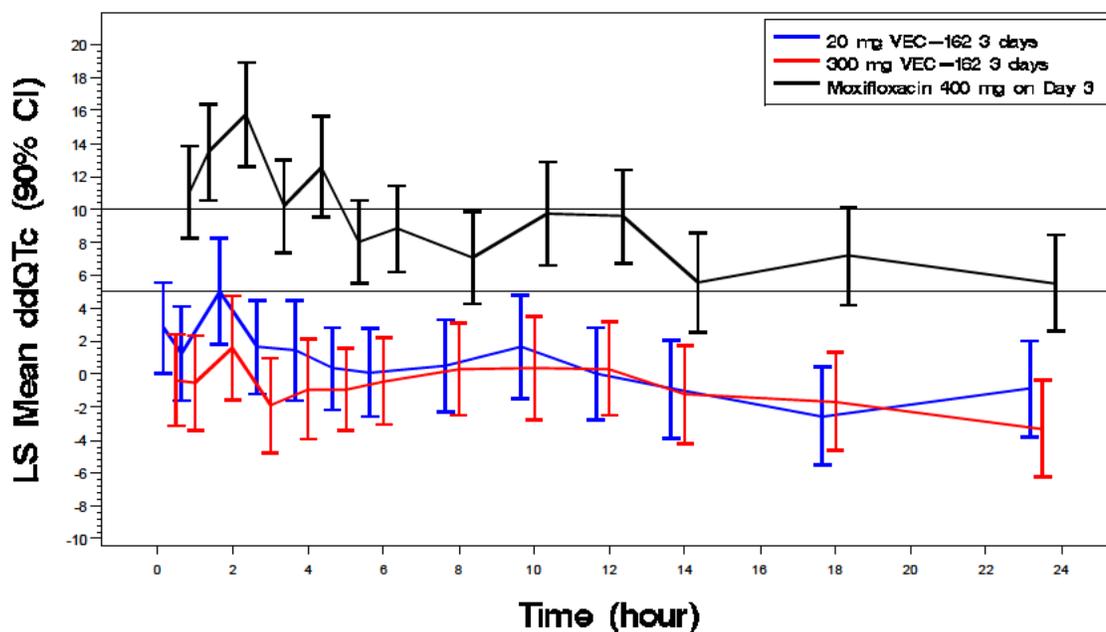
### 5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 6. The largest unadjusted of the 2-sided 90% lower confidence interval is 12.6 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 11.4 ms, which indicates that an at least 5 ms QTcI effect due to moxifloxacin can be detected from the study.

### 5.2.1.3 Graph of $\Delta\Delta$ QTcI Over Time

Figure 3 displays the time profile of  $\Delta\Delta$ QTcI for different treatment groups and moxifloxacin 400 mg.

**Figure 3: Mean and 90% CI  $\Delta\Delta$ QTcI Time Course for VEC-162 20 mg, VEC-162 300 mg and Moxifloxacin 400 mg**



### 5.2.1.4 Categorical Analysis

Table 7 lists the number of subjects as well as the number of observations whose QTcI values are  $\leq 450$  ms, and between 450 ms and 480 m, and changes from baseline QTc  $\leq 30$  ms, between 30 and 60 ms, and  $>60$  ms. No subject's QTcI is above 480 ms. No subject's change from baseline is above 60 ms (see Table 8).

**Table 7: Categorical Analysis for QTcI**

Treatment Group	Total N	Value<=450 ms	450 ms<Value<=480 ms
20 mg VEC-162	43	43 (100%)	0 (0.0%)
300 mg VEC-162	44	44 (100%)	0 (0.0%)
Moxifloxacin 400 mg	42	41 (97.6%)	1 (2.4%)
Placebo 3 days	43	43 (100%)	0 (0.0%)

**Table 8: Categorical Analysis for  $\Delta$ QTcI**

Treatment Group	Total N	Value<=30 ms	30 ms<Value<=60 ms
20 mg VEC-162	43	42 (97.7%)	1 (2.3%)
300 mg VEC-162	43	43 (100%)	0 (0.0%)
Moxifloxacin 400 mg	42	41 (97.6%)	1 (2.4%)
Placebo	43	43 (100%)	0 (0.0%)

### 5.2.2 HR Analysis

The statistical reviewer used mixed model to analyze the  $\Delta$ HR effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 9. The largest upper bounds of the 2-sided 90% CI for the mean differences between VEC-162 20 mg and placebo, and between VEC-162 300 mg and placebo are 2.1 bpm and 1.5 bpm, respectively. Table 10 presents the categorical analysis of HR. No subject who experienced HR interval greater than 100 bpm is in VEC-162 groups.

**Table 9: Analysis Results of  $\Delta$ HR and  $\Delta\Delta$ HR for VEC-162 20 mg, VEC-162 300 mg, and Moxifloxacin 400 mg**

Time (h)	Placebo	20 mg VEC-162				300 mg VEC-162				Moxifloxacin 400 mg			
	$\Delta$ HR	$\Delta$ HR		$\Delta\Delta$ HR		$\Delta$ HR		$\Delta\Delta$ HR		$\Delta$ HR		$\Delta\Delta$ HR	
	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.5	0.9	86	0.8	-0.0	(-1.8, 1.7)	87	-1.0	-1.8	(-3.6, -0.1)	84	2.9	2.0	(0.2, 3.8)
1	1.4	86	-0.4	-1.8	(-3.8, 0.2)	87	0.2	-1.2	(-3.3, 0.8)	84	3.7	2.3	(0.3, 4.3)
2	0.4	83	-1.7	-2.1	(-4.1, -0.1)	86	-1.0	-1.3	(-3.3, 0.7)	84	2.2	1.9	(-0.2, 3.9)
3	-1.1	85	-1.7	-0.6	(-2.6, 1.3)	87	-1.5	-0.5	(-2.4, 1.5)	84	0.9	1.9	(-0.0, 3.8)
4	-1.1	85	-1.1	-0.1	(-2.2, 2.1)	87	-2.9	-1.8	(-4.0, 0.3)	84	2.0	3.1	(1.0, 5.2)
5	-0.4	86	-1.3	-1.0	(-3.0, 1.1)	87	-2.8	-2.5	(-4.5, -0.4)	84	-1.6	-1.2	(-3.3, 0.9)
6	0.0	85	-2.0	-2.0	(-4.4, 0.4)	87	-2.0	-2.0	(-4.3, 0.3)	84	0.3	0.2	(-2.1, 2.6)
8	-1.0	85	-2.0	-0.9	(-3.0, 1.1)	85	-1.6	-0.5	(-2.6, 1.5)	84	0.6	1.7	(-0.4, 3.7)
10	-0.3	85	-1.8	-1.5	(-3.7, 0.6)	87	-3.6	-3.3	(-5.5, -1.2)	84	0.0	0.3	(-1.8, 2.5)
12	-0.5	86	-2.1	-1.6	(-3.9, 0.7)	86	-4.0	-3.5	(-5.8, -1.2)	83	-0.1	0.4	(-1.9, 2.7)
14	0.6	86	-0.5	-1.1	(-3.1, 0.8)	87	-3.5	-4.1	(-6.1, -2.2)	84	1.6	1.0	(-1.0, 2.9)
18	-0.4	86	-0.7	-0.3	(-2.2, 1.5)	85	-2.7	-2.3	(-4.2, -0.4)	84	-0.4	0.0	(-1.9, 1.9)
23.5	1.0	84	-0.3	-1.3	(-3.5, 0.9)	86	-0.4	-1.4	(-3.6, 0.9)	83	0.7	-0.3	(-2.5, 1.9)

**Table 10: Categorical Analysis for HR**

Treatment Group	Total N	HR < 100 ms	HR ≥100 ms
20 mg VEC-162	43	43 (100%)	0 (0.0%)
300 mg VEC-162	44	44 (100%)	0 (0.0%)
Moxifloxacin 400 mg	42	41 (97.6%)	1 (2.4%)
Placebo	43	42 (97.7%)	1 (2.3%)

**5.2.3 PR Analysis**

The statistical reviewer used mixed model to analyze the  $\Delta$ PR effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 11. The largest upper bounds of the 2-sided 90% CI for the mean differences between VEC-162 20 mg and placebo, and between VEC-162 300 mg and placebo are 3.6 ms and 3.8 ms, respectively. Table 12 presents the categorical analysis of PR. Seven subjects who experienced PR interval greater than 200 ms are in both VEC-162 20-mg and 300-mg groups.

**Table 11: Analysis Results of  $\Delta$ PR and  $\Delta\Delta$ PR for VEC-162 20 mg, VEC-162 300 mg, and Moxifloxacin 400 mg**

Time (h)	20 mg VEC-162					300 mg VEC-162				Moxifloxacin 400 mg			
	$\Delta$ PR	$\Delta$ PR		$\Delta\Delta$ PR		$\Delta$ PR		$\Delta\Delta$ PR		$\Delta$ PR		$\Delta\Delta$ PR	
	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.5	-0.5	86	0.6	1.1	(-1.3, 3.5)	87	-0.1	0.4	(-2.0, 2.9)	84	0.5	1.0	(-1.5, 3.4)
1	0.6	86	1.0	0.4	(-2.1, 2.8)	87	2.0	1.4	(-1.1, 3.8)	84	-1.1	-1.7	(-4.2, 0.8)
2	1.6	83	1.1	-0.5	(-3.2, 2.1)	86	0.7	-1.0	(-3.6, 1.6)	84	-1.7	-3.4	(-6.0, -0.7)
3	1.8	85	1.6	-0.2	(-2.9, 2.5)	87	0.1	-1.7	(-4.4, 1.1)	84	-0.3	-2.1	(-4.8, 0.7)
4	3.3	85	1.0	-2.4	(-4.8, 0.1)	87	2.0	-1.4	(-3.8, 1.1)	84	-1.2	-4.5	(-7.0, -2.1)
5	2.7	86	1.6	-1.0	(-3.5, 1.5)	87	0.8	-1.9	(-4.4, 0.6)	84	-1.3	-4.0	(-6.5, -1.5)
6	0.2	85	1.7	1.5	(-0.7, 3.6)	87	0.2	-0.0	(-2.2, 2.1)	84	-3.2	-3.4	(-5.6, -1.3)
8	-0.0	85	0.6	0.6	(-1.5, 2.7)	85	1.2	1.3	(-0.8, 3.4)	84	-1.3	-1.2	(-3.3, 0.9)
10	0.7	85	-0.8	-1.6	(-3.8, 0.7)	87	0.8	0.0	(-2.2, 2.3)	84	-1.8	-2.6	(-4.8, -0.3)
12	-0.9	86	-1.1	-0.2	(-3.3, 2.9)	86	3.5	4.3	(1.2, 7.5)	83	-3.1	-2.2	(-5.4, 0.9)
14	0.6	86	0.0	-0.6	(-2.5, 1.3)	87	1.4	0.8	(-1.1, 2.7)	84	-1.9	-2.5	(-4.4, -0.6)
18	0.3	86	-1.2	-1.5	(-3.9, 1.0)	85	1.3	1.0	(-1.5, 3.5)	84	-0.0	-0.3	(-2.8, 2.2)
23.5	0.4	84	1.2	0.8	(-1.5, 3.1)	86	-0.4	-0.8	(-3.1, 1.5)	83	0.8	0.4	(-1.9, 2.7)

**Table 12: Categorical Analysis of PR**

Treatment Group	Total N	PR < 200 ms	PR ≥200 ms
20 mg VEC-162	43	37 (86.0%)	6 (14.0%)
300 mg VEC-162	44	38 (86.4%)	6 (13.6%)
Moxifloxacin 400 mg	42	38 (90.5%)	4 (9.5%)
Placebo	43	38 (88.4%)	5 (11.6%)

**5.2.4 QRS Analysis**

The statistical reviewer used mixed model to analyze the  $\Delta$ QRS effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 13. The largest upper bounds of the 2-sided 90% CI for the mean differences between VEC-162 20 mg and placebo, and between VEC-162 300 mg and placebo are 2.7 ms and 2.8 ms, respectively. Table 14 presents the categorical analysis of QRS. No subject who experienced QRS interval greater than 110 ms is in VEC-162 groups.

**Table 13: Analysis Results of  $\Delta$ QRS and  $\Delta\Delta$ QRS for VEC-162 20 mg, VEC-162 300 mg, and Moxifloxacin 400 mg**

Time (h)	Placebo	20 mg VEC-162				300 mg VEC-162				Moxifloxacin 400			
	$\Delta$ QRS	$\Delta$ QRS		$\Delta\Delta$ QRS		$\Delta$ QRS		$\Delta\Delta$ QRS		$\Delta$ QRS		$\Delta\Delta$ QRS	
	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.5	0.5	86	0.7	0.1	(-1.3, 1.5)	87	0.3	-0.2	(-1.6, 1.2)	84	-0.7	-1.3	(-2.7, 0.2)
1	0.4	86	0.7	0.3	(-1.0, 1.6)	87	0.3	-0.1	(-1.4, 1.2)	84	-0.5	-0.9	(-2.2, 0.4)
2	0.4	83	1.6	1.2	(-0.1, 2.6)	86	1.0	0.6	(-0.8, 1.9)	84	-0.2	-0.5	(-1.9, 0.8)
3	0.8	85	0.6	-0.2	(-1.6, 1.2)	87	0.6	-0.2	(-1.6, 1.2)	84	-0.3	-1.1	(-2.5, 0.2)
4	0.4	85	0.5	0.1	(-1.2, 1.5)	87	0.5	0.1	(-1.2, 1.4)	84	-0.3	-0.7	(-2.1, 0.6)
5	0.6	86	0.3	-0.3	(-1.7, 1.1)	87	1.1	0.5	(-0.9, 1.9)	84	-0.7	-1.3	(-2.7, 0.1)
6	0.1	85	0.4	0.3	(-1.0, 1.6)	87	0.6	0.5	(-0.8, 1.7)	84	-0.1	-0.3	(-1.6, 1.0)
8	0.0	85	0.3	0.3	(-1.0, 1.6)	85	-0.1	-0.2	(-1.5, 1.1)	84	-0.5	-0.5	(-1.8, 0.8)
10	0.1	85	0.2	0.0	(-1.2, 1.3)	87	0.5	0.4	(-0.9, 1.6)	84	-0.2	-0.3	(-1.5, 0.9)
12	0.2	86	1.1	0.9	(-0.3, 2.1)	86	0.6	0.4	(-0.9, 1.6)	83	-0.5	-0.7	(-2.0, 0.5)
14	-0.6	86	0.6	1.2	(-0.1, 2.5)	87	0.9	1.4	(0.1, 2.8)	84	-0.4	0.1	(-1.2, 1.4)
18	0.1	86	-0.4	-0.5	(-1.7, 0.7)	85	0.0	-0.0	(-1.3, 1.2)	84	-1.1	-1.1	(-2.4, 0.1)
23.5	-0.9	84	0.6	1.5	(0.2, 2.7)	86	0.2	1.1	(-0.2, 2.3)	83	-0.7	0.2	(-1.0, 1.5)

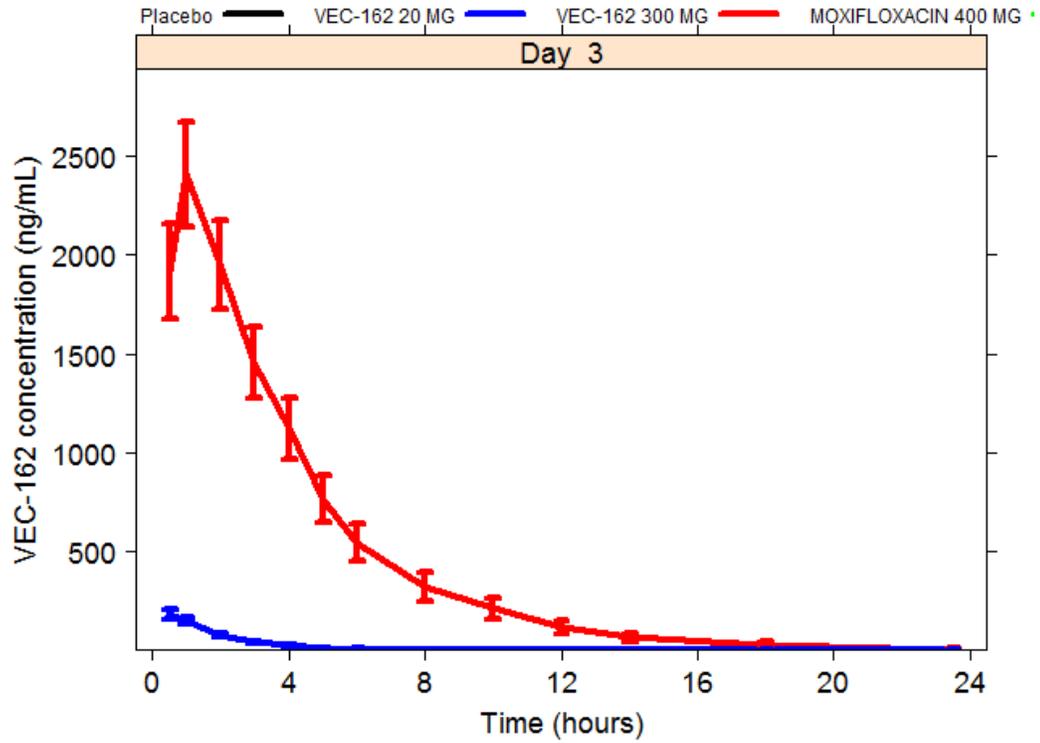
**Table 14: Categorical Analysis for QRS**

Treatment Group	Total N	QRS < 110 ms	QRS $\geq$ 110 ms
20 mg VEC-162 3 days	43	43 (100%)	0 (0.0%)
300 mg VEC-162 3 days	44	44 (100%)	0 (0.0%)
Moxifloxacin 400 mg on Day 3	42	42 (100%)	0 (0.0%)
Placebo 3 days	43	43 (100%)	0 (0.0%)

### 5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

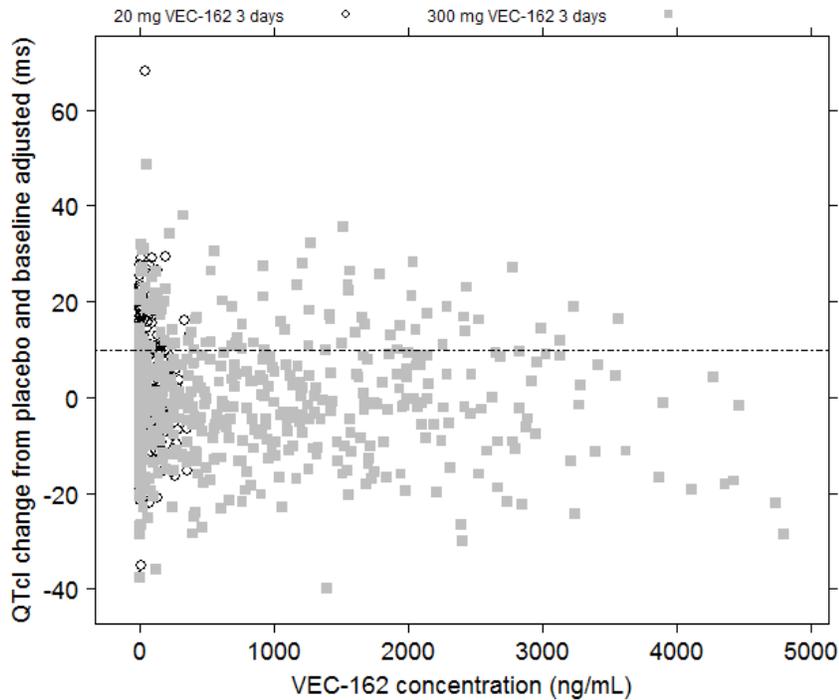
The mean drug concentration-time profile is illustrated in Figure 4.

**Figure 4: Mean VEC-162 concentration-time profiles for 20 mg (blue line) and 300 mg VEC-162 (red line) with error bar for 90% Confidence Interval**



The relationship between  $\Delta\Delta\text{QTcI}$  and VEC-162 concentrations is visualized in Figure 5 with no evident exposure-response relationship.

**Figure 5:  $\Delta\Delta$ QTcI vs. VEC-162 concentration**



## 5.4 CLINICAL ASSESSMENTS

### 5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

### 5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics 94 % of the ECGs were annotated in the primary lead II, with less than 0.5 % of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

### 5.4.3 PR and QRS Interval

Six subjects had PR > 200 ms without clinically meaningful increase over baseline. An additional subject had a postbaseline PR increase of 78 ms (55% increases over baseline values), postbaseline PR was 225 ms.

No subject had a QRS > 110 ms.

## 6 APPENDIX

### 6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Target dose	The target dose is 20 mg. (VP-VEC-162-3201 and VP-VEC-162-3203)	
Maximum tolerated dose	300 mg/day (CN116-001 and VP-VEC-162-1103)	
Principal Adverse Events	The most frequent events reported in Phase 1 studies were somnolence, headache, sleep disorder, and nausea. None of these events occurred at an appreciably more frequent rate in the tasimelteon group compared to the placebo group, and did not appear to be dose-dependent. The safety profile was similar across studies regardless of the dose administered. (Module 2.7.4 Section 4.6 and ISS Table 5.0.5.1.2)	
Maximum dose tested	Single Dose	300 mg (CN116-001)
	Multiple Dose	150 mg QD for 28 days (CN116-002) and 300 mg QD for 3 days (VP-VEC-162-1103)
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean ± SD (CV%) C <sub>max</sub> : 1,011 ± 519 ng/ml (51.3%) AUC(inf): 3,230 ± 1,480 ng×hr/ml (45.8%) (CN116-001)
	Multiple Dose	Mean ± SD (CV%) 150 mg QD for 28 days: C <sub>max</sub> : 935 ± 379 ng/ml (40%); AUC(inf): 4,038 ± 1,585 ng×hr/ml (39%) (CN116-002) 300 mg QD for 3 days: C <sub>max</sub> : 2,492 ± 1,058 ng/ml (42.5%); AUC(inf): 10,610 ± 5,780 ng×hr/ml (54.9%) (VP-VEC-162-1103)
Range of linear PK	In studies with doses ranging from 1- to 300 mg the values of the slopes of log- log plots for AUC versus dose were approximately 1, indicating linearity over single doses for this range. (CN116-001, CN116-002, CN116-003, Studies VP- VEC-162-1105, -1106, -1107, -1108, -1110, -1111, and -1112; Module 2.7.2)	
Accumulation at steady state	The pharmacokinetics of tasimelteon and its metabolites did not change with continued QD dosing of tasimelteon 20 mg for 16 days. (VP-VEC-162-1110)	

Metabolism	<p>CYP1A2 and CYP3A4 are the major isozymes involved in the metabolism of tasimelteon. CYP1A1, CYP2C9/19, and CYP2D6 also minimally contribute to the metabolism of tasimelteon. (Study BMS-10Nov97 and Study <sup>(b) (4)</sup> 08639)</p> <p>Tasimelteon has many metabolites, 8 of which have been characterized — M1, M3, M8, M9, M11, M12, M13, and M14. All of these metabolites are present in plasma and M1, M3, M8, and M9 are also present in urine. The characterized metabolites represent greater than 72% of the total AUC. M12, M9, and M13 are the most abundant metabolites. M12 and M9 are present at higher plasma levels (180% and 130%, respectively) than the parent drug and M13 is present at about the same level. The pharmacokinetic profiles of the most abundant metabolites as well as other main metabolites (M3, M11, and M12) were studied in the clinical pharmacology program. Of the glucuronidated metabolites (M1, M3, and M8), M3 was assayed in samples from some clinical pharmacology studies because it is expressed at about the same concentration than tasimelteon in plasma, and it is the second most abundant metabolite in urine (after M9). (VP-VEC-162-1101 and VP-VEC-162-1110)</p>	
Absorption	Absolute/Relative Bioavailability	Total oral absorption of tasimelteon is at least 80.4%. (VP- VEC-162-1101) Absolute oral bioavailability has not
	T <sub>max</sub>	Tasimelteon was found to have a typical median T <sub>max</sub> value of 0.5 hours. (Module 2.7.2, Table 4) T <sub>max</sub> of major metabolites range from 0.5 to 1.0 hours. (Module 2.7.2, Table 4)
Distribution	Vd/F or Vd	The apparent oral volume of distribution at steady state of tasimelteon in young healthy subjects is approximately 59
	% bound	At therapeutic concentrations, tasimelteon is about 88.6 - 90.1% protein bound. Renal impairment does not affect the protein binding of tasimelteon. (Module

	Blood\Plasma ratio	Data from the human Absorption, Metabolism and Excretion study (VP-VEC-162-1101) demonstrated that the mean $C_{max}$ and AUC values for total radioactivity in plasma were higher than those for total radioactivity in whole blood, indicating that tasimelteon is not highly associated with red blood cells. The theoretical blood-to- plasma ratio is 0.6, consistent with the observed $C_{max}$ ratio ( $2,385/3,987 = 0.60$ ).
Elimination	Route	The main route of elimination of tasimelteon and its metabolites in humans is by way of the urine, with biliary excretion to feces contributing a minor portion. Following oral administration of radiolabeled tasimelteon, <1% of the unchanged parent was detectable in the urine, consistent with the presence of metabolites. Mean recovery of total radioactivity in urine was 80.4% and 3.72% was recovered in feces resulting in a mean recovery of 84.1%. (VP-VEC-162-1101)
	Terminal $t_{1/2}$	The mean terminal elimination half-life $\pm$ standard deviation of tasimelteon is $1.32 \pm 0.431$ . (Module 2.7.2, Table 4) The mean terminal elimination half-life $\pm$ standard deviation of the main metabolites ranges from $1.26 \pm 0.480$ to $3.67 \pm 2.22$ . (Module 2.7.2, Table 4)
	CL/F or CL	The apparent clearance ranged from 51 L/hour to 139 L/hour. (Module 2.7.2, Table 9)
Intrinsic Factors	Age, Gender, Race and BMI	The PK characteristics of tasimelteon are highly variable amongst individuals. Intrinsic factors that might influence the PK variability of tasimelteon include age, gender, race, and body composition. Due to the overall inter-subject variability of tasimelteon, contributions to this variability by these factors, if present, are probably small and not clinically meaningful. Therefore, no dose adjustment is necessary based on age, gender, or body mass index (BMI). (Module 2.7.2 Section 5)

	Cardiac Effects	<p>Clinical study <a href="#">VP-VEC-162-1103</a> demonstrated that tasimelteon showed no signal of any effect on cardiac repolarization. The time-matched analysis for the QTcI endpoint revealed no subject on tasimelteon crossed the 10 msec upper bound for all time points for both the clinical and suprathreshold doses. The moxifloxacin group met the assay sensitivity criteria as outlined in the statistical plan, and all time points for moxifloxacin were more than five msec.</p> <p>No clinically relevant effect of tasimelteon was noted for heart rate or for PR or QRS interval duration. No new morphologic changes were considered clinically significant.</p>
	Hepatic Impairment	<p>For subjects with mild hepatic impairment, tasimelteon CL/F was reduced to 850 mL/min compared to 1128 mL/min for matched controls. For subjects with moderate hepatic impairment, CL/F was 721 mL/min compared to 1318 mL/min for matched controls. This resulted in a corresponding increase in exposure, as measured by AUC(inf), of 144% and 189% in subjects with mild and moderate hepatic impairment, respectively, less for the metabolites. The geometric mean ratios (GMR) of tasimelteon C<sub>max</sub> for subjects with mild or moderate hepatic impairment were 122.15% and 118.51%, respectively, as compared to healthy matched</p>
	Renal Impairment	<p>Consistent with the lack of renal excretion as a pathway of elimination for tasimelteon, there was no apparent relationship between tasimelteon CL/F and renal function as measured by either creatinine clearance (CL<sub>cr</sub>) or estimated glomerular filtration rate (eGFR). Two of tasimelteon's metabolites, M3 and M9, could potentially accumulate in patients with severe renal impairment and/or ESRD patients. In patients with renal impairment, the clinical significance of the projected accumulation rates in</p>

		<p>either ESRD (20% for M9 and at least 135% for M3) or severely impaired patients (120% for M3) is unknown but not expected to be a safety concern. Therefore, reducing the daily clinical recommended dose is not deemed necessary.</p> <p>The geometric mean ratios (GMR) of tasimelteon C<sub>max</sub> for subjects with end stage renal disease or severe renal impairment were 95.66% and 143.22%, respectively, as compared to healthy matched control subjects. The GMRs of tasimelteon AUC for subjects with end stage renal disease or severe renal impairment were 102.23% and 141.80%, respectively, as compared to healthy matched control subjects. (VP-VEC-162-1106)</p>
Extrinsic Factors	DDI: Tasimelteon as a Perpetrator	Repeated daily oral dosing of 20 mg tasimelteon QD for 16 days did not induce CYP2C8 using rosiglitazone as a substrate. (VP-VEC-162-1110)
		Repeated daily oral dosing of 20 mg tasimelteon QD for 14 days did not induce CYP3A4 using midazolam as a substrate. (VP-VEC-162-1110)
	DDI: Tasimelteon as a Victim	Consistent with the major role of CYP1A2 in the metabolism of tasimelteon, administration of fluvoxamine increased tasimelteon exposure by approximately 700%, and the C <sub>max</sub> by approximately 200%, compared to tasimelteon administered alone. Tasimelteon should be administered with caution in combination with fluvoxamine or other strong CYP1A2 inhibitors. (VP-VEC-162-1111)
		Induction of CYP1A2 by cigarette smoking decreased exposure and C <sub>max</sub> of tasimelteon by approximately 40% as compared to the exposure in subjects that did not smoke. A dose adjustment may be considered. (VP-VEC-162-1107)
	Tasimelteon's exposure increased by approximately 54% and C <sub>max</sub> by 33% when a single 20 mg dose of tasimelteon was administered on the fifth day of ketoconazole 400 mg per day administration, compared to administration of tasimelteon alone. No dose adjustment is recommended as the clinical significance of this change is unclear. (VP-VEC-162-1112)	

		Administration of rifampin 600 mg once daily for 11 days resulted in a mean decrease in exposure of approximately 89% and C <sub>max</sub> of 83% after a single 20 mg dose of tasimelteon. Efficacy may be reduced when tasimelteon is used in combination with strong CYP3A4 inducers such as rifampin. A dose adjustment may be considered. (VP-VEC-162-1112)
	Ethanol	In a healthy volunteer study where 0.6 g/kg for women and 0.7 g/kg for men of ethanol (2-5 standard alcohol drinks) over 15 minutes was co-administered with 20 mg tasimelteon no additive effects were seen on psychomotor performance or memory task. (VP-VEC-162-1106)
	Food Effects	There is a 44% reduction in the C <sub>max</sub> of tasimelteon in healthy volunteers fed a high fat/high calorie meal compared to fasted individual. T <sub>max</sub> increases from 0.75 hours to 2.5 hours in fasted versus fed subjects. There is no food effect on the total AUC. (VP-VEC-162-1102)
Expected High Clinical Exposure Scenario	Fluvoxamine is a strong CYP1A2 and CYP2C19 inhibitor and is also classified as a weak inhibitor of CYP2C8, 2C9 and 3A4. The effect of combined inhibition of CYP1A2 and 2C19 with at least some impact on other enzymes involved in the metabolism of tasimelteon, namely CYP2C9 and 3A4 likely approximates a near worst-case scenario. At a dose of 20 mg tasimelteon, the expected AUC would be approximately 2804 h×ng/mL which is well below the mean AUC observed after suprathreshold dosing with 300 mg tasimelteon (AUC = 3,230 ± 1,480 ng×hr/ml). (VP-VEC-162-1111 and CN116-001)	

	CL/F or CL	The apparent clearance ranged from 51 L/hour to 139 L/hour. (Module 2.7.2, Table 9)
Intrinsic Factors	Age, Gender, Race and BMI	The PK characteristics of tasimelteon are highly variable amongst individuals. Intrinsic factors that might influence the PK variability of tasimelteon include age, gender, race, and body composition. Due to the overall inter-subject variability of tasimelteon, contributions to this variability by these factors, if present, are probably small and not clinically meaningful. Therefore, no dose adjustment is necessary based on age, gender, or body mass index (BMI). (Module 2.7.2 Section 5)
	Cardiac Effects	Clinical study VP-VEC-162-1103 demonstrated that tasimelteon showed no signal of any effect on cardiac repolarization. The time-matched analysis for the QTcI endpoint revealed no subject on tasimelteon crossed the 10 msec upper bound for all time points for both the clinical and suprathreshold doses. The moxifloxacin group met the assay sensitivity criteria as outlined in the statistical plan, and all time points for moxifloxacin were more than five msec. No clinically relevant effect of tasimelteon was noted for heart rate or for PR or QRS interval duration. No new morphologic changes were considered clinically significant.
	Hepatic Impairment	For subjects with mild hepatic impairment, tasimelteon CL/F was reduced to 850 mL/min compared to 1128 mL/min for matched controls. For subjects with moderate hepatic impairment, CL/F was 721 mL/min compared to 1318 mL/min for matched controls. This resulted in a corresponding increase in exposure, as measured by AUC(inf), of 144% and 189% in subjects with mild and moderate hepatic impairment, respectively, less for the metabolites. The geometric mean ratios (GMR) of tasimelteon C <sub>max</sub> for subjects with mild or moderate hepatic impairment were 122.15% and 118.51%, respectively, as compared to healthy matched control subjects. Taking into account the therapeutic margin of tasimelteon, i.e., doses up to at least 300 mg are well tolerated; dose adjustments may not be necessary. (VP-VEC-162-1105)

	Renal Impairment	<p>Consistent with the lack of renal excretion as a pathway of elimination for tasimelteon, there was no apparent relationship between tasimelteon CL/F and renal function as measured by either creatinine clearance (CLcr) or estimated glomerular filtration rate (eGFR). Two of tasimelteon's metabolites, M3 and M9, could potentially accumulate in patients with severe renal impairment and/or ESRD patients. In patients with renal impairment, the clinical significance of the projected accumulation rates in either ESRD (20% for M9 and at least 135% for M3) or severely impaired patients (120% for M3) is unknown but not expected to be a safety concern. Therefore, reducing the daily clinical recommended dose is not deemed necessary.</p> <p>The geometric mean ratios (GMR) of tasimelteon Cmax for subjects with end stage renal disease or severe renal impairment were 95.66% and 143.22%, respectively, as compared to healthy matched control subjects. The GMRs of tasimelteon AUC for subjects with end stage renal disease or severe renal impairment were 102.23% and 141.80%, respectively, as compared to healthy matched control subjects. (VP-VEC-162-1106)</p>
Extrinsic Factors	DDI: Tasimelteon as a Perpetrator	Repeated daily oral dosing of 20 mg tasimelteon QD for 16 days did not induce CYP2C8 using rosiglitazone as a substrate. (VP-VEC-162-1110)
		Repeated daily oral dosing of 20 mg tasimelteon QD for 14 days did not induce CYP3A4 using midazolam as a substrate. (VP-VEC-162-1110)
	DDI: Tasimelteon as a Victim	Consistent with the major role of CYP1A2 in the metabolism of tasimelteon, administration of fluvoxamine increased tasimelteon exposure by approximately 700%, and the Cmax by approximately 200%, compared to tasimelteon administered alone. Tasimelteon should be administered with caution in combination with fluvoxamine or other strong CYP1A2 inhibitors. (VP-VEC-162-1111)
		Induction of CYP1A2 by cigarette smoking decreased exposure and Cmax of tasimelteon by approximately 40% as compared to the exposure in subjects that did not smoke. A dose adjustment may be considered. (VP-VEC-162-1107)

		<p>Tasimelteon's exposure increased by approximately 54% and C<sub>max</sub> by 33% when a single 20 mg dose of tasimelteon was administered on the fifth day of ketoconazole 400 mg per day administration, compared to administration of tasimelteon alone. No dose adjustment is recommended as the clinical significance of this change is unclear. (VP-VEC-162-1112)</p>
		<p>Administration of rifampin 600 mg once daily for 11 days resulted in a mean decrease in exposure of approximately 89% and C<sub>max</sub> of 83% after a single 20 mg dose of tasimelteon. Efficacy may be reduced when tasimelteon is used in combination with strong CYP3A4 inducers such as rifampin. A dose adjustment may be considered. (VP-VEC-162-1112)</p>
	Ethanol	<p>In a healthy volunteer study where 0.6 g/kg for women and 0.7 g/kg for men of ethanol (2-5 standard alcohol drinks) over 15 minutes was co-administered with 20 mg tasimelteon no additive effects were seen on psychomotor performance or memory task. (VP-</p>
	Food Effects	<p>There is a 44% reduction in the C<sub>max</sub> of tasimelteon in healthy volunteers fed a high fat/high calorie meal compared to fasted individual. T<sub>max</sub> increases from 0.75 hours to 2.5 hours in fasted versus fed subjects. There is no food effect on the total AUC. (VP-VEC-162-1102)</p>
Expected High Clinical Exposure Scenario	<p>Fluvoxamine is a strong CYP1A2 and CYP2C19 inhibitor and is also classified as a weak inhibitor of CYP2C8, 2C9 and 3A4. The effect of combined inhibition of CYP1A2 and 2C19 with at least some impact on other enzymes involved in the metabolism of tasimelteon, namely CYP2C9 and 3A4 likely approximates a near worst-case scenario. At a dose of 20 mg tasimelteon, the expected AUC would be approximately 2804 h×ng/mL which is well below the mean AUC observed after suprathreshold dosing with 300 mg tasimelteon (AUC = 3,230 ± 1,480 ng×hr/ml). (VP-VEC-162-1111 and CN116-001)</p>	

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

**Label, Labeling and Packaging Review**

Date: September 26, 2013

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

Team Leader: Irene Z. Chan, PharmD, BCPS  
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Tasimelteon Capsules, 20 mg

Application Type/Number: NDA 205677

Applicant: Vanda Pharmaceuticals

OSE RCM #: 2013-1436

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

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## 1 INTRODUCTION

This review evaluates the proposed labels, labeling, and Braille Label Comprehension Study Protocol for Tasimelteon Capsules, NDA 205677, for areas of vulnerability that could lead to medication errors in response to a request from the Division of Neurology Products (DNP).

### 1.1 PRODUCT INFORMATION

Tasimelteon is a New Molecular Entity (NME). The following product information is provided in the August 20, 2013 insert labeling submission.

- Active Ingredient: Tasimelteon
- Indication of Use: Treatment of non-24-hour disorder in the totally blind
- Route of Administration: Oral
- Dosage Form: Capsules
- Strength: 20 mg
- Dose and Frequency: 20 mg per day taken (b) (4) prior to bedtime, (b) (4) at the same time every night
- How Supplied: Bottles of 30 capsules
- Storage: Controlled room temperature
- Container and Closure System: High Density Polyethylene (HDPE) bottles with (b) (4) closures containing induction seals

## 2 METHODS AND MATERIALS REVIEWED

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>1</sup> along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted August 20, 2013 (Appendix A)
- Insert Labeling submitted August 20, 2013 (No image)
- Braille Label Comprehension Study Protocol submitted August 20, 2013 (No image)

## 3 MEDICATION ERROR RISK ASSESSMENT

Our risk assessment of the labels and labeling determined the container label lacks a Medication Guide statement and a usual dosage statement, which is required by the Code of Federal Regulations (CFR). Additionally, the container labels can be revised to

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

increase the prominence of important information, such as the strength. The original container is a unit-of-use bottle and the label contains Braille for the product name and strength, which may be helpful to the patient. Therefore, we recommend including a statement to dispense the product in the original container and to affix the pharmacy label so it does not cover the Braille.

Important information about (b) (4) appears in the insert labeling and should be added to the Medication Guide. In addition, the insert labeling states to take 20 mg (b) (4) at the same time every night. It is unclear if there is a time frame (b) (4) that is acceptable. This issue was discussed with the Medical Officer (MO) and will be addressed at future labeling meetings.

The Applicant submitted a Braille Comprehension Study Protocol for the container label. We recommend asking the participant to read what is presented on the container label instead of specifically asking for the medication name and strength on the container label.

#### 4 CONCLUSIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product. Additionally, the acceptability of the Braille on the container label will be a separate review issue that depends on the results of the Braille Comprehension Study.

#### 5 RECOMMENDATIONS

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

A. Comments to the Division

1. General Comment: At the time of the Braille Label Comprehension Study request for the container label, we were unaware the Applicant proposed

(b) (4)

2. Insert Labeling

- a. In Section 2, it states to take 20 mg (b) (4) at the same time every night. It is unclear if there is a time frame (b) (4) that is acceptable. If data is available, we recommend adding the acceptable time frame for taking the medication each night or removing the term (b) (4)

(b) (4)

B. Comments to the Applicant

1. Container Label

- a. Add the dosage form “capsules” following the active ingredient “Tasimelteon.” The dosage form should be presented in the same font as the active ingredient.
- b. Relocate the strength to underneath the established name for customary placement. Additionally, increase the prominence of the strength by bolding or other means. See example below:  
(Tasimelteon) Capsules  
**20 mg**
- c. Relocate the NDC number to the principal display panel per 21 CFR 207.35(b)(3)(i).
- d. Revise the storage information from (b) (4) to “15°C to 30°C (59°F to 86°F)” for clarity.
- e. Decrease the size of the (b) (4) to the left of the proposed proprietary name or remove it since it takes attention away from important information on the label, such as the established name and strength.
- f. Add a usual dosage statement to the side panel per 21 CFR 201.100(b)(2). In order to accommodate this statement, decrease the size of the company logo.
- g. Since the original container is a unit-of-use bottle and contains Braille, which may be helpful to the patient, we recommend adding a statement to the principal display panel similar to “Dispense in original container. Do not cover the Braille.”

- i. Debold the net quantity and Rx only statements.

2. Braille Label Comprehension Study Protocol

- a. We recommend asking the patient to read the information on the bottle label aloud without clues as to what is printed in Braille instead of asking what the name and strength of the medication are.

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

1 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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JULIE V NESHIEWAT  
09/26/2013

IRENE Z CHAN  
09/27/2013

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # 205677 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Hetlioz (pending) Established/Proper Name: tasimelteon Dosage Form: capsules, oral Strengths: 20 mg		
Applicant: Vanda Pharmaceuticals, Inc. Agent for Applicant (if applicable):		
Date of Application: May 31, 2013 Date of Receipt: May 31, 2013 Date clock started after UN:		
PDUFA Goal Date: January 31, 2014		Action Goal Date (if different):
Filing Date: July 30, 2013		Date of Filing Meeting: July 11, 2013
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): <b>Non-24 hour sleep-wake disorder in blind patients without light perception</b>		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> and refer to Appendix A for further information.</i>		
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
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 type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division ( <i>if OTC product</i> ):				
List referenced IND Number(s): 54776				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
<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: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>		X		
<b>If yes, explain in comment column.</b>				
<b>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</b>				
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?			X	Orphan product

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid  <input checked="" type="checkbox"/> Exempt (orphan)  <input type="checkbox"/> Waived (e.g., small business, public health)  <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input type="checkbox"/> Not in arrears  <input type="checkbox"/> In arrears</p>																			
<p><b>505(b)(2)</b> (NDAs/NDA Efficacy Supplements only)</p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>			<p>x</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>																				
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><b>Check the Electronic Orange Book at:</b>  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p> <table border="1" data-bbox="203 1488 1349 1623"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p><b>Exclusivity</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <b>Check the Orphan Drug</b></p>		<p>X</p>																		

<p><b>Designations and Approvals list at:</b>  <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a></p>				
<p><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)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>	X			
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDA/NDA efficacy supplements only</i>)</p> <p><b>If yes</b>, # years requested: 5</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	X			
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDA only</i>)?</p>				
<p><b>If yes</b>, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

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>	X			
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDA/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

1

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

<input type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only)				
<b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?				
<b>If yes, BLA #</b>				
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	x			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	x			
<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)?	x			
<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)?	x			
<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>				
<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?	x			
<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>				
<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>	x			
<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>	x			
<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: 6/6/13</i>  <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff :</i>	x			
<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b><u>PREA</u></b>  Does the application trigger PREA?  <i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i>  <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be</i>		x		Orphan – Prea exempt

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

<i>reviewed by PeRC prior to approval of the application/supplement.</i>				
<b>If the application triggers PREA</b> , are the required pediatric assessment studies or a full waiver of pediatric studies included?				
<b>If studies or full waiver not included</b> , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?  <i>If no, request in 74-day letter</i>				
<b>If a request for full waiver/partial waiver/deferral is included</b> , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?  <i>If no, request in 74-day letter</i>				
<b>BPCA (NDAs/NDA efficacy supplements only):</b>  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>		x		
<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>	x			Review pending
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>		x		Med Guide only
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL	x			

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

format?				
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? <sup>4</sup>	x			
<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>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	x			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	x			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	x			
<b>OTC Labeling</b>	<b>X 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>
Is electronic content of labeling (COL) submitted?				
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?				
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?				
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
<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)	x			Qt consult; nonclin carci consult sent

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

<i>If yes, specify consult(s) and date(s) sent:</i>				
<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> 1.6.11	x			
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> 2.21.13	x			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b> 10.28.11	x			
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** July 12, 2013

**BLA/NDA/Supp #:** 205677

**PROPRIETARY NAME:** Hetlioz

**ESTABLISHED/PROPER NAME:** tasimelteon

**DOSAGE FORM/STRENGTH:** 20 mg Capsules, oral

**APPLICANT:** Vanda Pharmaceuticals, Inc.

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):** treatment of NON-24 sleep wake disorder in blind patients without light perception

**BACKGROUND:** Tasimelteon- NME, a circadian regulator that resets the master body clock acts as a Dual Melatonin Receptor Agonist (DMRA) with selective agonist activity at the MT1 and MT2 receptors.

Non-24 is a severe chronic disorder that occurs when individuals are unable to synchronize their endogenous body clock to the 24-hour light-dark cycle. The majority of reported cases occur in blind patients with no perception of light.

Fourteen Phase I clinical pharmacology and pharmacokinetics studies were conducted; 4 additional Phase II and Phase III trials in healthy volunteers, patients with primary insomnia, including one in an elderly population support the safety and efficacy of tasimelteon. A total of 1,652 patients participated in these trials (306: placebo, 1,346: tasimelteon). Two efficacy trials in Non-24 patients, VP-VEC-162-3201 and VP-VEC-162-3203 (designed specifically to evaluate the maintenance of effect of tasimelteon after long-term use), met the protocol-specified primary efficacy endpoint and are considered positive studies.

**REVIEW TEAM:**

<b>Discipline/Organization</b>	<b>Names</b>		<b>Present at filing meeting? (Y or N)</b>
Regulatory Project Management	RPM:	C. Michaloski	Y
	CPMS/TL:	J. Ware	N
Cross-Discipline Team Leader (CDTL)	R. Farkas		Y
Clinical	Reviewer:	D. Jillapalli	Y

	TL:	R. Farkas	
Clinical Pharmacology	Reviewer:	J. Parepally A. Bhattaram K.Riviere (biopharm)	Y Y Y
	TL:	A. Men A.Dorentes (biopharm)	Y N
Biostatistics	Reviewer:	J. Luan	N
	TL:	K. Jin	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	M. Banks-Muckenfuss	Y
	TL:	L. Freed	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:	K. Lin	N
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	R. Kambhampati M. Ramanadham M. Heimann B. Riley (micro CMC)	Y Y Y N
	TL:	R. Sood	
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	J. Neshiewat	Y
	TL:	I.Chan	N
OSE/DRISK (REMS)	Reviewer:	N/A	

	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	
	TL:		
Bioresearch Monitoring (OSI)	Reviewer:	A. El Hage	N
	TL:	S. Leiberhaut	N
Controlled Substance Staff (CSS)	Reviewer:	K. Bonson	Y
	TL:	S. Calderon	
Other reviewers	A. Pariser (OND Rare Diseases) K. O'Connell (OND Rare Diseases)		Y
Other attendees Patient Labeling  Safety RPM	T.Scales		N
	M. McLawhorn		Y
	E. Zerislassie		Y

**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> <p>Describe the scientific bridge (e.g., BA/BE studies):</p> </li> </ul>	<input type="checkbox"/> Not Applicable  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Per reviewers, are all parts in English or English translation?</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>• Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE

<p><b>Comments:</b> review issues for 60 day filing letter</p>	<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> New NME</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 checked="" type="checkbox"/> YES Date if known: 11.14.13 <input type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason:
<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
<ul style="list-style-type: none"> <li>If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</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 pharmacology study site(s) inspections(s)</li> </ul>	<input type="checkbox"/> YES

needed?	<input type="checkbox"/> NO
<b>BIostatistics</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable X FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable X FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b>  <b>Comments:</b>	X Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>PRODUCT QUALITY (CMC)</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable X FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b><u>Environmental Assessment</u></b>  <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <b>If no</b> , was a complete EA submitted?  <b>If EA submitted</b> , consulted to EA officer (OPS)?  <b>Comments:</b>	X YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<b><u>Quality Microbiology (for sterile products)</u></b>  <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</li> </ul> <b>Comments:</b>	X Not Applicable  <input type="checkbox"/> YES <input type="checkbox"/> NO

<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 type="checkbox"/> YES <input type="checkbox"/> NO</p> <p>X YES <input type="checkbox"/> NO</p>
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<p>X Not Applicable FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</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 type="checkbox"/> N/A</p> <p>X YES <input type="checkbox"/> NO</p> <p>X 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>	<p>X YES <input type="checkbox"/> NO</p>

<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 checked="" 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 checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>REGULATORY PROJECT MANAGEMENT</b>	
<p><b>Signatory Authority:</b> Ellis Unger, M.D., Director, ODE I</p> <p><b>Date of Mid-Cycle Meeting</b> (for NME NDAs/BLAs in “the Program” PDUFA V): 9.12.13</p> <p><b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):</p> <p><b>Comments:</b> there are potential CMC review issues but CMC has recommended filing the application</p>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <u>Review Issues:</u>  <input type="checkbox"/> No review issues have been identified for the 74-day letter.  <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): 60 day letter  <u>Review Classification:</u>  <input type="checkbox"/> Standard Review  <input checked="" type="checkbox"/> Priority Review
<b>ACTIONS ITEMS</b>	
<input 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, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter

<input type="checkbox"/>	
<input type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</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 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 NME NDAs in the Program)
<input type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at:</p> <p><a href="http://erom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f">http://erom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f</a> ]</p>
<input type="checkbox"/>	Other

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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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CATHLEEN B MICHALOSKI  
07/25/2013

# Selected Requirements of Prescribing Information (SRPI)

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## Highlights (HL)

### GENERAL FORMAT

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

**Comment:**

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

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

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

**Comment:**

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

**Comment:**

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

**Comment:**

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

**Comment:**

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

Section	Required/Optional
• <b>Highlights Heading</b>	Required
• <b>Highlights Limitation Statement</b>	Required

## Selected Requirements of Prescribing Information (SRPI)

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

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

***Comment:** Specific sub-sections added.*

**YES**

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

***Comment:***

### HIGHLIGHTS DETAILS

#### Highlights Heading

**YES**

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

***Comment:***

#### Highlights Limitation Statement

**YES**

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

***Comment:***

#### Product Title

**YES**

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

***Comment:***

#### Initial U.S. Approval

**YES**

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

***Comment:***

#### Boxed Warning

**N/A**

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

***Comment:***

**N/A**

## Selected Requirements of Prescribing Information (SRPI)

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

Comment:

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

Comment:

- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

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

Comment:

### Recent Major Changes (RMC)

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

Comment:

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

Comment:

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

Comment:

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

Comment:

### Indications and Usage

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

Comment: *No pharmacologic class given; TBD*

### Dosage Forms and Strengths

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

Comment:

## Selected Requirements of Prescribing Information (SRPI)

### Contraindications

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

Comment:

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

Comment:

### Adverse Reactions

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

Comment:

### Patient Counseling Information Statement

- NO** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

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

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

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

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

Comment: Medication Guide is missing. Will discuss at filing meeting 6/27/13.

### Revision Date

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

Comment:

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## Contents: Table of Contents (TOC)

### GENERAL FORMAT

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

Comment:

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

Comment:

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

Comment:

- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

## Selected Requirements of Prescribing Information (SRPI)

Comment:

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

Comment:

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

Comment:

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

Comment:

- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Comment:

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### Full Prescribing Information (FPI)

#### GENERAL FORMAT

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

Comment: *font is small.*

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

Comment: *Need to remove extra periods.*

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

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

## Selected Requirements of Prescribing Information (SRPI)

<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
<b>13 NONCLINICAL TOXICOLOGY</b>
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

**Comment:** Subsections added as per product-specific.

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

**Comment:** Missing Medication Guide (MGs are class labeling for sedative-hypnotics).

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

**Comment:**

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

**Comment:**

### FULL PRESCRIBING INFORMATION DETAILS

#### Boxed Warning

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

**Comment:**

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

**Comment:**

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

**Comment:**

#### Contraindications

- YES** 45. If no Contraindications are known, this section must state “None”.

**Comment:** Will verify this labeling statement at filing meeting 6/27/13.

#### Adverse Reactions

**NO**

## Selected Requirements of Prescribing Information (SRPI)

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

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

**Comment:** *Missing this statement.*

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

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

**Comment:**

### **Patient Counseling Information**

- NO** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

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

**Comment:** *Medication Guide (MG) missing; reference to MG missing.*

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/s/  
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CATHLEEN B MICHALOSKI  
06/19/2013