

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205677Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 205677

SUPPL #

HFD #

Trade Name HETLIOZ

Generic Name Tasimelteon, 20 mg Capsules

Applicant Name Vanda Pharmaceuticals, Inc.

Approval Date, If Known January 31, 2014

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES X NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES X NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES X NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

7 years (orphan)

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO X (exempt

due to orphan status)

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO X

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO X

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA

#(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical

investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or

sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES <input type="checkbox"/>	NO <input type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input type="checkbox"/>

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND #	YES <input type="checkbox"/>	! NO <input type="checkbox"/>
		! Explain:

Investigation #2		!
		!
IND #	YES <input type="checkbox"/>	! NO <input type="checkbox"/>
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not

identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Cathleen Michaloski
Title: Senior Regulatory Project Manager
Date: 1.14.14

Name of Office/Division Director signing form:
Title:

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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/s/

CATHLEEN B MICHALOSKI
01/13/2014

ERIC P BASTINGS
01/14/2014

3. DEBARMENT CERTIFICATION

Vanda Pharmaceuticals Inc. 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.

BL B.12

Paolo Baroldi, M.D., Ph.D.
Chief Medical Officer

02 May 2013

Date

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

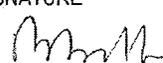
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See Attachment	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Paolo Baroldi, M.D., Ph.D.	TITLE Chief Medical Officer
FIRM/ORGANIZATION Vanda Pharmaceuticals Inc.	
SIGNATURE 	DATE (mm/dd/yyyy) 07 May 2013

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right.

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, 420A
Rockville, MD 20850

Michaloski, Cathleen

From: Michaloski, Cathleen
Sent: Thursday, January 09, 2014 10:00 AM
To: Michaloski, Cathleen
Subject: FW: CMC info for 205677 - Action package

From: Heimann, Martha R
Sent: Wednesday, January 08, 2014 11:52 AM
To: Michaloski, Cathleen; Wilson, Wendy
Cc: Stephens, Olen; Kambhampati, Rao V
Subject: RE: CMC info for 205677 - Action package

Hi Cathy,

We are happy to assist with getting any needed information together but multiple e-mails chains can cause a lot of confusion. Answers to this and your earlier e-mail to me:

1. Chemical classification is 1 (New Molecular Entity).
2. (and attached e-mail) The original application includes a claim for categorical exclusion that is acceptable per Rao's review. Since there is a categorical exclusion an environmental assessment, which would be much more detailed, is not required.
3. No everything is done and signed off appropriately.

Field copy certification – They are OK

The only thing that we will have to do is double check EES right before the action is due to make sure nothing about the facilities have changed. It rarely happens.

Regards,
Martha

From: Michaloski, Cathleen
To: ["Marlene Dressman"](#)
Subject: Carton and container labeling NDA 205677
Date: Friday, December 27, 2013 10:51:00 AM
Importance: High

Good Morning Marlene,

We note that the carton and container labeling includes text in Braille. In order for us to evaluate this content, we request that a "certificate of translation" be submitted. Please submit this certificate to the NDA asap.

Thank you.

Cathleen Michaloski, BSN, MPH, RAC

*Sr. Regulatory Project Manager
Division of Neurology Products
FDA / CDER / OND / ODEI /DNP
White Oak Building 22 room 4342
301-796-1123
Cathleen.michaloski@fda.hhs.gov*

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/s/

CATHLEEN B MICHALOSKI
12/27/2013



NDA 205677

**REQUEST FOR METHODS
VALIDATION MATERIALS**

Vanda Pharmaceuticals
Attention: Marlene Dressman, Ph.D.
2200 Pennsylvania Ave NW
Washington, DC
FAX: (202) 296-1450

Dear Dr. Dressman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Hetlioz (tasimelteon) capsules, 20 mg.

We will be performing methods validation studies on Hetlioz (tasimelteon) capsules, 20 mg, as described in NDA 205677.

In order to perform the necessary testing, we request the following sample materials and equipments:

Method, current version

Method: ID 903200 VEC-162 Capsules Assay, Related Substances, (b) (4)
Content Uniformity, Identification by RT, and Identification by UV

Method: Drug Substance Purity (HPLC), Method 10 in testing monograph (b) (4)
(current version (b) (4))

Samples and Reference Standards

- 3 x 30 Hetlioz (tasimelteon) capsules, 20 mg
- 2 x 300 mg VEC-162 reference standard (b) (4)
- 2 x (b) (4)

Equipment

- 1 (b) (4) particle size
- 2 (b) (4) particle size

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: MVP Sample Custodian
645 S Newstead
St. Louis, MO 63110

Please notify me upon receipt of this FAX. You may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (michael.trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
12/20/2013

From: Michaloski, Cathleen
To: ["Marlene Dressman"](#)
Subject: Hetlioz (Tasimelteon) NDA 205677 DMEPA information request
Date: Wednesday, November 13, 2013 1:34:00 PM
Importance: High

Good Afternoon,

DMEPA reviewed the proposed container label submitted on October 30, 2013 and the reviewers have the following additional comments:

Container Labels

1. Relocate the NDC number to the top third of the principal display panel per 21 CFR 207.35(b)(3)(i).



3. Relocate the  and "Dispense in original container. Do not cover Braille." statements to below the strength presentation.
4. For increased prominence, use bold font for the statements "Dispense in original container. Do not cover Braille."
5. Revise all upper case presentations of "HETLIOZ" to title case, "Hetlioz" to improve readability.

Please let me know if you have any questions. Thank you.

Cathleen Michaloski, BSN, MPH

Sr. Regulatory Project Manager

Division of Neurology Products

FDA / CDER / OND / ODEI / DNP

White Oak Building 22 room 4342

301-796-1123

Cathleen.michaloski@fda.hhs.gov

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CATHLEEN B MICHALOSKI
11/13/2013

From: Michaloski, Cathleen
To: ["Marlene Dressman"](#)
Subject: N 205677 Resp to question and new clinical information request
Date: Thursday, October 24, 2013 4:32:00 PM
Attachments: [image003.png](#)
Importance: High

Good Afternoon Dr. Dressman,

We have the following information request and response to your question (email dated 10/23/14 4:12 pm):

- Your efficacy analyses, in response to Information Request dated 9/19/13, were conducted in the Analysis Population, which was defined as all subjects in the ITT population that had at least 70% of one cycle of data reported during each of Pre-randomization *and* Randomization phases. However, these analyses do not involve a change from baseline, and therefore, subjects with at least 70% of one cycle of data during the Randomization phase should be included in the analyses. Please refer to the following table, from the Statistical Review of the FDA's AC briefing book. The highlighted subjects have $\geq 70\%$ of one cycle of data reported in the Randomization phase. Please include these subjects and perform analyses of the *Absolute Value* of the Difference of nTST and dTSD for In-phase and Out-of-phase (there is no need for analyses with exclusion of subjects with incorrect phase). Thus, the *new Analysis Population* will have 38 subjects in the placebo group and 39 subjects in the tasimelteon group (n=77).

Table 10: The 12 Patients Excluded from Efficacy Analysis (Study 3201)

Subject ID	Treatment Group	Cycle Length	% Cycle Base	% Cycle Postbaseline
(b) (6)	PLACEBO	32	275.0	53.1
	PLACEBO	54	148.1	13.0
	PLACEBO	54	94.4	11.1
	PLACEBO	58	36.2	129.3
	PLACEBO	59	113.6	27.1
	PLACEBO	79	65.8	160.8
	PLACEBO	81	60.5	145.7
	PLACEBO	96	49.0	79.2
	VEC-162	72	70.8	2.8
	VEC-162	85	116.5	23.5
	VEC-162	94	66.0	107.4
	VEC-162	97	84.5	36.1

Source: Reviewer's Analysis

- Perform analyses of the *Absolute Value* of the Difference of nTST and dTSD for In-phase and Out-of-phase on all subjects (n=42 in placebo and n=42 in the tasimelteon group), using available raw data in the 0-20% and 50-70% windows in Cycle 1 and Cycle 2 for those subjects who have < 70% data in the Randomization phase (it may be reasonable to exclude those subjects that do not have even one night/day data in these windows in a given cycle).
- In addition, perform analyses of the *Absolute Value* of the Difference of nTST and dTSD for In-phase and Out-of-phase on all subjects in each treatment group (n=42 in placebo and n=42 in the tasimelteon group) using the following imputation methods for subjects with <70% data in the Randomization phase, i.e., for the 4 placebo subjects and 3 tasimelteon subjects.
 - Impute the data for subjects with < 70% of data in the Randomization phase with mean of the 77 subjects in the *new analysis population*.
 - Impute the data for subjects with <70% of data in the Randomization phase with mean of their respective treatment group mean (38 subjects in the placebo group and 39 subjects in the tasimelteon group).

Please use both ANCOVA and Permutation ANCOVA t-test for the above requested analyses.

Any questions, feel free to contact me. Thank you.

Cathleen Michaloski, BSN, MPH

*Sr. Regulatory Project Manager
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CATHLEEN B MICHALOSKI
10/24/2013



NDA 205677

MID-CYCLE COMMUNICATION

Vanda Pharmaceuticals, Inc.
2200 Pennsylvania Ave., NW
Suite 300E
Washington, D.C. 20037

Attention: Paolo Baroldi, M.D.
Chief Medical Officer

Dear Dr. Baroldi:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hetlioz (tasimelteon) oral Capsules, 20 mg.

We also refer to the teleconference between representatives of your firm and the FDA on September 26, 2013. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call me at (301) 796-1123.

Sincerely,

{See appended electronic signature page}

Cathleen Michaloski, BSN, MPH
Sr. Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: September 26, 2103, 12 pm- 1pm EST
Application Number: NDA 205677
Product Name: tasimelteon
Indication: Non-24 hour sleep-wake disorder in blind patients without light perception
Applicant Name: Vanda Pharmaceuticals, Inc.
Meeting Chair: Ronald Farkas, M.D., Ph.D.
Meeting Recorder: Cathleen Michaloski, BSN, MPH

FDA ATTENDEES

Ronald Farkas, M.D., Ph.D. Clinical Team Leader, Division of Neurology Products (DNP)
Devanand Jillapalli, M.D., Clinical Reviewer, DNP
Julia Luan, Ph.D., Statistical Reviewer, OTS
Kun Jin, Ph.D., Statistical Team Leader, OTS
Ramesh Sood, Ph.D., Division Director (Acting), ONDQA
Lopa Thambi, PharmD, Division of Pharmacovigilance, OSE
Mahesh Ramanadham, Ph.D, Office of Compliance, OMPQ
Christina Capacci-Daniel, Ph.D., Office of Compliance, OMPQ
Kimberly Taylor, Ph.D., Operations Research Analyst, CDER
Julie Neshiewat, PharmD, Safety Evaluator, DMEPA
Irene Z. Chan, PharmD, BCPS, Team Leader, DMEPA

(b) (4)

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

APPLICANT ATTENDEES

Mihael Polymeropoulos, M.D., President & Chief Executive Officer, Vanda Pharmaceuticals
Paolo Baroldi, M.D., Ph.D., Senior Vice President & Chief Medical Officer, Vanda Pharmaceuticals
Marlene Dressman, Ph.D, Vice President, Clinical Program, Vanda Pharmaceuticals
Joseph Sliman, M.D., Senior Medical Director, Vanda Pharmaceuticals
Louis Licamele, Ph.D., Senior Director, Vanda Pharmaceuticals
Derek Xiao, Ph.D., Biostatistics Manager, Vanda Pharmaceuticals
Deepak Phadke, Ph.D., Vice President, Chemistry and Manufacturing, Vanda Pharmaceuticals
Eugene Laska, Ph.D., Professor of Psychiatry at the Department of Psychiatry at NYU Medical Center and Director of Statistical Sciences and Epidemiology Division of the Nathan Kline Institute for Psychiatric Research
Charles Czeisler, M.D., Ph.D., Baldino Professor of Sleep Medicine, Harvard Medical School, and Chief, Division of Sleep Medicine, Brigham and Women's Hospital

1.0 INTRODUCTION

We are providing these summary comments (based on the 9/26/13 Mid-Cycle teleconference) to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, the comments from the teleconference do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

Label Comprehension Study

With reference to the Agency's letter dated 9/16/13, which provided preliminary approval of the proprietary name, Hetlioz, the following question was asked:

- How did you arrive at the sample size of 10 patients and the 80% threshold for letter comprehension analysis?

The sponsor responded that they assumed these parameters were adequate.

The sponsor was referred to the guidance document, *Label Comprehension Studies for Nonprescription Drug Products published August 2010*, and asked to provide further rationale for their criteria and also advised that the study population be a representative sample as per the guidance. The Agency also recommended that in the study, the patients should be asked to read the information in Braille instead of specifically asking the patients what the name and strength of the medication in Braille are.

The sponsor assured the Agency that they would review the guidance and respond.

The sponsor stated that only 10% of the blind population actually read Braille and that they have allowed for (b) (4)

Office of Compliance, OMPQ

The Agency asked whether the sponsor was aware of the status of their pre-approval inspections. The sponsor stated that they were aware of their 483 findings and that they recently responded with a submission. The sponsor asked when they will hear back from the Agency on these issues. The Agency responded that the review is on-going and that review findings will proceed through CDER for final recommendation.

3.0 INFORMATION REQUESTS

Chemistry, Manufacturing and Controls

A response to the CMC information request dated 9/20/13 is expected by 10/9/13.

Post meeting note: Submission has been received at FDA.

Clinical and Statistical

There is currently 1 outstanding clinical information request. The sponsor is expected to respond to the request by 10/28/13.

The Agency asked the sponsor provide the date of unblinding for Study 3203.

Referencing the Information Request dated 9/19/13, the Sponsor described a few considerations related to predicting phase that has the potential to make the requested analyses challenging. There was a brief discussion of the proposed analysis of the absolute value of the difference between in-phase and out-phase mean values for nTST and dTSD, and a sensitivity analysis after excluding subjects with highly negative difference between in-phase and out-phase mean values.

4.0 ADVISORY COMMITTEE MEETING

The sponsor was reminded that the Advisory Committee (AC) meeting is November 14, 2013 and that they should expect to hear from the Agency's AC staff regarding details of that meeting.

5.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES

The sponsor was reminded that the Late-Cycle Meeting (LCM) is scheduled for 10/30/13 from 12:30 pm to 2 pm. A briefing package will be sent to sponsor 8 days prior to the LCM.

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/s/

CATHLEEN B MICHALOSKI
10/22/2013

From: Michaloski, Cathleen
To: ["Marlene Dressman"](#)
Subject: Information request - clinical NDA 205677
Date: Thursday, October 17, 2013 6:48:00 PM

Dr. Dressman,

We have the following information request from the clinical team:

Pharmacokinetic data indicate that cigarette smoking decreases tasimelteon AUC by approximately 40%. Was cigarette smoking (YES/NO; if YES, daily quantity) systematically collected in Study 3201? If so, for all randomized subjects (regardless of entrainment), using all available LQ-nTST data (no imputation for missing data), perform analyses (ANCOVA and Permutation ANCOVA t-test) of change from baseline in average for LQ-nTST between treatment groups comparing subjects with cigarette smoking with those who do not. Then perform similar analyses for UQ-dTSD.

Please respond within 7-10 days; otherwise let us know the soonest you can provide the analysis. Any questions, do not hesitate to contact me.

Thank you.

Cathleen Michaloski, BSN, MPH

*Sr. Regulatory Project Manager
Division of Neurology Products
FDA / CDER / OND / ODEI /DNP
White Oak Building 22 room 4342
301-796-1123
Cathleen.michaloski@fda.hhs.gov*

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/s/

CATHLEEN B MICHALOSKI
10/24/2013

Bouie, Teshara

From: Bouie, Teshara
Sent: Thursday, October 17, 2013 12:15 PM
To: Marlene Dressman (Marlene.Dressman@vandapharma.com)
Cc: Michaloski, Cathleen
Subject: NDA 205677

Hi Marlene,

The Biopharm team has the following comments and requests regarding your October 10, 2013 amendment:

Recommendation 11

FDA response to Vanda's proposal:

We do not agree with your proposal of Q= (b) (4). Your product is (b) (4) and the dissolution data from the clinical and primary stability batches at release and under long term stability (12 months) support an acceptance criterion of Q= (b) (4) at 15 minutes. Nevertheless, it must be recognized that some batches may require Stage 2 and, occasionally, Stage 3 testing.

Accordingly, please implement the dissolution acceptance criterion of Q= (b) (4) at 15 minutes and provide the revised specification table for your drug product.

We request a response by October 23, 2013.

Regards,

Teshara G. Bouie, MSA, OTR/L

CDR, United States Public Health Service
Regulatory Health Project Manager
FDA/CDER/OPS/ONDQA
Division of New Drug Quality Assessment I
Phone (301) 796-1649
Fax (301) 796-9749

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/s/

TESHARA G BOUIE
10/17/2013

Executive CAC

Date of Meeting: October 8, 2013

Committee: David Jacobson-Kram, Ph.D., OND-IO, Chair
Abigail Jacobs, Ph.D., OND-IO, Member
Paul Brown, Ph.D., OND-IO, Member
Aisar Atrakchi, Ph.D., DPP, Alternate Member
Lois M. Freed, Ph.D., DNP, Supervisor
Melissa K. Banks-Muckenfuss, Ph.D., DNP, Presenting Reviewer

Author of Draft: Melissa K. Banks-Muckenfuss

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA #: 205-677

Drug Name: Hetlioz (tasimelteon, VEC-162, BMS-214778)

Sponsor: Vanda Pharmaceuticals, Inc.

Background Information

Tasimelteon is a melatonin MT₁ and MT₂ receptor agonist being developed for the treatment of Non-24 Hour (Sleep-Wake) Disorder in the totally blind. A battery of genetic toxicology tests was conducted for tasimelteon, and two *in vitro* tests were conducted for metabolite M11 (not a major human circulating metabolite); tasimelteon and M11 were positive only in *in vitro* chromosomal aberration assays in mammalian cells. The sponsor conducted 2-year carcinogenicity bioassays in rats and mice. Executive CAC concurrence was obtained for the doses used in both studies (cf. letter dated 8/23/99 for IND 54,776). However, the protocol reviewed by the Executive CAC proposed two vehicle (PEG-400) control groups per sex and only one was used. The dose-ranging studies were conducted in the United States, while the carcinogenicity studies were conducted 7 years later in Europe.

Rat Carcinogenicity Study

Tasimelteon was administered orally (by gavage) at doses of 0 (vehicle: PEG-400), 20 (LD), 100 (MD), and 250 (HD) mg/kg male and female Sprague Dawley rats (65/sex/group) for up to 104 weeks. Dosing was suspended for HDF during week 101/102 when the number of survivors fell to 20, and this group was terminated at 104 weeks. All male groups were terminated at 103 weeks due to low survival in the male control group. Overall, there was no statistically

significant drug-related effect on survival rates in males or females. Body weights at 102 weeks were 96%, 96%, and 93% those of control males in the LD, MD and HD groups, respectively. In females, body weights at 104 weeks were 108%, 97%, and 95% those of controls in the LD, MD, and HD groups, respectively; however, during weeks 76-88, body weight in HDF was approximately 87% that of control females. FDA statistical evaluation indicated that only the incidence of uterine endometrial adenocarcinomas in HDF reached statistical significance.

Mouse Carcinogenicity Study

Tasimelteon was administered orally (by gavage) at doses of 0 (vehicle: PEG-400), 30 (LD), 100 (LMD), and 300 (HD) mg/kg male and female CD-1 mice (66/sex/group) for up to 104 weeks. There was no drug-related effect on survival rates in males or females. At week 104, body weight in HDM was reduced approximately 10% compared to control males. Body weight was not affected in females. No drug-related neoplasms were identified.

Executive CAC Recommendations and Conclusions:

Rat

The Committee agreed that the study was acceptable but noted that blood samples should not have been collected from 20 main study animals at week 52 or from all animals at week 101-102. The Committee concluded that the following neoplasms were drug related, based on statistical significance or exceeding the historical control (HC) range:

- Uterus- Endometrial Adenocarcinomas at the HD, based on statistical significance
- Liver- Adenomas in MD and HD females, based on exceeding HC range
- Liver- Adenomas and Carcinomas combined in MD and HD males, based on exceeding the HC range
- Uterus & Cervix- Squamous Cell Carcinomas at the HD, based on exceeding the HC range

<u>Organ/Tumor</u>	<u>Sex</u>	<u>Incidences</u>				<u>p values</u>				<u>HC (Range)</u>
		<u>Con</u>	<u>LD</u>	<u>MD</u>	<u>HD</u>	<u>Trend</u>	<u>LD vs C</u>	<u>MD vs C</u>	<u>HD vs C</u>	
Uterus, Endometrial Adenocarcinoma	F	2	2	2	11	0.0002	0.6360	0.6360	0.0035	0
Liver, Adenoma	F	2	1	6	7	0.0087	0.8511	0.0980	0.0539	0 – 3
Liver, Adenoma + Carcinoma	M	2	2	8	8	0.0145	0.6222	0.0746	0.0444	2 – 4
Uterus + Cervix, Squamous Cell Carcinoma	F	1	0	1	5	0.0059	1	0.7160	0.0765	0

Mouse

The Committee concluded that the study was acceptable and that there were no drug-related neoplasms.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\n
/Division File, DNP
/LFreed, DNP
/MBanks-Muckenfuss, DNP
/CMichaloski, DNP
/ASeifried, OND-IO

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ADELE S SEIFRIED
10/16/2013

DAVID JACOBSON KRAM
10/16/2013

From: Michaloski, Cathleen
To: "[Marlene Dressman](#)"
Subject: Information Request - Clinical Pharmacology NDA 205677
Date: Monday, October 07, 2013 2:33:00 PM

Good Afternoon,

We continue our review of your NDA application for tasimelteon.

We have the following information request from the clinical pharmacology reviewer:

We note that the experimental conditions used in the gastric stability experiments of tasimelteon are not according to the BCS guidance

(<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm128219.htm>). You need to evaluate gastric stability using gastric and intestinal fluids obtained from human subjects, for (b) (4) respectively. Alternatively, simulated gastric and intestinal fluids USP can be substituted.

Please respond within 3 weeks or by COB on 10.28.13. Thank you.

Cathleen Michaloski, BSN, MPH

*Sr. Regulatory Project Manager
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White Oak Building 22 room 4342
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CATHLEEN B MICHALOSKI
10/07/2013

From: Michaloski, Cathleen
To: ["Marlene Dressman"](#)
Subject: NDA-205677 Labeling - Carton and Container
Date: Wednesday, October 02, 2013 9:20:00 AM
Importance: High

Good Morning Dr. Dressman,

We have the following comments on the carton and container labeling for NDA 205677:

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."
(b) (4)
 - 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, as always, feel free to contact me. Thank you.

Cathleen Michaloski, BSN, MPH

*Sr. Regulatory Project Manager
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CATHLEEN B MICHALOSKI
10/02/2013

From: Michaloski, Cathleen
To: ["Marlene Dressman"](#)
Subject: NDA 205677 clinical information request - Study 3201- 9.24.13
Date: Wednesday, September 25, 2013 10:56:00 AM
Importance: High

Good Morning,

As we continue our review of your NDA, we have the following information requests from the clinical review team:

Evaluation of the effects of tasimelteon on endocrine function was performed in Study 3201. Confirm that the effects of tasimelteon at doses higher than 20 mg have not been evaluated in other clinical studies that have been conducted to date. Summary of endocrine parameter values over time by treatment groups have been provided in Study 3201 Study Report, as well as shift tables and summary of subjects with endocrine values outside the reference range.

- Please analyze the mean change in prolactin, total testosterone, free testosterone, luteinizing hormone, follicle stimulating hormone, and progesterone values from baseline over time between the treatment groups by sex.
- Additionally, please provide shift tables (low, normal, high at baseline to low, normal, high on-treatment) for prolactin, total testosterone, free testosterone, luteinizing hormone, follicle stimulating hormone, and progesterone between treatment groups by sex.
- Please provide summary table of subjects with prolactin, total testosterone, free testosterone, luteinizing hormone, follicle stimulating hormone, and progesterone values outside the reference range between treatment groups by sex. Then for each subject who had values outside the reference range, provide a Table of baseline value (reference range and units), and values over time, for each endocrine parameter with values outside the range.
- Subject VP-VEC-162-COSET (b) (6) experienced three events (blood follicle stimulating hormone increased, blood luteinising hormone increased, and blood prolactin decreased). Provide a summary table of these values at baseline (reference range and units) and over time for each of these parameters.

Please provide a response within a week's time. If that is not possible, let us know when we can expect a response.

Any questions please feel free to contact me.

Thank you.

Cathleen Michaloski, BSN, MPH

Sr. Regulatory Project Manager
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CATHLEEN B MICHALOSKI
09/25/2013

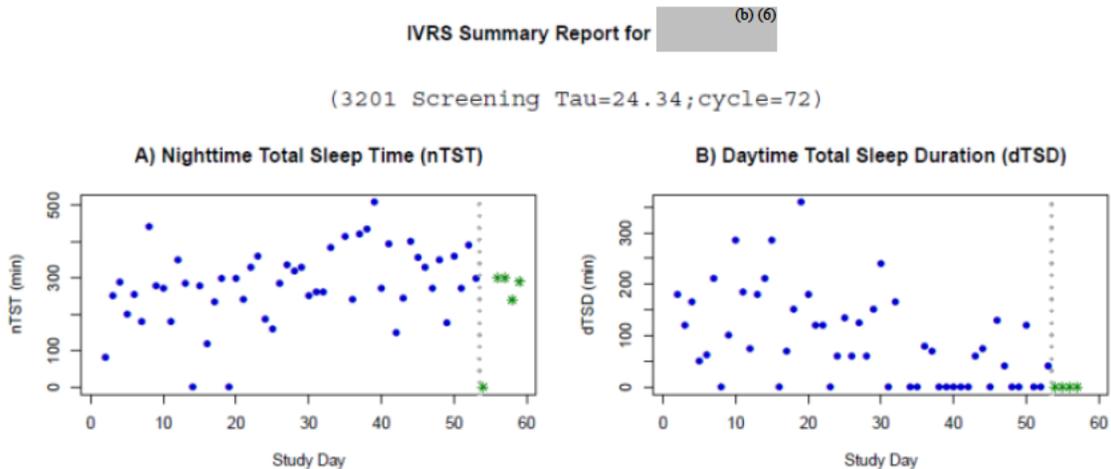
From: Michaloski, Cathleen
To: "Marlene Dressman"
Subject: NDA 205677 clarification of IVRS summary report Appendix 2 in Module 2.7.3
Date: Tuesday, September 24, 2013 7:29:00 PM
Attachments: [image002.png](#)

Dr. Dressman,

We have a question from the statistical reviewer. Please clarify the following discrepancy on Thursday at the mid-cycle communication tcon.

Thank you.

Below is a plot from Appendix 2 in Module 2.7.3. Does each dot represent one night (day)? From this plot, this patient had 5 data points for nTST after randomization. However, based on dataset QS (NDA205677\0000\m5\datasets\vp-vec-162-3201\tabulations\sdm\QS), this patient only had 2 nTST data points after randomization. Please clarify.



USUBJID	(b) (6)	tstpostn
VP-VEC-162-COSET-	(b) (6)	17
VP-VEC-162-COSET-	(b) (6)	7
VP-VEC-162-COSET-	(b) (6)	16
VP-VEC-162-COSET-	(b) (6)	6
VP-VEC-162-COSET-	(b) (6)	35
VP-VEC-162-COSET-	(b) (6)	2
VP-VEC-162-COSET-	(b) (6)	20

Cathleen Michaloski, BSN, MPH
 Sr. Regulatory Project Manager
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CATHLEEN B MICHALOSKI
09/25/2013



NDA 205677

INFORMATION REQUEST

Vanda Pharmaceuticals Inc.
Attention: Marlene Dressman, Ph.D., Senior Director
2200 Pennsylvania Ave NW
Suite 300E
Washington, DC 20037

Dear Dr. Dressman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for tasimelteon capsules.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

We noticed that the synthesis of tasimelteon drug substance manufacturing process used by the (b) (4)

[Redacted]

(b) (4) These experiences indicate that acceptance criteria for critical attributes (b) (4)

[Redacted] could lead to unacceptable drug substance lots. We also noticed that the proposed acceptance criteria for some of the tests in the specifications (b) (4)

[Redacted] are not supported by the manufacturing experience, therefore, we propose tightening of the acceptance criteria as indicated in the individual comments listed below:

1. On the basis of the results observed for the four batches (b) (4) [Redacted] we recommend tightening of the acceptance criteria as indicated in the table below:

Test	(b) (4) observed results from batch analysis	(b) (4) Proposed Acceptance Criteria (AC)	FDA Recommended AC
Assay (HPLC)	(b) (4)		
Total Impurities (HPLC, area %)			
Related substances: Unspecified impurities (% a/a) Individual			
Enantiomeric purity (HPLC)			
(b) (4) (HPLC)			

In addition, we noticed that the impurity profiles of all four (b) (4) batches (b) (4) are not consistent. For example, Batch# (b) (4) contained only two impurities at Relative Retention Time (RRT) (b) (4) whereas the Batch# (b) (4) contained six impurities ranging from RRT (b) (4). Provide explanation for the variability.

- On the basis of the results observed for the four batches (b) (4) of the drug substance, we recommend tightening of the acceptance criteria as indicated in the table below:

Test	(b) (4) observed results from batch analysis	(b) (4) Proposed Acceptance Criteria (AC)	FDA Recommended AC
Total Impurities (HPLC, area %)	(b) (4)		

In addition, we noticed that the impurity profiles of all four (b) (4) batches (b) (4) are not consistent. For example, Batch# (b) (4) contained 3 impurities at RRT ranging from (b) (4) whereas the Batch# (b) (4) contained 9 impurities ranging from RRT (b) (4). Provide explanation for the variability.

- On the basis of the results observed for the five batches (b) (4) of the drug substance, we recommend tightening of the acceptance criteria as indicated in the table below:

Test	(b) (4) observed results from batch analysis	Vanda's Proposed Acceptance Criteria (AC)	FDA Recommended AC
(b) (4)			
Total Impurities (HPLC, area %)	(b) (4)		

4. On the basis of (b) (4) lot release and stability data, we recommend tightening of the acceptance criteria for some of the tests in the (b) (4) drug substance specification as indicated in the table below:

Test	Vanda's Proposed Acceptance Criteria (AC)	FDA Recommended AC
Chiral Purity HPLC: (1R,2R) (1S,2S)	(b) (4)	
Total Impurities	(b) (4)	
Residue on ignition	(b) (4)	

5. On the basis of (b) (4) lot release and stability data, we recommend tightening of the acceptance criteria for some of the tests in the (b) (4) drug substance specification as indicated in the table below:

Test	Vanda's Proposed Acceptance criteria	FDA Recommended Acceptance Criteria
Residue on ignition	(b) (4)	
Chiral purity (1R, 2R) Enantiomer (1R, 2S) Enantiomer	(b) (4)	
Total impurities	(b) (4)	

6. Since tasimelteon (b) (4) drug substance has a tendency to (b) (4) the proposed (b) (4) retest date is not acceptable. Provide data that support the stability of the (b) (4) drug substance (b) (4). Upon review of this data, a retest date will be recommended.
7. On the basis of the lot release and stability data of tasimelteon capsules, we recommend tightening of the acceptance criteria for some of the tests as indicated in the following table:

Test	Vanda's Proposed Acceptance Criteria	FDA Recommended Acceptance Criteria
Total impurities	NMT (b) (4)	NMT (b) (4)
Disintegration	NMT (b) (4) for complete disintegration (n=6)	NMT (b) (4) for complete disintegration (n=6)

8. We observed that in the registration stability lots of tasimelteon 20 mg capsules, there was a gradual increase in the number of individual unknown related substances (impurities) from the initial time point to the last time point. Provide explanation for this phenomenon.
9. The proposed acceptance criterion for the particle size in the (b) (4) drug substance specification for D₉₀ is (b) (4). However, (b) (4) of the (b) (4) drug substance at (b) (4) is conducted with (b) (4). Provide reasons and justification for using (b) (4).
10. When we evaluated (b) (4) (b) (4) using (quantitative) structure-activity relationship [(Q)SAR] models for Salmonella mutagenicity, we got positive result. Therefore, we recommend you to control this impurity (b) (4) and include a test and acceptance criterion in the specification. When setting the acceptance criterion, it should be noted that the exposure of this impurity to the patient should not exceed (b) (4). In addition, provide test results or justification for all the impurities/byproducts/degradants that contain structural alerts for genotoxicity but not discussed in the initial NDA submission.
11. Your proposed dissolution criterion of Q = (b) (4) is not supported by the provided data and is not acceptable. Your dissolution data from the clinical and primary

stability batches at release and under long term stability (12 months) support an acceptance criterion of $Q = \text{[REDACTED]}^{(b)(4)}$ at 15 minutes. Implement this change and provide a revised drug product specification table incorporating the updated dissolution acceptance criterion.

If you have any questions, contact Teshara G. Bouie, Regulatory Project Manager, at (301) 796-1649.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Acting Division Director
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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RAMESH K SOOD
09/20/2013

From: Michaloski, Cathleen
To: ["Marlene Dressman"](#)
Subject: NDA 205677 IR requests - clinical and statistical 9.19.13
Date: Thursday, September 19, 2013 4:29:00 PM
Importance: High

Dr. Dressman,

The clinical review team would like you to perform some additional analyses and clarify a few questions. For the new analyses, we will need the response in 3 weeks (before 10/10/13).

If you are not able to respond by then please, let us know how long it may take.

We have the following information requests:

1. In Study 3201, the lengths of circadian cycle varied among the enrolled subjects. Circadian cycle length expressed as a percentage (actual time/circadian cycle length) is a potential means of comparing effects at a given point in a circadian cycle in one subject to a similar time point in another subject. For example, the time point at 50% circadian cycle time is when patients are expected to be most symptomatic since the endogenous circadian rhythm is most out-of sync with the 24-hour day, and time points 0% or 100% are when there is synchronization. For the following analyses, use all available nTST data in the randomization phase of Study 3201 (and the Study 3203 run-in phase for tasimelteon subjects who enrolled seamlessly into the run-in phase) for each subject randomized in Study 3201 (regardless of entrainment status).

- For each randomized subject who was in the trial for at least 70% of the duration of his/her first circadian cycle in the randomization period in Study 3201, use all available nTST data collected between the time points at 0% and 20% of the first circadian cycle to calculate the mean, and all available nTST data collected between the time points 50% to 70% of first circadian cycle to calculate the mean. The difference between these two means is a reflection of the most symptomatic phase after correcting for the within subject most-likely-to-be asymptomatic period. Do similar analysis for subjects with a second circadian cycle in the randomized phase. Provide a summary of these means (0%-20%, 50%-70%, difference between these means) for the first cycle, and then for the second cycle if available, for each subject by treatment group. There may be a few subjects with a 3rd cycle if the contiguous run-in phase of Study 3203 is counted. Provide a summary table (shell below) for all subjects in placebo group and another table for subjects in the tasimelteon group.

Summary of nTST data in each circadian cycle.

Subject ID	Statistic	1 st cycle		2nd cycle		Difference	1 -20% 50-70%		Difference
		1	-20%	50-70%	Difference		1	-20%	
xx-xx	mean								
	median								
xx-xx	mean								
	median								
xx-xx	mean								
	median								
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	median								
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	median								
xx-xx	mean								
	median								

- Then, compare the mean Difference for tasimelteon group for the first cycle to the mean Difference for the placebo group for the first cycle, using both ANCOVA and Permutation ANCOVA t-test.
- Compare the mean Difference for tasimelteon group for all available cycles (first, second, etc.) to the mean Difference for the placebo group for all available cycles (first, second, etc.), using both ANCOVA and Permutation t-test (due to the small sample size and heterogeneity).
- Perform similar analyses for dTSD.
- For the analyses requested above, please provide the SAS programs which were used to derive the dataset and perform the analyses, along with detailed documentation to facilitate the review.

2. For eligibility in Study 3201, subjects had to answer YES to at least one question from the Sleep Complaint Questionnaire, one of which was “Do you go through periods of good sleep and periods of bad sleep?”. Of the subjects who were randomized, how many subjects answered yes to this question and how many answered no? For all randomized subjects (regardless of entrainment), using all available LQ-nTST data (no imputation for missing data), perform analyses (ANCOVA and Permutation ANCOVA t-test) of change from baseline in average for LQ-nTST comparing subjects who answered YES to those who answered NO to this question. Then perform similar analyses in each treatment group (YES/NO among tasimelteon group, and YES/NO among placebo group). For these analyses requested, please provide the SAS programs which were used to derive the dataset and perform the analyses, along with detailed documentation to facilitate the review.

3. In Study Group 1, 'withdrawal by subject's' as a reason for early termination was reported in 20 subjects in the tasimelteon group (6 in the placebo group), and 'other' was reported in 15 subjects in the tasimelteon group versus 2 in the placebo group. What were the specific reasons cited in the 'Other' category? Is there any additional information on the specific reason for withdrawal by subjects in the 'withdrawal by subject's' category? Did any of these subjects report any ongoing TEAEs at the last visit prior to early withdrawal, or report frequently recurring TEAEs or experience recurring abnormal laboratory values at previous on-treatment visits prior to withdrawal?

4. In Figure 7 (page 29) of the Integrated Summary of Efficacy, there were 8 and 7 subjects in the Randomization and open-label extension, respectively, for whom 'Study Termination' was listed as reason for early termination/not completing the open-label extension. Study 3201 was completed. If the study was terminated because it was completed, please explain how that would result in early withdrawal of subjects rather than study completion?

5. In Figure 9 (page 47) of the Integrated Summary of Efficacy, Tau was not calculated for 9 subjects who entered the Run-in phase. What was the reason for not calculating the Tau?

As always, any questions, please feel free to contact me. Thank you.

Cathleen Michaloski, BSN, MPH

Sr. Regulatory Project Manager

Division of Neurology Products

FDA / CDER / OND / ODEI /DNP

White Oak Building 22 room 4342

301-796-1123

Cathleen.michaloski@fda.hhs.gov

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/s/

CATHLEEN B MICHALOSKI
09/25/2013



NDA 205677

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Vanda Pharmaceuticals, Inc.
2200 Pennsylvania Ave, NW
Suite 300E
Washington, D.C. 20037

ATTENTION: Paolo Baroldi, M.D., PhD.
Senior Vice President, Chief Medical Officer

Dear Dr. Baroldi:

Please refer to your New Drug Application (NDA) dated May 30, 2013, received May 31, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Tasimelteon Capsules, 20 mg.

We also refer to your June 17, 2013 correspondence, received June 18, 2013, requesting reconsideration of your proposed proprietary name, Hetlioz. We also refer to your amended correspondence, dated July 26, 2013, received July 31, 2013.

We have completed our review of the external report conducted by the [REDACTED] (b) (4) [REDACTED] submitted as part of your request for reconsideration of the proposed proprietary name Hetlioz and have the following comments:

1. HETLIOZ WILL BE DISPENSED USING SPECIALTY PHARMACIES

You noted that Hetlioz will be dispensed in specialty pharmacies and products such as Haltran and over the counter (OTC) ibuprofen would not be typically dispensed in a specialty pharmacy. Although specialty pharmacies may not typically dispense OTC products, if a patient took a prescription for Hetlioz to a retail pharmacy, the pharmacist may misinterpret Hetlioz as Haltran, and OTC ibuprofen could be dispensed. Furthermore, although a patient does not need a prescription to obtain OTC ibuprofen, health care practitioners issue prescriptions for OTC products.

We note that you intend physicians to fax a patient enrollment form to a specialty pharmacy to obtain Hetlioz. However, there is still potential for a physician to give a hard copy prescription for Hetlioz to a patient. Since Hetlioz is a capsule and does not have special administration instructions and does not require limited distribution under a Risk Evaluation and Mitigation Strategy (REMS), the potential for patients to take a hard copy prescription for Hetlioz to a retail pharmacy still exists. In addition, since your proposed limited distribution plan is voluntary and not enforceable, as it is not part of a REMS, we are

concerned that the limited distribution plan may change at any time without prior approval by the Agency. We do not have any means of enforcing or monitoring this plan and cannot rely on the limited distribution plan as a mechanism to prevent confusion. Furthermore, we have reports of name confusion with other products marketed under limited distribution systems and therefore our safety concern is not diminished with your product.

2. HETLIOZ WILL BE PRESCRIBED QHS (b) (4) BEFORE BEDTIME

We acknowledge that Hetlioz is intended to be prescribed once daily (b) (4) prior to bedtime; however, health care practitioners may not always write Hetlioz QHS or Hetlioz 1 PO (b) (4) before bedtime. (b) (4) data based on physician survey shows that the marketed melatonin receptor agonist, Rozarem (Ramelteon), which is in the same pharmacologic and therapeutic category as Hetlioz, can be prescribed “once a day (QD).”¹ Additionally, (b) (4) data based on physician survey shows that Ibuprofen OTC 200 mg has been prescribed “four times daily (QID)”². The similarity between “QD” for Hetlioz and “QID” for Haltran increases the risk for confusion between these products³.

3. NO MISINTERPRETATIONS OF HETLIOZ WITH HALTRAN IN THE NAME STUDY CONDUCTED BY (b) (4)

You provided handwriting samples to demonstrate lack of similarity between Hetlioz and Haltran. This technique of comparing the orthographic similarities of Hetlioz and Haltran is limited because you only compared scripted samples side by side from the same provider, whereas prescriptions presented to a pharmacy are likely to have a single drug written in isolation that can be misinterpreted.

You note a multifaceted name safety research study was conducted and none of the prescription interpretations resulted in the identification of Haltran or any other marketed drug products. This study included handwriting and verbal prescriptions for Hetlioz, in which 27 U.S. based healthcare practitioners interpreted the prescriptions in a simulation study. A name simulation study of this size does not provide conclusive evidence that a proposed name does not pose a risk of confusion given the small sample size used. A simulation study designed to detect close to a zero percentage error rate with statistical significance would require an extremely large sample size (e.g. a sample of approximately 26,000 would be required to detect an error rate of 0.001 at the 0.05 significance level)⁴.

In summary, none of the information provided by (b) (4) was adequate to support the reconsideration of the proposed name Hetlioz. However, based on our independent review of the name pair and drug use information we conclude that the name Hetlioz does not appear to be vulnerable to confusion with Haltran. This conclusion is based primarily upon the orthographic differences between these names, in conjunction with drug use data that shows that the

(b) (4)
Institute for Safe Medication Practices. List of Error-Prone Abbreviations, Symbols, and Dosage Designations. 2013.

⁴ This calculation was made to determine whether the error rate differs from 0.001 at a 0.05 significance level and 80% power, assuming the medication error rate of the sample is 0.0005. (published in FDA’s PDUFA Pilot Project Proprietary Name Review Concept Paper)

discontinuation of the Haltran product did eliminate the prescribing of that name despite the fact that ibuprofen generics are available.

The proposed proprietary name, Hetlio^z, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you. Additionally, if **any** of the proposed product characteristics as stated in your May 30, 2013 and July 26, 2013, submissions are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Ermias Zerislassie, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301)796-0097. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Cathleen Michaloski at (301) 796-1123.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
09/16/2013

From: Michaloski, Cathleen
Sent: Thursday, September 05, 2013 8:25 AM
To: 'Marlene Dressman'
Subject: NDA 205677 Information request- re: nonclinical carci studies
Importance: High

Good Morning Dr. Dressman,

We have an information request from the nonclinical review staff. It is as follows:

Please provide the following information for carcinogenicity studies TAJ0001 and TAJ0002:

- 1) A summary table of all (not just selected) clinical signs. The table should list the sign and the # of occurrences/# of animals affected for each group.**
- 2) Verification that all tissues listed in Section 2.5.4 were examined microscopically for all animals.**

We request this information as soon as possible; no later than COB Thursday 9/12/13.

As always any questions, please contact me. Thank you.

Cathleen Michaloski, BSN, MPH

Sr. Regulatory Project Manager

Division of Neurology Products

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CATHLEEN B MICHALOSKI
09/05/2013

From: Michaloski, Cathleen
To: ["Marlene Dressman"](#)
Subject: NDA 205-677 Statistical Information Request for Study 3201 (8.23.2013)
Date: Tuesday, August 27, 2013 11:23:00 AM
Importance: High

Good Morning,

Please provide the statistical files identified below. These files were used in the derivation of clinical measures for study 3203, but not provided in the submission. Please respond at your earliest convenience.

Thank you.

Please provide the following four files (these files were used in ADEFF.SAS for study 3203):



Cathleen Michaloski, BSN, MPH

*Sr. Regulatory Project Manager
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CATHLEEN B MICHALOSKI
08/27/2013

From: Michaloski, Cathleen
To: ["Marlene Dressman"](#)
Subject: NDA 205-677 Statistical Information Request for Study 3201 (08.023.2013)
Date: Friday, August 23, 2013 10:34:00 AM
Importance: High

Good Morning,

Please provide the following small data files (flag files from adjudication committee review used in the derivation of the clinical endpoints). Please send these files ASAP. The biostatistician needs the files in order to continue her analysis.

Please provide the following five files (these files were used in ADEFF.SAS for study 3201):



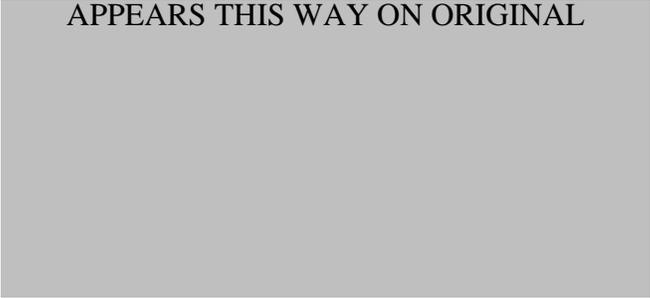
As always, any questions, do not hesitate to contact me. Thank you.

Cathleen Michaloski, BSN, MPH

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APPEARS THIS WAY ON ORIGINAL



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CATHLEEN B MICHALOSKI
08/23/2013

From: Michaloski, Cathleen
To: ["Marlene Dressman"](#)
Subject: NDA 205677-Statistical questions- follow-up from FDA reviewer
Date: Wednesday, August 14, 2013 10:59:00 AM
Importance: High

Good Morning,

We have additional questions from the statistical review team:

NDA 205-677 Information Request for Study 3201 and 3203 (08.13.2013)

1. It seems that the define.xml document and entrainment analysis datasets aren't available (raw data folder location: m5\datasets\vp-vec-162-3201\analysis\legacy-csv\datasets). Please provide a define document for A3201. In addition, please provide a SAS XPT analysis dataset for entrainment. In this dataset, there is one row for each collection vessel, corresponding to a collection interval. Please include the following variables in this data set:

- All variables in the dataset A3201.xpt
- Midpoint time (in hours relative to an arbitrary starting point) and duration for the collection interval
- Rate of excretion of aMT6s during the interval
- USUBJID, treatment flags, population flags and other core variables as listed in page 2 of Reviewer's Guide for Study 3201.
- Day: referenced to the first urine collection.

Please submit the executable SAS program which derives the above data set based on A3201 and ADSL.

Similarly, please provide a SAS analysis dataset for C3201, A3203 and C3203, respectively. All the SAS datasets should be accompanied by define documents.

2. From Appendix A of Statistical Analysis Plan for Study 3201, it appears that the (b) (4) code on page 4 doesn't exactly implement the model proposed in equation (1) since (b) (4) isn't equivalent to (b) (4). Please clarify which model you intended to apply and which model is actually used in the acrophase

calculation.

We request this information within 1 week, by COB 8.21.13. Thank you.

Cathleen Michaloski, BSN, MPH

Sr. Regulatory Project Manager

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[*Cathleen.michaloski@fda.hhs.gov*](mailto:Cathleen.michaloski@fda.hhs.gov)

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CATHLEEN B MICHALOSKI
08/21/2013

Email sent : Aug 9, 2013

To: Marlene.Dressman@Vandapharam.com

Information request - clinical

Good Afternoon,

The NDA review is on-going. The clinical team has the following comments/information requests:

1. For the raster plots, what exactly do the lines for nighttime sleep represent - for example, do the lines show 'time in bed to time out of bed', or time actually asleep? If it's time asleep, how is it calculated? What entries in the morning questionnaire were used to calculate the length and position of the line?
2. Is it correct that patients who entered 3203 after being in 3201 just have a raster plot generated for the combined 3201 + 3203 time course? If so, can you generate plots for these patients that show their course just over 3201 (and include the nTST and dTSD scatter plot, in the same format as for the other patients)?
3. For the gaps in the raster plot data between study 3201 and 3203, were the patients on open-label tasimelteon in those periods?
4. For some treatments did any gaps in treatment occur, e.g. between completion of SET study and enrolling in RESET study, or for any other reason - and would the gaps in treatment be represented on the raster plots?
5. Please generate the following raster plots:
 - a. a set of raster plots *without* the acrophase time on the plot
 - b. a set that shows *both* time in bed and out of bed, and time asleep in that period
6. Please generate scatter plots for nTST and dTSD that also show an average line based on the weekly averages.
7. Please send us the exact "wording" the patient heard for the morning and evening questionnaire?

We would like a response to these questions within 7-10 days (COB 8/19/13) if possible. Thank you.

Any questions do not hesitate to contact me.

Cathleen Michaloski, BSN, MPH

Sr. Regulatory Project Manager

Division of Neurology Products

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CATHLEEN B MICHALOSKI
08/09/2013

From: Michaloski, Cathleen
Sent: Monday, August 05, 2013 6:44 PM
To: 'Marlene Dressman'
Subject: NDA 205677 tasimelteon- Information Request for Study 3201
Importance: High

Good Afternoon,

We have additional questions from the statistical team:

Please provide the following information or indicate the location of the information in the current submission:

- For Study 3201, 84 patients were randomized and 78 patients were included in the ITT population by your definition. For each of the 6 patients who were excluded from ITT, please clarify the reason of exclusion from the ITT population in details. Please add these 6 patients to the existing ADEFF dataset and conduct the primary efficacy analysis, primary step-down analysis and secondary efficacy analysis on the randomized population (n=84). Please describe how the missing data is handled in the analysis.
- Sixteen (16) patients in the ITT population (n=78) didn't complete the study and some of them were classified as "entrained". Please clarify if this classification is based on data or based on adjudication review. In addition, please provide a table which describes the entrainment status, population flags, basis of the classification of entrainment (data based or adjudication review based), and the date of the decision of entrainment status for each of the 84 patients.
- The study report states that "efficacy analysis included no imputation for missing data". However, CGI-C information is missing for 7 patients in ADEFF dataset and it appears that for these 7 patients CGI-C was considered as "0" in the calculation of N24CRS. Please clarify. In addition, please describe how missing data were handled for other efficacy variables or clarify that there are no missing data based on your definition of ITT population and Analysis Population.
- Please clarify if Pre-sleep Questionnaire (PreSQ) and Post-sleep Questionnaire are included in blankcrf.PDF. If yes, please specify the page number. If not, please provide both questionnaires or indicate the location of these two questionnaires in the current submission.

- It seems that the raw data used to derive LQ-nTST, UQ-dTSD and MoST are included in the dataset QS. Please provide detailed description of the derivation process (e.g., variables names and dataset names in the derivation) and the executable SAS programs used to derive these three variables. The SAS programs should include sufficient documentation. If any special consideration or handling were applied to some subjects, please provide detailed relevant information.
- Please provide a table which describes the dates when ITT and Analysis Population flags are generated for each of the 84 patients.

Please provide your response within 1 week (COB 8.12.13). Any questions, do not hesitate to contact me. Thank you.

Cathleen Michaloski, BSN, MPH

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CATHLEEN B MICHALOSKI
08/09/2013



NDA 205677

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

Vanda Pharmaceuticals, Inc.
2200 Pennsylvania Ave., NW
Suite 300E
Washington, D.C. 20037

Attention: Paolo Baroldi, M.D.
Chief Medical Officer

Dear Dr. Baroldi:

Please refer to your New Drug Application (NDA) dated and received May 31, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Hetlioz (tasimelteon) 20 mg oral capsules.

We also refer to your amendments dated July 1, 2013, and July 3, 2013.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>). Therefore, the user fee goal date is January 31, 2014.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by December 15, 2013. In addition, the planned date for our internal mid-cycle review meeting is September 12, 2013. We are tentatively planning to hold an advisory committee meeting to discuss this application on November 14, 2013.

During our filing review of your application, we identified the following potential review issues:

Chemistry, Manufacturing and Controls

1. Based on our initial evaluation of the information provided in the application, it is unclear whether you have adequate understanding and control of the manufacturing process for the drug substance. We note that two of the five batches of (b) (4) tasimelteon manufactured by (b) (4) to date have required (b) (4) (b) (4) in order to conform to specification. Of these, batch (b) (4) was (b) (4) and then (b) (4) Clarify whether this batch was tested for residual metals per the specification for (b) (4) tasimelteon (Table 3.2.S.2.4-5) prior to release for (b) (4)
2. You indicate that (b) (4) of (b) (4) tasimelteon is observed after long-term storage (b) (4) but not in formal stability studies. Thus, we are concerned that results from studies performed (b) (4) would not be indicative of the effects of the storage and shipping conditions (b) (4) Provide any available data obtained from drug substance stored or shipped (b) (4)
3. The proposed manufacturing process for tasimelteon capsules provides for (b) (4) (b) (4)

Division of Medication Error Prevention and Analysis

4. We recommend conducting a label comprehension study once a proposed proprietary name is found acceptable for your product. The label comprehension study should include the potential users of the product and should evaluate that the intended patient population can understand the information in braille presented on the label. In addition, there should be a subjective component of the study to determine what information could be confusing for patients on the label, as well as to gather input on how to improve the label.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We also request that you submit the following information:

Nonclinical

1. Submit a signed and dated Pathology Report for the pivotal 6-month toxicity study in rats (Study TAJ0007-98348) (cf. IND 54776, Pre-NDA Meeting Minutes, 3/22/2013).

Biopharmaceutics

2. Provide complete dissolution profile data (raw data and mean values) from the pivotal clinical and primary stability batches supporting the selection of the proposed dissolution acceptance criteria (i.e., specification-sampling time points and values) for your proposed product.
3. Clarify whether you are requesting FDA to designate your proposed product as a BCS Class ^a drug product. Note that solubility, permeability, gastric stability, and dissolution data will be needed to support the BCS-Class ^b designation for your product. For the specific information/data that are needed to classify your proposed product, please refer to the attached BCS document and the BCS guidance (link is below).

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070246.pdf>

LABELING

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

Highlights (HL)

Patient Counseling Information Statement:

1. Must include the following bolded verbatim statement (without quotation marks):

“See 17 for PATIENT COUNSELING INFORMATION
Comment: Add this statement

(b) (4)

Full Prescribing Information (FPI)

2. The following heading must appear at the beginning of the FPI in UPPER CASE and bolded: “FULL PRESCRIBING INFORMATION”.
Comment: Font is lower case; must be in UPPER case.
3. All section and subsection headings and numbers must be bolded.
Comment: Remove excess periods behind subsections.
4. Adverse Reactions: 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: Add this statement to the Adverse Reactions section.
5. Patient Counseling Information:
Comment: Must reference any FDA-approved patient labeling, include the type of patient labeling, and use the following statement at the beginning of Section 17: See FDA-approved patient labeling (Medication Guide)

Carton and Container Labeling

6. Provide your rationale for only presenting the proprietary name and strength in braille on the container label. Clarify whether you considered if other important information, such as the established name or usual dosage, should also appear in braille on the container label to promote the safe use of the product. In addition, how did you determine the container label is the only place where braille is appropriate to ensure proper use of the medication by patients?

We request that you resubmit labeling that addresses these issues by August 14, 2013. The resubmitted labeling will be used for further labeling discussions.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because the drug product for this indication has orphan drug designation, you are exempt from this requirement.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

If you have any questions, contact Cathleen Michaloski, BSN, MPH, Sr. Regulatory Project Manager, at (301) 796-1123 or by email at Cathleen.michaloski@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Eric Bastings, M.D.
Acting Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

ERIC P BASTINGS
07/29/2013

From: Michaloski, Cathleen
To: ["Marlene Dressman"](#)
Subject: NDA-205677 Statistical Information and Data Request
Date: Monday, July 29, 2013 3:31:00 PM
Importance: High

Good Afternoon:

As part of our on-going review we have comments from the statistical team:

Please provide the following information or indicate the location of the information in the NDA submission:

- For Study 3201, Please explain why for primary efficacy analysis the entrainment rate was based on variable ENTRAIN for ITT population while for primary step-down analysis the entrainment rate was based on variable ENTRAIN1 for Analysis Population. Please justify the definition of ITT Population and Analysis Population. Please explain the difference between variable SITEGR1 and variable SITEGR2.
- Please add variable ITT* (Population includes all patients who received at least one dose of treatment and who had at least one assessment) to all analysis datasets for Study 3201.
- On Page 67 of Statistical Analysis Plan (SAP) for Study 3201, it states that “Numerous issues related to the handling of special conditions are beyond the scope of this document.” Please provide detailed information regarding how special conditions were handled in the calculations of acrophase, tau and N24CRS, and for which subjects and data points these special considerations were applied.
- Based on Section 5.3.5 of SAP for Study 3201, it states that “An adjudication panel reviewed the blinded and anonymized data for individuals who have a tau value <24.1 and a 95% CI that includes 24.0 only and will flag an individuals’ tau if the data is of poor quality and consequently such an individual would be considered not-entrained.” Please provide detailed information regarding the rules and implementations of this blind review and results of this blind review at subject level.

We request this information within one week, by COB Monday August 5, 2013. As always, any questions please contact me. Thank you.

Cathleen Michaloski, BSN, MPH

*Sr. Regulatory Project Manager
Division of Neurology Products
FDA / CDER / OND / ODEI / DNP
White Oak Building 22 room 4342
301-796-1123
Cathleen.michaloski@fda.hhs.gov*

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received this e-mail message in error, please e-mail the sender immediately at cathleen.michaloski@fda.hhs.gov.

APPEARS THIS WAY ON ORIGINAL

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/s/

CATHLEEN B MICHALOSKI
07/29/2013

From: Michaloski, Cathleen

Sent: Thursday, June 20, 2013 12:52 PM

To: 'Marlene Dressman'

Subject: NDA 205677 tasimelteon in Non24 sleep wake d/o in blind individuals.

Importance: High

We are in the process of reviewing the NDA. At this time, the clinical team has taken an initial look at the proposed labeling. You will need to submit a Medication Guide for tasimelteon, using Medication Guides for approved sedative hypnotics as a model. You will need to submit the MG on or before July 10, 2013. The Medication Guide is not a REMS but is part of the patient counseling section of the prescribing information. Thank you.

Cathleen Michaloski, BSN, MPH

Sr. Regulatory Project Manager

Division of Neurology Products

FDA / CDER / OND / ODEI /DNP

White Oak Building 22 room 4342

301-796-1123

Cathleen.michaloski@fda.hhs.gov

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/s/

CATHLEEN B MICHALOSKI
06/20/2013



NDA 205677

NDA ACKNOWLEDGMENT

Vanda Pharmaceuticals, Inc.
2200 Pennsylvania Ave., NW
Suite 300E
Washington, D.C. 20037

Attention: Paolo Baroldi, M.D.
Chief Medical Officer

Dear Dr. Baroldi:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Hetlioz (tasimelteon) oral Capsules, 20 mg

Date of Application: May 31, 2013

Date of Receipt: May 31, 2013

Our Reference Number: NDA 205677

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on July 30, 2013, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neurology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, do not hesitate to contact me at (301) 796-1123.

Sincerely,

{See appended electronic signature page}

Cathleen Michaloski, BSN, MPH
Sr. Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

CATHLEEN B MICHALOSKI
06/05/2013



IND 054776

MEETING MINUTES

Vanda Pharmaceuticals
2200 Pennsylvania Ave NW
Suite 300E
Washington, D.C. 20037

Attention: Marlene Dressman, Ph.D.
Senior Director, Clinical Development

Dear Dr. Dressman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tasimelteon.

We also refer to the February 21, 2013 multidiscipline pre-submission meeting between representatives of your firm and the FDA. The purpose of the meeting was to discuss the contents of the NDA submission.

A copy of the official minutes is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Cathleen Michaloski, BSN, MPH, Sr. Regulatory Project Manager at (301) 796-1123.

Sincerely,

{See appended electronic signature page}

Russell G. Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Meeting Type B
Meeting Category: Pre-NDA; multidiscipline pre-submission meeting

Meeting Date and Time: February 21, 2013
Meeting Location: White Oak Building 22, room 1309

Application Number: IND 54776
Product Name: tasimelteon
Indication: Non-24-Hour Disorder in blind individuals with no light perception
Sponsor/Applicant Name: Vanda Pharmaceuticals

Meeting Chair: Russell Katz, M.D., Director, Division of Neurology Products (DNP)

FDA ATTENDEES

Ellis Unger, M.D, Director, Office of Drug Evaluation I
Russell Katz, M.D., Director, Division of Neurology Products (DNP)
Ron Farkas, M.D., Ph.D., Clinical Team Leader, DNP
Devanand Jillapalli, M.D., Clinical Reviewer, DNP
Andrew Sostek, PhD., Clinical Reviewer, DNP
Lois Freed, Ph.D., Supervisory Nonclinical Team Leader, DNP
Melissa Banks-Muckenfuss, Ph.D., Nonclinical Reviewer, DNP
Julia Luan, Ph.D. Statistical Mathematician
Ta Chen Wu, Ph.D., Clinical Pharmacology Reviewer
Jagan Parepally, Ph.D., Clinical Pharmacology Reviewer
Katherine Bonson, Ph.D., Controlled Substance Staff
Kathryn O'Connell, M.D., Orphan Disease Program
Hong Vu, PharmD, MSc, Orphan Disease Program
Cathleen Michaloski, BSN, MPH, Project Manager

(b) (4)

SPONSOR ATTENDEES

Mihael Polymeropoulos, M.D., Chief Executive Officer, Vanda Pharmaceuticals
Paolo Baroldi, M.D., Ph.D., Acting Chief Medical Officer, Vanda Pharmaceuticals
Deepak Phadke, Ph.D., Vice President of Manufacturing, Vanda Pharmaceuticals
Marlene Dressman, Ph.D., Project Head, Vanda Pharmaceuticals
Eugene Laska, Ph. D., Statistical Consultant, Nathan Kline Institute for Psychiatric Research,
New York University School of Medicine
Charles Czeisler, Ph.D., M.D., Circadian Expert, Brigham and Women's Hospital, Harvard
Medical School

(b) (4)

1.0 BACKGROUND

The purpose of the meeting is to discuss the submission of a New Drug Application for tasimelteon in the treatment of Non-24-Hour Disorder in blind individuals with no light perception. VEC-162, tasimelteon (proposed trade name Hetlioz) is a sedative hypnotic capsule 20 mg oral formulation to be administered once daily, (b) (4) before bedtime.

Vanda has conducted a pivotal phase 3 study (VP-VEC-162-3201) as well as a randomized withdrawal study to evaluate the maintenance of effect (VP-VEC-162-3203). Long term safety was evaluated in two phase 3 open-label studies (3202 and 3201 or SET). All four studies will be used to evaluate the safety of 20 mg of tasimelteon.

The sponsor has obtained orphan status for their product and indication from the Office of Orphan Products (reference: [2009-2974](#) Vanda Pharmaceuticals, Inc. tasimelteon - Designated Treatment of non-24 hour sleep/wake disorder in blind individuals without light perception)

The sponsor seeks guidance on the composition of the NDA submission.

2. DISCUSSION

Summary of Effectiveness

Background

Study 3201 will serve as the pivotal study for assessing the efficacy of tasimelteon to treat Non-24-Hour Disorder in blind individuals with no light perception and 3203 will be presented for evidence of maintenance of effect with long-term tasimelteon dosing. An overview of the proposed structure and presentation of the summary of effectiveness for tasimelteon capsules is presented in Section 3 of this briefing book.

Question 1: Does the division agree that data from the pivotal efficacy studies are adequate to support filing?

Preliminary Response

The efficacy data, on face, appear adequate to support filing, but you should clarify if the efficacy results in Appendix A are based on the ITT population. If not, what are the ITT efficacy results? What are the top line efficacy results for Study 3203?

Meeting Discussion

The Sponsor stated that the efficacy results presented in Appendix A were based on Per Protocol population. The Sponsor stated that the efficacy results based on the modified ITT and ITT populations were consistent with what was presented in Appendix A, and that the top line results of Study 3203 support the efficacy demonstrated in Study 3201.

Question 2: Does the Division agree with the proposed presentation of efficacy described in Appendix B, and Appendix C?

Preliminary Response:

- In addition to what you have proposed, please provide all the raw data for all the efficacy endpoints. If an efficacy endpoint is a derived endpoint, please provide all the programs which are used to derive the efficacy endpoint based on the raw data. Especially, all the raw data and programs involved in the calculation of acrophase and tau should be provided.
- For all the datasets and programs, please provide sufficient documentation which can assist the understanding of the structure of datasets, description of variables and analysis programs.
- It seems that the Analysis Population will be used for the analysis of all other endpoints except the primary endpoint. Please provide the analyses results based on ITT population for the primary endpoint, step-down primary endpoint and all other efficacy endpoints.
- Please clarify when acrophase and tau were calculated and locked. Were these endpoints calculated before data unblinding or after data unblinding?
- Please clarify if the proposed algorithm for calculating acrophase and tau is the most commonly accepted method in the field or if this algorithm was designed specifically for this study.

Meeting Discussion

The sponsor agreed to comply with the requests. There was a discussion on the apparent 20% responder rate in the placebo group in Study 3203, and regarding non-visual cues for entrainment in blind individuals.

Clinical Pharmacology

Background

The tasimelteon program includes fourteen phase I clinical pharmacology and clinical pharmacokinetic studies. The studies to be included in the NDA are described in Section 5.

Question 3: Does the Division agree that the clinical pharmacology program is adequate to support filing?

Preliminary Response

On face, no. There is no detailed information related to Clinical Pharmacology studies in the briefing package to comment on the adequacy. You should expect to provide, at the meeting, justification for not conducting/including the planned clinical studies to evaluate the effect of CYP2C9 and 2D6 inhibitors on drug disposition.

In addition, the followings should be included in the NDA submission:

- Justification for the dose selection.
- The role of P-gp and other major transporters on drug disposition should be evaluated.
- An in vitro study to evaluate the potential for induction of CYP2B6 should be conducted. Based on the results from the in vitro study an in vivo study may be warranted.
- Due to the large variability in PK parameters, characterization of gender differences in drug disposition should be evaluated with appropriate sample size. You claimed that there is no effect of gender on tasimelteon PK. Please provide details of such analysis.
- In the population PK analysis report you mentioned that four Clinical Pharmacology studies (1105, 1106, 1107, and 1110) will be included. Please provide justification as to why other Phase I PK studies will not be included.
- Please provide detailed information, which includes both in-vitro and in-vivo results, to justify that food effect on 20 mg tasimelteon would be similar to 100 mg strength in the NDA submission.

We request that you provide the summary section as a review aid for the Clinical Pharmacology/Biopharmaceutics reviewer. The outline of the summary section of the HPBIO section is provided. At the time of NDA submission you can use this template to write the summary of the Clinical Pharmacology and Biopharmaceutics section of the NDA or provide it to the agency as a review aid. This summary section should be submitted electronically with appropriate hyperlinks to the relevant supporting data (Document is provided separately).

Meeting Discussion

The sponsor stated that from the in-vivo studies the contributions of CYP1A2 and CYP3A4 to tasimelteon disposition account for the great majority of CYP-mediated metabolism (greater than 1.0) and the contribution of CYP2C9 and CYP2D6 are minor. The Agency asked the sponsor to provide these details in the NDA submission.

Integrated Summary of Safety

Background

An overview of the proposed structure and presentation of the integrated summary of safety for tasimelteon capsules is presented in (Section 6) of this briefing book.

Question 4: Does the Division agree that the safety database and the proposed methodology for pooling the safety data are adequate to assess the safety of tasimelteon in the indicated population?

Preliminary Response

The safety database, on face, appears adequate to support filing.

We agree with the pooling strategy. However, the reason for placebo-controlled pool sub-group (2.1) is not clear, possibly related to the absence of a 20 mg dose group in the elderly insomnia study.

Please populate the two *exposure* shell tables provided in the Safety Table Shells section of this document below [i.e., Summary of all subjects (unique subjects) who received at least one dose of tasimelteon in all clinical trials; Summary of subjects (unique subjects) who received at least one dose of 20 mg (cumulative dose) by duration and exposure interval (safety population)]. These tables are in addition to the exposure tables that you propose to submit in the NDA.

You state that adverse events will be coded by MedDRA version 14.1 System Organ Class (SOC) and Preferred Term (PT). It is not clear how big the safety database is and, therefore, the need for inclusion of High Level Term (HLT) or even High Level Group Term (HLGT). Confirm that all legacy studies included in the safety database were recoded by MedDRA version 14.1. If not, identify which studies were not recoded, and whether these were included in pooled integrated safety analyses datasets, and how you propose to analyze terms that were coded using different versions of MedDRA. For those legacy studies that were recoded to MedDRA version 14.1, was recoding done using the original Verbatim Terms? What was the procedure used for recoding?

In Section 6.7 (page 44), you provide a definition of an *Adverse Event* (AE), which appears to be similar to the typical definition of a *Treatment-Emergent Adverse Event* (TEAE). In the context of the regulatory definition (21CFR§312.32) of an adverse event (i.e., any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related), it is not clear if you are using the terms AE and TEAE interchangeably.

Confirm that all adverse events were included in the integrated safety databases and datasets for the various pools regardless of seriousness or relationship to the investigational product. Clarify if adverse events were those that were spontaneously reported by patients or observed by the investigator, and whether they included “medically relevant” clinical laboratory tests (biochemistry, hematology, urinalysis, electrocardiogram, etc), medically relevant vital signs measurements and physical examinations. Clinical laboratory tests may be considered “medically relevant” if meeting certain pre-defined criteria (e.g., patient was symptomatic, required corrective treatment, led to discontinuation of the investigational product, or fulfilled a seriousness criterion) for the purpose of reporting those laboratory abnormalities as an adverse

event. Where possible, were symptoms grouped together as a single syndrome or diagnosis? Were the definitions of an adverse event and the method of collecting these adverse events (as noted above) uniformly applied to all clinical studies in the safety database and integrated safety datasets? If not, provide a summary table listing the key areas of similarities and differences between the methodologies used in various clinical studies.

Confirm that the definition of a serious adverse event is consistent with the regulatory definition (21CFR§312.32), and includes those adverse events that were considered serious based on the appropriate medical judgment. Confirm that this definition was uniformly applied to all clinical studies in the safety database.

Please populate the table shell [Incidence of subjects reporting any TEAE in placebo-controlled studies by treatment group and by study population] provided in the Safety Table Shells section of this document below, which is a summary table of the incidence of the number of subjects reporting any TEAE between treatment groups (tasimelteon dose groups and placebo) by study population in placebo-controlled studies. Include only placebo-controlled studies (list studies included in the foot note). Subjects in cross-over studies reporting a TEAE in different treatment periods using different doses may be counted more than once across the dose categories.

For Pool 3, provide a summary table of the incidence of the number of subjects reporting any TEAE between treatment groups (tasimelteon versus placebo) by country (all countries, US sites combined, Germany sites combined). For Pool 3, provide a summary table of the incidence of the number of subjects reporting any TEAE between treatment groups (tasimelteon versus placebo) by Study Site (all sites combined, and by each study site).

We acknowledge the mock Shell Table 2.0.5.1.2 (Treatment-emergent AEs by SOC and PT: Placebo-controlled Pool) in the briefing book summarizes the TEAEs by SOC and PT. In addition, for Pool 2, Pool 2.1 and Pool 3, include a summary table of common TEAEs for each of these pools (see the shell for Common TEAEs across placebo-controlled studies as an example provided in the Safety Table Shells section of this document below) in descending order of incidence of any tasimelteon dose. Provide separate but similar tables for each age category (18-49, 50-65 and >65 years), sex (male, female), Race (White, Black, Asian, Other), and BMI category. Common TEAEs may be defined as occurring in at least 3% of all tasimelteon subjects in Pool 2, and in at least 5% of all tasimelteon subjects in for Pool 2.1 and Pool 3.

It is not clear how you proposed to provide summary tables of common TEAEs for Pool 4 (tasimelteon only pool of subjects with N24HSWD). One example of such a summary table is the Summary of common ($\geq 5\%$ in overall tasimelteon) TEAEs in subjects with N24HSWD (Studies 3201: double-blind phase and open-label phase) which is provided in the Safety Table Shells section of this document below. Comparing the incidence of TEAEs (using the total number of subjects at risk in the denominator) in the double-blind phase of placebo-controlled studies with the incidence in the open-label studies may be informative. However, such direct comparison may be limited due the long duration of exposures in open-label studies relative to the exposure during the double-blind phase of the placebo-controlled studies. In order to account for these differences in exposure, incidence rates of TEAEs using total person-time of all subjects at risk in the denominator may also be performed. Then provide summary tables for

common TEAEs, one table using total number of subjects at risk in the denominator and another table using total person-time of all subjects at risk in the denominator.

Please populate (or provide similar tables) the shell tables of common TEAEs in subjects with N24HSWD provided in the Safety Table Shells section of this document below [i.e., Summary of common ($\geq 5\%$ in overall tasimelteon) TEAEs in subjects with N24HSWD (Studies 3201: double-blind phase and open-label phase); and Summary of common ($\geq 5\%$ in overall tasimelteon) TEAEs in subjects with N24HSWD (Studies 3201 and 3203)]. For the second table, the column labels assume that the majority of subjects enrolled in Study 3203 were from Study 3201 and that only a trivial number of subjects from Screening were enrolled.

What are the analyses of time dependency for treatment-emergent adverse events planned? In addition to those that you plan, provide Kaplan-Meier analyses of cumulative incidence of time to any treatment-emergent adverse event for each dose by treatment group in Pool 2, and for the 20 mg dose by treatment group in Pool 3. Provide similar analyses for each of the demographic subgroups you have outlined in section 6.5.2 (page 43) of the briefing book, and BMI category. Provide graphical display by treatment group of common TEAEs whose incidence either increases or decreases over time.

On page 44 of the briefing book, you state that “Incidences for specific AEs will be graphed and analyzed by dose level or duration subgroup or other characteristics as appropriate”. It is not clear what these “specific AEs” are, or their criteria. You need to provide comprehensive analyses and presentation of treatment-emergent adverse events that are significant based on any of the following criteria: a) quantitatively [any TEAE occurring in at least 3% (or 5% depending on the pool) of tasimelteon group with relative risk (i.e., incidence of tasimelteon /incidence of placebo) is ≥ 1.5 (or relative risk of 2 if 1.5 is appears to be very sensitive)]; b) TEAEs that are specific to this submission (potential safety signals that you have identified or those related to class effect such as Warnings/Precautions of other approved drugs in the same class); c) medically relevant adverse events (medically designated events such as agranulocytosis, Steven-Johnson’s syndrome, liver failure, etc) even if rare or infrequent. Include in these analyses of significant adverse events, daytime somnolence, dizziness and falls including related terms. For each of the significant TEAEs identified quantitatively, provide the following analyses:

- Summary table listing the different verbatim terms from which the TEAE of interest was coded to.
- Evaluation for potential under ascertainment by identification of additional verbatim or preferred (among those occurring less frequently) terms related to the TEAE of interest. For example, in the analyses of dizziness identified quantitatively, other less frequently reported Preferred Terms such as dizzy, lightheaded, dizziness intermittent, etc will be of interest.
- Exploration of risk factors (based on Medical history, Concomitant medications, or relevant baseline laboratory test results, or known epidemiological data, etc).
- A summary table of subjects reporting that TEAE or a related event across integrated clinical Studies irrespective of investigational drug administered or active comparator in Pool

1 including open-label studies (see table shell in Safety Table Shells section of this document below), and provide a separate line listing of all these subjects such that a given subject can easily be identified.

- A summary table of subjects reporting that TEAE or a related event across integrated placebo-controlled and open-label Studies in subjects with insomnia and N24HSWD - see table shell “Summary of subjects reporting XYZ TEAE or a related event across integrated placebo-controlled and open-label Studies (Adult insomnia Study 3104, Elderly insomnia Study 004, Study 3201, N24HSWD Study 3201, N24HSWD open-label Studies 3202 and 3204” in Safety Table Shells section of this document below. Provide a similar analysis across all integrated placebo-controlled Phase I trials in healthy volunteers.
- Summary table(s) of analyses of the TEAE by gender, age category, race, dose, concomitant therapy, duration of TEAE, and time to first occurrence of TEAE. Perform an analysis of median duration exposure by treatment groups.
- Provide a graphical display of the TEAE as a function of time by treatment group in Pool 2 and another display for Pool 3. For example, the y-axis of the graphical display will be the number of patients experiencing the TEAE (0, 2, 4, 6, 8, 10, etc) and the x-axis is the time line (in weeks). Small color-coded (different color for placebo, <20mg, 20 mg and >20 mg tasimelteon groups) circles are placed in the graph based on the number of subjects experiencing the TEAE at a given time point in a given treatment group. The dots of a particular color are then connected.
- If the given TEAE is associated with a laboratory, electrocardiogram or vital sign abnormality, then provide a summary table of the relevant parameter listing the abnormal values over time (provide reference values for each parameter).
- Provide narratives of all TEAEs reported as serious or which led to withdrawal from the study. Or you may list each TEAE reported as serious event or which led to withdrawal from the study and against each in this list provide a functioning hyperlink to each specific narrative (hyperlink to the general location where all narratives reside is not acceptable). For a description of what needs to be included in a narrative, please see further below.
- Provide your conclusion for each of the TEAEs quantitatively identified regarding differences in incidence observed between treatment groups, association with risk factors, subgroups (if any) with increased propensity to experience the TEAE, time or dose dependency, and whether or not causality can be determined.

Include a comprehensive discussion of each of the medically relevant adverse events (medically designated events such as agranulocytosis, Steven-Johnson’s syndrome, liver failure, etc) identified even if rare or infrequent. Provide a detailed narrative of the individual cases with sufficient details including recurrence after rechallenge to reach an independent (for a description of what need to be included in a narrative, please see further below). Functioning hyperlink to each specific narrative is acceptable (hyperlink to the general location where all narratives reside is not acceptable). Include a search for related terms (verbatim and preferred) in the entire safety

database for underestimation of cases or to identify cases early in the course of that event. For each event, you will need to provide your conclusion regarding causality. When *appropriate*, conduct analyses to identify risk factors (based on medical history, concomitant medications, or relevant baseline laboratory test results, or known epidemiological data, etc), calculate odds of developing the event given the risk factors identified, and develop a risk mitigation strategy.

You must submit **Case Report Forms (CRF)** for all deaths, non-fatal serious adverse events, adverse events leading to withdrawal, and medically relevant adverse events (medically designated events such as agranulocytosis, Steven-Johnson's syndrome, liver failure, etc). You may also submit CRFs for events related to an important safety signal identified by you.

You must submit **comprehensive narrative summaries** for all **deaths, non-fatal serious adverse events, adverse events leading to withdrawal, and medically relevant adverse events** (medically designated events such as agranulocytosis, Steven-Johnson's syndrome, liver failure, etc). You may also submit comprehensive narrative summaries for events related to an important safety signal identified by you. Comprehensive narrative summaries must include information to enable assessment of appropriate coding, determine whether there is likely explanation for the event other than the study drug (other drugs, concomitant illnesses, etc), exposure time-line to assess whether a relationship with the study drug is temporally plausible, attenuation/resolution of the event upon dechallenge, and importantly information to determine positive rechallenge (recurrence or worsening upon rechallenge with the study drug) or negative rechallenge (event does not result upon rechallenge with the study drug). At the minimum, each narrative summary must include the following:

- Subject ID, Subject initials, Unique Subject ID number and Individual Subject ID number as well as their respective Study IDs in which the subject experienced the event(s) of interest.
- Provide not only calendar dates but also the Study Day in brackets appended to the calendar day (example "13 Feb 2012 (Day 23)"). For a given Study, date of randomization is Study Day 0 (or 1 depending on your convention), positive digits for days *after* randomization and negative digits and for days *prior* to randomization. If a given subject enrolled in a study and without break in exposure subsequently enrolled in an open-label study, provide not only calendar days with Study Day appended for each Study, but an annotated Study Day referencing the dates in the open-label study to the randomization day in the first study. Provide all inclusive (all gaps allowed and gap days included) and cumulative (all gaps allowed but not gap days) exposure for each subject in a given study. Thus, for example, a narrative will read as "... on 18APR 2009 (Day 0), subject was randomized to the tasimelteon 20 mg group in Study 3201 and completed the study on 16 JUN2009 (Day 61) with all inclusive exposure of 61 days and cumulative exposure of 55 days. Subsequently, subject enrolled in Study 3204 on 16JUN2009 (Day 0; Day 61*) and prematurely withdrew from this study on 15JUL2009 (Day 31; Day 91*). On 20APR2009 (Day 2), subject experienced 'abdominal pain' for which he was hospitalized the same day. He was discharged on 22APR2009 (Day 4)...."

- Provide age, sex, race if available, and a concise relevant medical history and concomitant medications (with generic names) prior to randomization.
- Then provide a discussion of events starting with when study drug was given, onset symptoms in verbatim terms (preferred terms they were coded to in parenthesis) and sequence of events in chronological order in sufficient detail to evaluate for a concomitant illness), hospitalization dates and details, if applicable surgery/procedure dates, corrective treatment provided and dates (treatment including other medications or dosage of concomitant medications increased), provide details of what was done to the study drug (continued, interrupted, permanently discontinued), and whether the event resolved, attenuated or is ongoing. Provided details on whether the study drug was rechallenged (restarted after a break), and if so whether or not the event recurred or worsened.
- Narratives should include relevant scheduled and unscheduled laboratory tests results (e.g., hospitalization) where appropriate.
- Provide an assessment of your conclusion regarding causality.

Provide a line listing of all **serious adverse events** in the entire safety database, with a **functioning hyperlink** to ***each specific narrative*** (hyperlink to the general location where all narratives reside is not acceptable). Submit a tabular summary of all serious adverse events by treatment group, one table each for Pool 2, Pool 2.1, Pool 3, and for all pooled placebo-controlled Phase I studies in healthy volunteers. If the total number of all serious adverse events exceed 30 in any summary table, include only those serious adverse events experienced by ≥ 2 subjects in any treatment group the summary tables, and then provide a line listing of all serious adverse events by treatment group and study in that pool. Submit a tabular summary of serious adverse events grouped by system organ class and by treatment group, one table each for Pool 2, Pool 2.1, Pool 3, and for all pooled placebo-controlled Phase I studies in healthy volunteers. Submit summary table(s) of analyses of the serious adverse events by gender, age category, race, dose, concomitant therapy, and time to first occurrence of SAEs. Perform an analysis of median duration exposure by treatment groups.

Provide all analyses for **adverse events leading to withdrawal** as outlined in the above paragraph for serious adverse events.

Submit a list of clinical laboratory tests (hematology, chemistry, urinalysis) that were performed, and whether they were performed across all clinical studies in the safety database. If not, what were the differences between the tests performed between clinical studies? State whether the laboratory tests in the integrated safety databases and datasets include unscheduled laboratory tests. State whether laboratory tests were performed at a central laboratory; if they were performed at a central laboratory only for a few clinical studies, identify those clinical studies. Identify those clinical studies for which laboratory tests were reported originally in Standard International (SI), and identify those studies which were originally reported in conventional units and were later converted to SI units; what were the conversion factors used? What were the normal reference values for laboratory parameters in SI units and for those originally reported in conventional units? During the conduct of the placebo-controlled and open-label studies (Pool 2,

Pool 2.1, Pool 3, and Pool 4), compared to the per protocol plan, were there any tests omitted or added, or frequency of testing changed? Were abnormal laboratory values followed until they were normalized or had an explanation? What is your definition of baseline values?

Mock Shell Table 2.0.6.3.1 provides criteria for potentially clinically significant abnormalities (PCSA) some laboratory values. The list does not appear to be complete (sodium, potassium, chloride, etc are not listed); please clarify.

Evaluate for a potential for severe hepatotoxicity using Hy's Law. We acknowledge the mock shell tables for Change from Baseline over time, Shift Tables and Incidence of PCSA for various Pools. Perform analyses of abnormal laboratory results reported as adverse events by treatment group for Pool 2 and 3.

State whether blood pressure and pulse rate was measured in a standardized manner (i.e., in supine position and after resting for a certain time, etc), and whether orthostatic blood pressure measurements were assessed in any clinical study. What is your definition of baseline values? Perform analyses of abnormal vital signs results reported as adverse events by treatment group for Pool 2 and 3.

Indicate if ECGs were read centrally for clinical studies, and whether the datasets include values from unscheduled visits. Perform analyses of abnormal ECG results reported as adverse events by treatment group for Pool 2 and 3.

Meeting Discussion

The Sponsor acknowledged the above listed safety analyses and tables/format requested by the Division in order to adequately assess the safety of tasimelteon, and stated that they will comply with all of the above requests.

Question 5: Does the Division agree with the proposed presentation of safety data described in Sections 2.4, 6 and Appendix D?

Preliminary Response

Provide one dataset with one row per subject, such that all subjects at risk for a given treatment arm or population subset can easily be identified.

The Integrated Adverse Event (AE) dataset will need to include the following variables: Unique Subject ID, Study ID, Study subject ID, age, sex, age category, treatment group, verbatim term, preferred term, system organ class, variables to flag AEs leading to withdrawal, serious adverse events, all treatment emergent AEs, AEs occurring in follow-up period, and a variable to flag the first occurrence of a TEAE.

Meeting Discussion

The Sponsor stated their intention to seek an electronic pre-submission meeting. The Division stated that it will discuss additional requests for dataset variables at this meeting.

Pharmacology and Toxicology

Background

The non-clinical toxicology, pharmacokinetics, and pharmacology studies conducted and planned for inclusion in the NDA are described in Section 7.

Question 6: Does the Division agree that the safety pharmacology package is adequate to support filing?

Preliminary Response

You have not provided a core battery of safety pharmacology studies for tasimelteon. However, considering the available clinical and nonclinical data, the lack of these studies would not preclude filing or approval of the NDA.

You should ensure that all major circulating metabolites in humans have been adequately assessed in animals (cf. ICH M3(R2) and Guidance for Industry: Safety Testing of Drug Metabolites, February 2008).

Meeting Discussion

The sponsor stated that all major circulating metabolites in humans have been adequately assessed in animals. The sponsor agreed to submit a summary table listing all identifiers used for each metabolite in order to facilitate the comparison of metabolites across species and studies.

Post meeting note: A signed and dated Pathology Report needs to be provided for each pivotal GLP nonclinical study for which histopathology was conducted; data should be provided in summary tables, as well as in individual animal line listings. Electronic datasets should be submitted for each carcinogenicity study, as described in guidance (cf. CDER/CBER Guidance for Industry, Providing Regulatory Submission in Electronic Format- Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008) and the associated Study Data Specifications document, available at: <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>.)]

eCTD Format and Electronic Submission

Background

The NDA dossier for tasimelteon will be submitted in eCTD format. The proposed format for the datasets to be included in the eCTD is presented in Section 8 of this briefing book.

Question 7: Given the small size of the clinical studies, the use of the same patients in studies 3201 and 3203, and the different study designs, Vanda proposes to include the narrative portion of the Integrated Summary of Effectiveness (ISE) and the Integrated Summary of Safety (ISS) in Module 2 (section 2.7). The appendices of tables, figures, and datasets will be located in Module 5. An explanation of where the parts are located will be included in both Module 2 (section 2.7)

and Module 5. Does the division agree that it is acceptable for the ISE and ISS narratives to replace the Summaries of Clinical Efficacy and Safety narratives in Module 2?

Preliminary Response

- To submit in eCTD format, the submission needs to comply with ICH and FDA guidance and specifications. Refer to the eCTD website, located at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>
- If this is your first eCTD submission, it is recommended that a sample eCTD be completed prior to submitting an actual eCTD submission. Refer to the eCTD Sample Web page located at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm> or contact ESUB (esub@fda.hhs.gov) for more information
- Summaries belong in Module 2 and analyses belong in Module 5, section 5.3.5.3. The ISS and ISE text and data should be placed in m5.3.5.3. However, if the data is concise enough to meet the suggested size limitations for Module 2, your proposal is acceptable. Refer to “Final Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document (PDF - 98KB)”, located at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf>
- Providing a Reviewer's Guide with a high level overview of what is provided in modules 1 through 5 with hyperlinks can be helpful to reviewers. For module 5, it usually references the pivotal studies, ISS, ISE and explains how data is being submitted and any documents which may be specific to the particular application being submitted. The Reviewer's Guide is usually provided as a separate document in the cover letter section, under section m1.2, with a clear and descriptive leaf title.
- Study Tagging Files (STF) files is required for submissions to the FDA when providing study information in modules 4 and 5 with the exception of module 4.3 Literature References, 5.2 Tabular Listing and 5.4 Literature References. Each study should have an STF and all components regarding that study should be tagged and placed under the study's STF including case report forms (crfs). Please refer to The eCTD Backbone File Specification for Study Tagging Files 2.6.1 (PDF - 149KB) (6/3/2008) <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>
- Please make sure you provide sufficient navigation (bookmarks, hyperlinks, TOCs) as well as descriptive\meaningful bookmarks (Appendix A is not a descriptive bookmark)

Meeting Discussion

The Division stated that in the context of requested analyses (Question 4), the ISS can potentially be larger than originally planned. Therefore, a larger and comprehensive ISS will need to be in Module 5.

Question 8: Does the Division agree that the proposed dataset formats presented in Section 8 are acceptable to assess the safety and efficacy of tasimelteon and sufficient for the FDA to create patient profiles?

Preliminary Response

Please refer to Question 2 and 5 for comments.

Meeting Discussion

There was no further discussion of this question.

Safety Table Shells

Summary of all subjects (unique subjects) who received at least one dose of tasimelteon in all clinical trials

Study phase category	Study population	< 20 mg	20 mg	> 20 mg	Any dose (Unique Exposures)
All Phase I, II, III studies including open-label studies	All subjects#				
All Phase I studies	All subjects combined#				
	Healthy subjects				
	Subjects with hepatic impairment				
	Subjects with renal impairment				
All Phase II, III studies (including open-label extension)	All subjects combined#				
	Healthy subjects – proof of concept of circadian regulation				
	Healthy subjects – night shift workers				
	Healthy subjects – induced transient insomnia				
	Subjects with insomnia/primary				

insomnia				
Subjects with major depressive disorder				
Subjects with Non-24 hour disorder				

Subjects exposed to more than one dose in different treatment periods or different studies may be counted in each dose category, but counted only once for the overall “Any dose” column.

#Unique subjects. “All Subjects” in all Phase I, II, III studies including open-label are counted once in a given column, i.e., those participating in more than one study are counted only once. “All Subjects” in all Phase I studies are counted once in a given column, i.e., those participating in more than one study are counted only once. Similarly, “All Subjects” in all Phase II, III studies including open-label are counted once in a given column; those participating in more than one study are counted only once.

As of cut off date for ongoing studies

Summary of subjects (unique subjects) who received at least one dose of 20 mg (cumulative dose) by duration and exposure interval (safety population)

		All studies combined N	Adult insomnia subjects N	Elderly insomnia subjects N	N24HSWD		
					All subjects N	≤65 years N	>65 years N
Duration of exposure# (days)	n						
	Mean (SD)						
	Median						
	Q1, Q3						
	Range						
Exposure interval, n (%)	≥90 days						
	≥180 days						
	≥360 days						

#Cumulative exposure (gap days excluded)

Subjects are counted only once in each column (e.g., a N24HSWD subject participating sequentially in studies 3201 and 3202 are counted only once)

Incidence of subjects reporting any TEAE in placebo-controlled studies by treatment group and by study population

		Tasimelteon				Placebo
		<20 mg	20 mg	>50 mg	Overall	
Pooled Phase I	Healthy volunteers: Single dose	N	N	N	N	N

studies		xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
		Healthy volunteers: Repeat dose				
Phase II/III studies	Healthy subjects with transient insomnia					
	Adult subjects with insomnia					
	Elderly subjects with insomnia					
	N24HSWD					

Subjects in cross-over studies reporting a TAEA in different treatment periods using different doses may be counted more than once across the dose categories.

Common (in at least 3% of all tasimelteon subjects) TEAEs across placebo-controlled studies (Pool 2).

TEAE	Tasimelteon				Placebo
	<20 mg	20 mg	>50 mg	Any dose	
	N	N	N	N	
Subject with any TEAE	n (xx%)	n (xx%)	n (xx%)	n (xx%)	n (xx%)
Headache					
etc					

Summary of common ($\geq 5\%$ in overall tasimelteon) TEAEs in subjects with N24HSWD (Study 3201: double-blind phase and open-label phase)

TEAEs	Study 3201 Double-blind	Study 3201 open-label	Overall Tasimelteon N=

	Tasimelteon N=	Placebo N=	Tasimelteon to Tasimelteon N=	Placebo to Tasimelteon N=	Others to Tasimelteon N=	
Subject with any TEAE	n (xx%)	n (xx%)	n (xx%)	n (xx%)	n (xx%)	n (xx%)
Headache						
etc						

Others: subjects with N24HSWD that did not qualify for enrollment in Study 3201 double-blind phase.

Summary of common ($\geq 5\%$ in overall tasimelteon) TEAEs in subjects with N24HSWD (Studies 3201 and 3203)

TEAEs	Study 3201 Double-blind		Study 3203			
			Run-in phase N=		Randomized Withdrawal phase N=	
	Tasimelteon N=	Placebo N=	Tasimelteon to Tasimelteon N=	Placebo to Tasimelteon N=	Tasimelteon to Tasimelteon N=	Tasimelteon to Placebo
Subject with any TEAE	n (xx%)	n (xx%)	n (xx%)	n (xx%)	n (xx%)	n (xx%)
Headache						
etc						

Summary of subjects reporting XYZ TEAE or a related event across integrated clinical Studies irrespective of investigational drug administered or active comparator (Pool 1: all clinical studies including open-label studies)

	Pool 1
	N=
Subjects with any event*	n(%)
Unique# subjects with any event	
Classified as SAE	
Event led to withdrawal from Study	
Event led to interruption of study drug	
Event needed corrective treatment (other than study drug interruption)	
Event ongoing	
Recovered from event	
Study completers	

*List the related terms that were used

#Subjects counted only once in the entire database. For all other parameters, subjects may be counted only once in any given study but counted more than once if the same subject reported the given adverse event in different studies, or counted more than once if while participating in a crossover study reported the TEAE in different treatment sequences, or counted more than once if participating in different sequential doses and experienced the event in one or more doses.

Summary of subjects reporting XYZ TEAE or a related event across integrated placebo-controlled and open-label Studies (Adult insomnia Study 3104, Elderly insomnia Study 004, Study 3201, N24HSWD Study 3201, N24HSWD open-label Studies 3202 and 3204)

	Study 3104		Study 004		Study 3201		Study 3202	Study 3204
	Tasim	Placeb	Tasim	Placeb	Tasim	Placeb		
	N=	N=	N=	N=	N=	N=	N=	N=
Subjects with any event*	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
Classified as SAE								
Event led to withdrawal from Study								

Event led to interruption of study drug								
Event ongoing								
Recovered from event								
Study completers								
Event needed corrective treatment (other than study drug interruption)								

Subjects may be counted only once in a given study, but can be counted more than once if the same subject reported the given TEAE in different studies.

E-Data Comments

- The proposed dataset formats as presented in Section 8 are acceptable for review. Please be clear as to which version(s) of SDTM and ADaM you will be utilizing. Also, please follow the Study Data Specifications document for the folder structure of your clinical and non-clinical study data.
- The review team will decide whether the proposed submitted data is sufficient for the creation of patient profiles.

Meeting Discussion

The Division will discuss additional requests for dataset variables at the electronic pre-submission meeting.

Controlled Substance Staff Comments

- The NDA should contain the study report for a completed human abuse potential study (full protocol and dataset) if the preclinical drug discrimination and self-administration studies show positive abuse-related signals.
- You should provide the location of information regarding solubility of tasimelteon for intravenous injection. You should also provide a statement regarding whether the solubilizing agents for a tasimelteon solution induce discomfort or physical detriment upon repeated exposure during self-administration.

Miscellaneous

Option of an “Electronic Pre-Submission Meeting”

If technical aspects of the submission need further review, we advise you to contact the Division of Regulatory Review Support (email: esub@fda.hhs.gov) to load any provided (mock) data sets on the FDA computer system that support review of electronic applications. The focus of the NDA/BLA electronic pre-submission meeting is on navigation, formatting of electronic files, and layout of the application. To request a meeting contact the Division RPM.

Post Meeting Note: The sponsor has requested a meeting with the e-data staff. It is tentatively scheduled for March 20, 2013 at 10 am. The meeting was held as scheduled.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. The following summarizes agreements:
 - A complete table of all clinical pharmacology studies will be submitted.
 - The adverse event dataset and narratives of adverse events will need to include the 'verbatim term'. The Sponsor acknowledged the listed safety analyses and tables/format (Question 4) requested by the Division in order to adequately assess the safety of tasimelteon, and stated that they will comply with all of the requests. The Division will discuss additional requests for dataset variables at the electronic pre-submission meeting.
 - A summary table listing all identifiers used for each metabolite will be included.
 - A complete definition of Tau will be provided.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- In addition, we note that a CMC pre-submission meeting was held on October 23, 2012. We refer you to the meeting minutes of February 21, 2103 for any additional agreements that may have been reached.

- A preliminary discussion on the need for a REMS was held and the sponsor recommended that no REMS was indicated.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

- The Sponsor will request Priority review at the time of the NDA submission.

- In response to the Sponsor's question, the Division replied that there is a reasonable possibility (based on novel indication and endpoints) that it will seek input from the Advisory Committee prior to a regulatory decision on the NDA application.

- There was a brief discussion on expanded access; the Sponsor will submit proposal to the IND.

PREA REQUIREMENTS

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012. If an EOP2 meeting occurred prior to November 6, 2012 or an EOP2 meeting will not occur, then:

- if your marketing application is expected to be submitted prior to January 5, 2014, you may either submit a PSP 210 days prior to submitting your application or you may submit a pediatric plan with your application as was required under the Food and Drug Administration Amendments Act (FDAAA).
- if your marketing application is expected to be submitted on or after January 5, 2014, the PSP should be submitted as early as possible and at a time agreed upon by you and FDA. We strongly encourage you to submit a PSP prior to the initiation of Phase 3 studies. In any case, the PSP must be submitted no later than 210 days prior to the submission of your application.

The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. For additional guidance on submission of the PSP, including a PSP Template, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57. In particular, please note the following formatting requirements:

- Each summarized statement in the Highlights (HL) must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- The section headings and subheadings (including title of the Boxed Warning) in the Table of Contents must match the headings and subheadings in the FPI.
- The preferred presentation for cross-references in the 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)*]".

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of

Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

Additional Post Meeting Comments - QT Study information:

When you submit your ‘thorough QT study’ report, please include the following items:

- Copies of the study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed
- Electronic copy of the study report
- Electronic or hard copy of the clinical protocol
- Electronic or hard copy of the Investigator’s Brochure
- Annotated CRF
- A data definition file which describes the contents of the electronic data sets
- Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses
- Please make sure that the ECG raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable)
- Data set whose QT/QTc values are the average of the above replicates at each nominal time point
- Narrative summaries and case report forms for any
 - Deaths
 - Serious adverse events
 - Episodes of ventricular tachycardia or fibrillation
 - Episodes of syncope
 - Episodes of seizure
 - Adverse events resulting in the subject discontinuing from the study
- ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)
- A completed Highlights of Clinical Pharmacology Table

Advancing in this field – and possibly reducing the burden of conducting QT studies – depends critically upon obtaining the most comprehensive understanding of existing data. Please consider making your data, at least placebo and positive control data, available for further research purposes; see, for examples, the Data Request Letter at www.cardiac-safety.org/library .

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items.

6.0 SPONSOR HANDOUTS DURING THE MEETING

Attached.

4 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

RUSSELL G KATZ
03/22/2013



DEPARTMENT OF HEALTH AND HUMAN
SERVICES

**Food and Drug
Administration Silver
Spring MD 20993**

MEETING MINUTES

IND 54,776

Vanda Pharmaceuticals, Inc.
9605 Medical Center Drive Suite 300
Rockville, MD 20850

Attention: Gunther Birznieks, M.S.
Program Director

Dear Mr. Birznieks:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for VED-162.

We also refer to the January 6, 2011 meeting between representatives of your firm and the FDA, Division of Neurology Products. The purpose of the January 6, 2011 meeting was to discuss the end of phase 2 development of VEC-162 for the treatment of non-24-hour sleep-wake disorder in totally blind individuals.

The FDA official minutes are enclosed. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Cathleen Michaloski, MPH, Sr. Regulatory Project Manager, at (301) 796-1123.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

Enclosure



FOOD AND DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Date and Time: January 6, 2011
Meeting Type: Type B
Meeting Category: EOP 2
Meeting Location: White Oak Bldg #22, Room 1409
Application Number: IND 54776
Product Name: VEC-162/tasimelteon in non-24-hour sleep-wake disorder (N24HSWD) in totally blind individuals
Sponsor Name: Vanda Pharma., Inc.
Meeting Requestor: Gunther Birznieks, M.S.
Meeting Chair: Russell Katz, M.D.
Meeting Recorder: Cathleen Michaloski, MPH

Meeting Attendees:

FDA Attendees:

Russell Katz, M.D., Director, Division of Neurology Products (DNP)
Robert Temple, M.D., Director, ODE 1
Ronald Farkas, M.D., Ph.D., Acting Clinical Team Leader, DNP
Lois Freed, Ph.D., Supervisory Pharmacologist, DNP
Andrew Sostek, Ph.D., Clinical Reviewer, DNP
Jagan Parepally, Ph.D., Clinical Pharmacology Reviewer, Office of Clinical Pharmacology
Angela Men, M.D., Ph.D. Supervisory Clinical Pharmacology, Office of Clinical Pharmacology
Carole Davis, DO, MPH, Clinical Reviewer, DNP
Cathleen Michaloski, BSN, MPH, Regulatory Project Manager, DNP
Peter Vaccari, Health Science Administrator, Office of Orphan Products Development

Sponsor Attendees:

Mihael Polymeropoulos, M.D., Chief Executive Officer
John Feeney, M.D., Chief Medical Officer
Marlene Dressman, Ph.D., Program Director
Charles Czeisler, Ph.D., M.D., Consultant, Circadian Rhythm Disorders
Curt Wolfgang, Ph.D., VP Program Director
Gene Lasko, Ph.D., Consultant, Statistics

(b) (4)

Sponsor Questions and FDA Responses

1.1.1 Clinical Efficacy

Two placebo-controlled trials are currently planned to support the efficacy of tasimelteon in the proposed indication for the treatment of N24HSWD in totally blind people. In the ongoing 3201 study, patients are randomized to tasimelteon or placebo and treated for 6 months. Assessments of total nighttime sleep, daytime sleep, and stabilization of the phase relationship between the circadian melatonin rhythm and the timing of sleep are assessed over two free-running cycles. The second planned study, 3203, is a randomized withdrawal study to assess the maintenance of effect of tasimelteon in N24HSWD patients after 6 months of open-label treatment. Patients will be treated with OL tasimelteon for 6 months and those patients considered to be responders would be randomized to either tasimelteon or placebo. The proportion of patients in each group with re-occurrence of a free-running rhythm upon randomization would be determined.

- 1. Does the division agree that the 2 studies, VP-VEC-162-3201 along with VP-VEC-162-3203, together are capable of supporting a chronic indication for tasimelteon for N24HSWD in blind individuals with no light perception?**

Preliminary Response:

No, we do not agree:

- 1. Specificity: The primary endpoint of study 3201 is subjective nighttime total sleep (nTST). However, this endpoint does not adequately distinguish between a potential effect of the drug on the specific condition of N24HSWD, versus a non-specific effect on insomnia. The division believes that blind patients may suffer from insomnia caused by a number of factors (Lockley et al., Sleep 1999), including (and perhaps in some cases mostly) circadian misalignment, but also including other types of insomnia that would fall under the indication of currently approved insomnia drugs. Tasimelteon treatment of blind patients might therefore show benefit on TST through, for example, a soporific effect, and not an effect specific to N24SWD*
- 2. Symptom versus syndrome: N24SWD is a syndrome generally characterized by progressively delayed sleep and wake times accompanied by disturbed nighttime sleep and daytime alertness. We do not believe that a claim for the broader disorder can be adequately supported with a primary endpoint that examines only total sleep time. Furthermore, while there are many examples of drugs that have been approved for specific symptoms of a larger syndrome, a claim limited, for example, to 'the insomnia of N24SWD' seems problematic because, as discussed in #1 above, if the other symptoms of the condition aren't also improved, it would*

3. *seemingly not be clear that tasimelteon was having more than a non-specific soporific effect in these patients.*
4. Subjective endpoints: *In general, in any sleep drug development program, over-reliance on a subjective sleep endpoint is problematic because, for example, the subjective endpoint might appear to be positive because of impaired memory of insomnia, not because of actual improvement in sleep. This appears to limit the confidence that can be placed in findings of study 3201, which has subjective total sleep time as the primary endpoint.*
5. Surrogate efficacy marker: *The primary endpoint of your second phase 3 efficacy study (study 3203), is a surrogate endpoint based on aMT6s. However, while you assert that data from study 3201 will support use of a surrogate endpoint in study 3203, we are skeptical that biomarkers are well-enough understood in N24SWD to take the place of clinically meaningful endpoints. It appears to us that use of clinically meaningful endpoints is more appropriate and more straightforward for this indication.*
6. Dose level: *It is not clear to us that you have done adequate dose-finding to support approval. We note, for instance, data suggesting that for melatonin, much lower doses than those that induce phase shift in sighted individuals have been reported to maintain entrainment (Sack 2000 NEJM). Similarly, doses of melatonin that are too high might cause 'spillover' effects that inhibit entrainment (Lewy et al J. Biol Rhythms 2004).*
7. Dose timing: *In your study, you propose to begin treatment with tasimelteon near the period of maximum circadian misalignment. (b) (4)*
(b) (4)
We are not convinced that this change in manner of use is inconsequential, and are particularly concerned by published reports that timing of melatonin initiation for this condition is important (e.g. Lockley et al, J. Endocrinology 2000; Sack et al, NEJM 2000; Lewy et al, J. Biol Rhythms 2004). (b) (4)
(b) (4)
8. Clinical meaningfulness: *It is not clear to us that a statistically significant but small change in sleep would necessarily be clinically meaningful in N24HSWD if broader measures of function were not also improved. For example, it is not clear that the disruption of daytime activities would be meaningfully improved if patients still had to take the same number of naps, even if the duration of each nap was somewhat shorter.*
9. Baseline severity/characteristics: *Your criteria for diagnosing N24HSWD do not appear adequately specific to exclude other sleep disorders, or to characterize the nature or severity of baseline abnormalities. While we note that you do not agree with ICSD-2 criteria for the disorder (meeting package page 22), to understand how sleep improves on treatment, and which patients are appropriate to treat, it appears necessary to characterize better, by daily diary or some other method, the baseline pattern of sleep disturbance.*

Meeting Discussion:

The division began the discussion by explaining that to support a claim for the *syndrome* of N24HSWD, benefit would have to be shown for the fundamental *clinical* symptoms of the disease. The sponsor asserted that the disease was best described by melatonin rhythms, and that benefit could be adequately represented by melatonin metabolite assay combined with the cardinal symptom of nighttime total sleep time. The sponsor argued that showing efficacy on additional clinical endpoints was not possible because of the difficulty recruiting and retaining blind patients.

At several times during the meeting, discussion returned to the number of endpoints needed for approval, and how they might be designated as primary, co-primary, or secondary. The sponsor argued that clinically meaningful endpoints, like daytime nap duration, were already included as secondary endpoints, but the division stated that since a study would normally be considered 'positive' by a sponsor on the basis of its primary endpoint alone, it was important that FDA ensure that the primary endpoint(s) was truly adequate to support the indication. There was agreement that nighttime sleep and daytime naps were the two most important direct measures of clinical benefit. There was some discussion about specific design of clinical endpoints, including mention of looking at 'worst few days' in each cycle to help decrease the effect of random variability. The division expressed openness to reviewing this type of proposal from the sponsor.

There was extended discussion about the division's concern that an effect on the cyclical nature of the condition would need to be demonstrated to support the specificity of the indication, and an effect beyond that of an ordinary soporific. The sponsor questioned if it was possible to satisfy this request, since at points in the cycle with circadian alignment, it would not be possible to show a difference between drug and placebo. The sponsor also explained that there was no clear pattern of progressively delayed sleep and wake times in the condition, increasing the difficulty of documenting effects on the periodicity that was present. To try to clarify the concern, the division suggested that, theoretically, zolpidem treatment of this disease might be expected to have a fairly constant effect, for example increasing nighttime sleep by about 15 minutes, regardless of the circadian alignment, whereas a specific effect of tasimelteon might be supported if the benefit was much larger at times of maximum misalignment. Another example given by the division to help clarify concern was that a specific effect would be suggested if patients treated every day for an extended period showed more benefit from drug than patients who were treated only when symptomatic (presumably, if the drug acted mainly as a soporific, there would not be added benefit to taking drug continuously even when not symptomatic). It did not seem to the division that the current design of measuring efficacy at the point of maximum misalignment over two cycles, but not at other points, could provide the type of information about periodicity that the two hypothetical scenarios above were trying to illustrate. The sponsor offered to collect nighttime sTST and daytime nap data more continuously throughout the post-randomization part of the trial in order to capture the cyclic nature of the clinical symptoms. The sponsor also

asserted that circadian period could address the division's concern about showing an effect on the cyclic nature of the disorder.

The division raised the question of whether it would be helpful to distinguish between the minimum data that might be needed for approval (even given the need to show that the treatment was specific for N24HSWD), versus data that might be needed to support more specific claims about circadian mechanism of action, given the generally greater difficulty of demonstrating 'cause and effect' versus only showing 'effect.'

Discussion then shifted to how the melatonin rhythm would be characterized. The sponsor explained the difficulty of more precisely characterizing the urinary melatonin metabolite. The division understood that the measurement was difficult, but questioned why it seemed that the melatonin rhythm was being better characterized in the pre-enrollment period than when measuring the melatonin endpoint during the placebo-control portion of the study. There was discussion about if entrainment or only phase shifting would be shown, and the sponsor responded that the proposed randomized withdrawal study would be able to show loss of entrainment.

Regarding the division's comments about the weaknesses of subjective endpoints (#4 above), the sponsor asserted that PSG endpoints were not practical to measure in this indication. The sponsor noted, for example, that on any given PSG night, the abnormality might not be observed (e.g. because of sleep pressure leading to sleep at night despite circadian misalignment), such that the study could not be adequately powered. Actigraphy was discussed as an alternative objective endpoint. The sponsor stated that actigraphy was problematic because it was not accurate, for example potentially recording lack of motion as sleep. The division expressed that actigraphy had been deemed appropriate to support other indications despite its shortcomings. The division reiterated concern that patient reported nighttime sleep time often poorly represents actual sleep, and that even if a drug does not have a strong amnestic effect, it would be hard to distinguish with confidence between an actual effect on sleep versus an effect only on patient perception of sleep. The sponsor argued that memory impairment was not part of the profile for this class of compounds, and that in previous studies of tasimelteon objective and subjective TST were well-correlated, supporting the validity of subjective TST measurement in blind patients.

Discussion returned at several points to the distinction that FDA makes between showing direct clinical benefit, versus showing changes in biomarkers. The sponsor noted that melatonin rhythm was the key characteristic of the condition. The division noted that no matter how invariable the association of a biomarker (even a 'causative' biomarker) with a disease in the natural setting, a drug effect on the biomarker might not have the predicted effect on patient symptoms.

Discussion returned at several points to the difficulty of enrolling sufficient patients. The division commented that patients could be enrolled sequentially in more than one study, and that other study designs, like crossover, would seemingly increase statistical power.

The sponsor asserted that adequate dose-finding had been conducted. The division expressed concern that published studies suggested that blind patients were more sensitive (at least to melatonin) than sighted patients. The sponsor explained that similar doses would still be needed for establishing entrainment. The sponsor asked if questions about appropriate dose could be addressed after approval. The division agreed that if a single dose was examined in efficacy studies (referring to 20 mg/day) this would not preclude the filing of an NDA.

The sponsor addressed the other specific points raised above by the division as follows:

Issue 1: The sponsor expressed doubt that it was possible to separate the soporific effects of tasimelteon from the circadian effects.

Issue 6: The sponsor proposed that starting dosing based on the patient's report of periodicity of symptoms would allow for appropriate timing for the desired effect on circadian rhythm.

Issue 7: The sponsor indicated that they thought clinical meaningfulness of effect size was an open question.

At the close of the meeting, the division requested that the sponsor submit the second phase 3 study for Special Protocol Assessment. The division also asked the sponsor to submit a proposal based on discussion at this meeting that would attempt to address the division's concerns, through any combination of changes in protocols, statistical analysis plans, or other scientific arguments. The division would review this proposal and respond in writing to the sponsor.

Post-meeting additional comments from division

Co-primary *categorical* endpoints for nTST and daytime naps could potentially address a number of our main concerns about efficacy evidence, including reliance on subjective endpoints, and support for a circadian, as opposed to soporific effect of tasimelteon. The cut-off for the categorical outcome would have to represent a benefit close to 'normalization,' at least to the degree that these patients are normal when endogenous melatonin rhythms are aligned.

1.1.1. Clinical Safety

N24HSWD is an orphan indication with an estimated prevalence of 65,000-95,000 in the United States. Vanda has begun a comprehensive outreach effort to identify and recruit patients with N24HSWD who are totally blind to a patient registry. Efforts to populate the registry have included contacts with national and local advocacy groups for the blind, advertisements in newsletters for the blind, and attendance and presentations at annual conventions, a media campaign including radio and television interviews, and partnering with key researchers that have previous experience working with the N24HSWD population. Recognizing the difficulty in recruiting a reasonable number of patients in the U.S. alone, Vanda also initiated an open-label safety study including totally blind individuals with N24HSWD in France and Germany.

2. Would a safety database consisting of exposures as shown in Table 2 and Table 3 of the Briefing Book be adequate to support a NDA submission for N24HSWD?

Preliminary Response:

For this indication we would apply the ICH E1 standards for exposure, since the drug is intended for long-term treatment of a condition that doesn't generally cause irreversible morbidity or mortality. The previous exposures outlined in Table 2 and 3 fall short of ICH expectations, even when both sighted and blind patients are counted. Additionally, we are concerned that exposure in sighted individuals might not adequately identify safety risks in totally blind patients. For example, it seems plausible that blind patients might be more susceptible to falls related to drug, which might not be discovered if adequate numbers of blind patients are not studied.

Meeting Discussion:

The sponsor argued that blind patients differ very little from sighted patients in terms of drug safety, and specifically noted that they did not think that blind patients were at increased risk of fall. The division agreed that for many aspects of safety, such as drug-associated laboratory abnormalities, there was little reason to think that blind patients would specifically need to be tested. The division also stressed that no specific exposure in blind patients was required. It was only required that the sponsor present a compelling case, through adequate actual experience in blind patients along with other sources of evidence, that safety issues that might be specific to blind patients had been adequately studied or excluded. The division added that in addition to falls, endocrine effects of tasimelteon might conceivably differ between sighted and blind patients, and that this should be specifically addressed in the NDA.

1.1.3. CMC/Non-Clinical/Clinical Pharmacology

Non-clinical and clinical pharmacology issues have been discussed with the division in previous meetings. Vanda does not expect to discuss any questions for these disciplines at the currently planned meeting. Instead, Vanda would prefer to address the few remaining questions from these areas in writing.

Additional Clinical Pharmacology Comments:

1. *Pharmacokinetics of tasimelteon are not evaluated in blind individuals with N24HSWD. We recommend you collect sparse blood samples for popPK analysis in the proposed Phase 3 study.*
2. *We suggest that a blood sample be collected as close in time as possible to the occurrence of serious adverse events (AE), to help determine the relationship of exposure to response (including AE).*

Meeting Discussion: The sponsor acknowledged receiving the OCP comments and informed the Division that they have a population PK analysis plan to address the impact of intrinsic and extrinsic factors on the PK of VEC-162. The sponsor also expressed difficulty in collected blood samples for PK analysis in the proposed study since this is an out-patient trial and the drug is administered at night. Therefore, there is no PK sample collection in the proposed Phase 3 study. The Division acknowledged their justification.

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

/s/

CATHLEEN B MICHALOSKI
02/02/2011

RUSSELL G KATZ
02/02/2011

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # 205677 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: HETLIOZ Established/Proper Name: tasimelteon Dosage Form: 20 mg Capsules		Applicant: VANDA Pharmaceuticals, Inc. Agent for Applicant (if applicable):
RPM: Cathleen Michaloski		Division: Division of Neurology Products (DNP)
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: X 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(For additional information regarding 505(b)(2)s, please refer to http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/RegulatoryAffairsTeam/ucm027499.htm)</p>		<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>
<p>❖ Actions</p> <ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is JANUARY 31, 2014 • Previous actions (<i>specify type and date for each action taken</i>) 		<p>X AP <input type="checkbox"/> TA <input type="checkbox"/> CR</p> <p>X None</p>

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<p><input type="checkbox"/> Received</p>
<p>❖ Application Characteristics ³</p> <p>Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input checked="" type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC <input type="checkbox"/> Breakthrough Therapy designation</p> <p>NDAs: Subpart H BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <input type="checkbox"/> Restricted distribution (21 CFR 601.42)</p> <p>Subpart I Subpart H <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Communication Plan <input type="checkbox"/> Submitted in response to a Pediatric Written Request <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input checked="" type="checkbox"/> REMS not required</p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<p><input type="checkbox"/> Yes, dates</p>
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>❖ Public communications (<i>approvals only</i>)</p> <p>• Office of Executive Programs (OEP) liaison has been notified of action X Yes <input type="checkbox"/> No</p> <p>• Press Office notified of action (by OEP) X Yes <input checked="" type="checkbox"/> No</p> <p>• Indicate what types (if any) of information dissemination are anticipated <input type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other </p>	

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ⁴	X
Officer/Employee List	
List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	X Included
Documentation of consent/non-consent by officers/employees	<input type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) 1/31/14
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	1/31/14
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	5/31/13
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

l in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	1/29/14
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	<input checked="" type="checkbox"/> accept letter 9/16/13 Review 9/16/13, 12/31/13
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM 6/19/13 <input checked="" type="checkbox"/> DMEPA 9/27/13 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) 12/20/13 <input checked="" type="checkbox"/> OPDP (DDMAC) 12/24/13 <input checked="" type="checkbox"/> SEALD 1/30/14 <input checked="" type="checkbox"/> CSS 11/26/13 <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	7/11/13
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte 	<input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC _____ If PeRC review not necessary, explain: orphan indication • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	Orphan (Perc waived) <input type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>) 	<input checked="" type="checkbox"/> Verified, statement is acceptable

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>)	See TOC
Internal memoranda, telecons, etc.	See TOC
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	X No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg 3/22/13
• EOP2 meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg 2/2/11
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	11/14/13
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None 1/31/14
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 1/23/14
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 1/21/14
PMR/PMC Development Templates (<i>indicate total number</i>)	X None
Clinical Information⁶	
Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	1/21/14
• Clinical review(s) (<i>indicate date for each review</i>)	11/29/13, 12/18/13
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	X None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See clinical review 12/18/13
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None Thorough QT study rev 10/7/13
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	X Not applicable Review 11/26/13
❖ Risk Management	
• REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)	
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	
• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	X None Review 10/22/13
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested Summary Review 11/7/13

ing reviews should be filed with the discipline reviews.

Clinical Microbiology		<input checked="" type="checkbox"/> None
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)		<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)		<input type="checkbox"/> None
Biostatistics		<input type="checkbox"/> None
❖ Statistical Division Director Review(s) (indicate date for each review)		<input type="checkbox"/> None 11/21/13
Statistical Team Leader Review(s) (indicate date for each review)		<input type="checkbox"/> None 11/19/13
Statistical Review(s) (indicate date for each review)		<input type="checkbox"/> None 11/9/13
Clinical Pharmacology		<input type="checkbox"/> None
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)		<input type="checkbox"/> None N/A
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)		<input type="checkbox"/> None 11/7/13
Clinical Pharmacology review(s) (indicate date for each review)		<input type="checkbox"/> None 11/7/13
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)		X None
Nonclinical		<input type="checkbox"/> None
❖ Pharmacology/Toxicology Discipline Reviews		
• ADP/T Review(s) (indicate date for each review)		<input type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)		<input type="checkbox"/> None LF 11/12/13; PB 1/24/14
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)		<input type="checkbox"/> None 10/30/13
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)		<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)		<input type="checkbox"/> Nonclin carc 11/5/13
❖ ECAC/CAC report/memo of meeting		<input type="checkbox"/> None 10/16/13 Included in P/T review, page 16
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)		X None requested
Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) (indicate date for each review)		<input type="checkbox"/> None 12/19/13
• Branch Chief/Team Leader Review(s) (indicate date for each review)		<input type="checkbox"/> None 12/4/13
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)		<input type="checkbox"/> None ONDQA 12/4/13 Biopharm 10/30/13
❖ Microbiology Reviews		<input type="checkbox"/> Not needed 6/6/13
X NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review)		
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (indicate date of each review)		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)		X None

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	Acceptable per CMC review 11/12/13
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
X NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷</i>)	Date completed: 12/11/13 X Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	X Completed 1/29/14 X Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 205677

LATE-CYCLE MEETING MINUTES

Vanda Pharmaceuticals, Inc.
2200 Pennsylvania Ave., NW
Suite 300E
Washington, D.C. 20037

Attention: Paolo Baroldi, M.D.
Chief Medical Officer

Dear Dr. Baroldi:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Hetlioz (tasimelteon) oral capsules, 20 mg.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on October 30, 2013.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Cathleen Michaloski, Sr. Regulatory Project Manager at (301) 796-1123, or by email to cathleen.michaloski@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Ronald Farkas, M.D., Ph.D.
Cross Discipline Team Leader
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: October 30, 2013 12:30 pm – 2 pm
Meeting Location: White Oak Building 22, Room 1415
Application Number: NDA 205677
Product Name: Hetlioz (tasimelteon)
Indication: Non 24-hour sleep-wake disorder in blind patients with no light perception (Non-24)
Sponsor/Applicant Name: Vanda Pharmaceuticals, Inc.

Meeting Chair: Ronald Farkas, M.D., Ph.D.
Meeting Recorder: Cathleen Michaloski, BSN, MPH

FDA ATTENDEES

Ellis Unger, M.D., Director, Office of Drug Evaluation I
Eris Bastings, M.D., Acting Director, Division of Neurology Products (DNP)
William Dunn, M.D., Deputy Director, DNP
Ronald Farkas, M.D., Ph.D., Cross Discipline Team Leader, DNP
Devanand Jillapalli, M.D., Clinical Reviewer, DNP
Kun Jin, Ph.D., Team Leader, Statistics, Office of Translational Science (OTS)
Jingyu (Julia) Luan, Ph.D., Mathematical Statistical Reviewer, OTS
Angela Men, M.D., Ph.D., Clinical Pharmacology Team Leader, OTS
Martha Heimann, Ph.D., CMC Lead, Division of New Drug Quality Assessment 1
Rao Kambhampati, Ph.D., Lead Chemist, Division of New Drug Quality Assessment 1
Christina Capacci-Daniel, Ph.D. Consumer Safety Officer, Office of Drug Manufacturing and Product Quality (DMPQ)
Lopa Thambi, PharmD, Division of Pharmacovigilance and Epidemiology I, Office of Surveillance and Epidemiology (OSE)
Irene Chan, PharmD, Team Leader, Division of Medication Error Prevention and Analysis, OSE
Kim Taylor, MBA, MPH, Operations Research Analyst, Office of Pharmaceutical Science
Cathleen Michaloski, BSN, MPH, Sr. Regulatory Project Manager, DNP

(b) (4)

SPONSOR ATTENDEES

Mihael Polymeropoulos, M.D., Chief Executive Officer, Vanda Pharmaceuticals
Paolo Baroldi, Ph.D., M.D., Chief Medical Officer, Vanda Pharmaceuticals
Deepak Phadke, Ph.D., Vice President, Manufacturing, Vanda Pharmaceuticals
Marlene Dressman, Ph.D., Vice President, Clinical Program, Vanda Pharmaceuticals

Curt Wolfgang Ph.D., Vice President, Clinical, Vanda Pharmaceuticals
Louis Licamele, Ph.D., Senior Director, Head of Informatics, Vanda Pharmaceuticals
Derek Xiao, Ph.D., Associate Director, Biostatistics, Vanda Pharmaceuticals
Eugene Laska, Ph.D., Statistical Consultant, Nathan Kline Institute for Psychiatric Research
Charles Czeisler, M.D., Ph.D. Circadian Expert, Harvard Medical School, Brigham and Women's Hospital

(b) (4)

1.0 BACKGROUND

NDA 205677 was submitted on May 31, 2013 for Hetlioz (tasimelteon).

Proposed indication: Non 24-hour sleep-wake disorder in blind patients with no light perception (Non-24)

PDUFA goal date: January 31, 2014

FDA issued a Background Package in preparation for this meeting on October 22, 2013.

2.0 DISCUSSION

1. Discussion of Substantive Review Issues

OFFICE OF MANUFACTURING AND PRODUCT QUALITY, OFFICE OF NEW DRUG QUALITY ASSESSMENT

Two facilities have received 483s for pre-approval inspection observations. These inspectional findings and any facility responses received within 15 days of the inspection will be reviewed.

We will communicate any additional requests directly with these sites. Please ensure that all facilities are ready for commercial CGMP manufacturing activities as described in the NDA. Satisfactory evaluation of all facilities is required for NDA approval.

We are currently reviewing your response to our CMC information request letter dated September 20, 2013. Additionally, note that if resolution of the inspection findings requires any changes to the drug product manufacturing process description (Module 3.2.P.3.3) submitted on September 30, 2013, Module 3 will need to be updated before we can finalize the CMC review.

Meeting Discussion:

The FDA has received the October 28, 2013 correspondence from Vanda Pharmaceuticals withdrawing (b) (4) and designating (b) (4) as the elemental impurity testing laboratory for ongoing and future tasimelteon drug substance batches.

The sponsor should provide a letter from (b) (4) confirming this change along with a list of method transfer and validation activities and the completion dates (actual or expected) for these items.

All other facilities are under review.

DIVISION OF MEDICATION ERROR PREVENTION AND ANALYSIS

We previously conveyed the need for a label comprehension study to evaluate whether the intended patient population can understand the information in Braille presented on the bottle label. The results of the study should be submitted as soon as available to facilitate review of the results prior to approval of the application. Please provide an update regarding your timeline for submission of the requested information.

Meeting Discussion:

The sponsor indicated they have completed a label comprehension study and that overall the study findings were positive. They will submit the results report to the NDA for review.

CLINICAL

During the development of tasimelteon, agreement was not reached on a primary efficacy endpoint for either Study 3201 or 3203. You proposed a primary endpoint of entrainment of the circadian melatonin rhythm as measured by the urinary metabolite of melatonin, aMT6s. We did not accept the biomarker-based endpoint because existing scientific knowledge suggested that the clinical benefit in Non-24 would occur in a reasonably brief period of time, and would be readily measurable in terms of benefit on sleep.

We are continuing to assess the clinical evidence that the circadian symptoms of Non-24 are improved by tasimelteon. We recently received and are reviewing the additional analysis based on the within-patient difference in sleep during aligned versus non-aligned portions of the predicted circadian cycle. We note that some patients were excluded from this analysis, and we would like you to explain at this meeting the basis for these exclusions and the effects of excluding patients on interpretability.

We are reviewing exposure-response effects, including possible effects of tobacco smoking. We recently sent you an information request regarding smoking history of patients and possible effects on findings.

Meeting Discussion:

The Sponsor stated that they wanted the Agency to acknowledge the teleconference between the Agency and the sponsor on 12/10/12 that was left out of the Agency's Briefing Document. The Agency replied that this teleconference will be acknowledged during the Agency's presentation at the Advisory Committee.

The Sponsor expressed concern that given the relatively small number of subjects with Non-24 Hour Disorder that were enrolled in clinical trials, certain patient specific information in the Briefing Documents might make it possible to identify individual patients. Therefore, the Sponsor asked if such patient-specific information could be redacted from the Briefing Document. The Agency replied that it would contact the appropriate personnel within the Agency to address this concern.

The Sponsor presented slides of the revised analyses based on the within-patient difference in sleep during aligned versus non-aligned portions of the predicted circadian cycle after including patients that met the Agency's suggested criteria, and with imputation of data for those subjects with missing data. The Sponsor asked whether the Agency had any questions about the above analyses or the analyses of the effects of smoking. The Agency replied that there were no questions and that these analyses were currently being reviewed.

Statistical:

Background: In Section 3.2.3.4 and Section 3.2.3.5 of the Statistical Review (dated Oct. 18, 2013), the results of ANCOVA analysis and permutation ANCOVA analysis were presented. In these two analyses, variable SITEGR1 was used as the pooled sites in the ANCOVA model and the 6 patients without SITEGR1 information was grouped as if they came from one site.

Meeting Discussion:

The sponsor informed the Agency that SITEGR1 was defined only for sponsor ITT population (n=78) and variable SITEGR3 was defined for all the 84 patients.

Post-meeting Action: The statistical reviewer will investigate this issue.

2. Additional Applicant Data

Meeting Discussion: No additional clinical data was discussed.

3. Information Requests

Meeting Discussion: Please see discussion under the Clinical section above.

Late-Cycle Meeting Minutes

4. Discussion of Upcoming Advisory Committee Meeting

The Advisory Meeting was discussed. Plans were made to share slide presentations a few days prior to the meeting so that any overlap could be minimized.

5. Postmarketing Requirements/Postmarketing Commitments

There was mention that review is still on-going.

6. Major Labeling Issues

The Division stated that labeling discussions are planned for early December.

7. Wrap-up and Action Items

The following issues were summarized:

- The sponsor will provide a letter from (b) (4) detailing the elemental impurity testing method transfer and validation activities and the timeline for completing these activities.
- The sponsor has completed a labeling comprehension study and will be submitting it soon.
- The Statistical Reviewer will investigate the issue raised by the Sponsor regarding impact of using variable SITEGR3 instead of SITEGR1 in the efficacy analyses.
- Slide presentations will be shared (a few days prior to the AC meeting) between the sponsor and DNP.

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

/s/

RONALD H FARKAS
11/25/2013



NDA 205677

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Vanda Pharmaceuticals, Inc.
2200 Pennsylvania Ave., NW
Suite 300E
Washington, D.C. 20037

Attention: Paolo Baroldi, M.D.
Chief Medical Officer

Dear Dr. Baroldi:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Hetlioz (tasimelteon) oral capsules, 20 mg.

We also refer to the Late-Cycle Meeting (LCM) scheduled for October 30, 2013. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Cathleen Michaloski, BSN, MPH, Sr. Regulatory Project Manager, at (301) 796-1123.

Sincerely,

{See appended electronic signature page}

Eric Bastings, M.D.
Acting Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:

Late-Cycle Meeting Background Information

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: October 30, 2013 12:30 pm – 2 pm
Meeting Location: White Oak Building 22, Room 1415
Application Number: NDA 205677
Product Name: Hetlioz (tasimelteon)
Indication: Non 24-hour sleep-wake disorder in blind patients with no light perception (Non-24)
Sponsor/Applicant Name: Vanda Pharmaceuticals, Inc.

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date. Informal information requests have been issued.

2. Substantive Review Issues

OFFICE OF MANUFACTURING AND PRODUCT QUALITY, OFFICE OF NEW DRUG QUALITY ASSESSMENT

Two facilities have received 483s for pre-approval inspection observations. These inspectional findings and any facility responses received within 15 days of the inspection will be reviewed.

We will communicate any additional requests directly with these sites. Please ensure that all facilities are ready for commercial CGMP manufacturing activities as described in the NDA. Satisfactory evaluation of all facilities is required for NDA approval.

We are currently reviewing your response to our CMC information request letter dated September 20, 2013. Additionally, note that if resolution of the inspection findings requires any changes to the drug product manufacturing process description (Module 3.2.P.3.3) submitted on September 30, 2013, Module 3 will need to be updated before we can finalize the CMC review.

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During the development of tasimelteon, agreement was not reached on a primary efficacy endpoint for either Study 3201 or 3203. You proposed a primary endpoint of entrainment of the circadian melatonin rhythm as measured by the urinary metabolite of melatonin, aMT6s. We did not accept the biomarker-based endpoint because existing scientific knowledge suggested that the clinical benefit in Non-24 would occur in a reasonably brief period of time, and would be readily measurable in terms of benefit on sleep.

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We are reviewing exposure-response effects, including possible effects of tobacco smoking. We recently sent you an information request regarding smoking history of patients and possible effects on findings.

ADVISORY COMMITTEE MEETING

Date of AC meeting: November 14, 2013.

Date AC briefing package sent under separate cover by the Division of Advisory Committee and Consultant Management: **Pending October 24, 2013.**

Potential questions and discussion topics for AC Meeting are as follows:

The Division plans to ask the Committee to discuss the appropriateness of Non-24 as a new indication for FDA approval. The Committee will also be asked about the appropriateness of the clinical endpoints used, and the persuasiveness of efficacy results. The Division will also ask the Committee if the safety of tasimelteon has been adequately addressed.

We look forward to discussing our plans for the presentations of the data and issues for the upcoming AC meeting. Final questions for the Advisory Committee are expected to be posted two days prior to the meeting at this location:

<http://www.fda.gov/AdvisoryCommittees/Calendar/default.htm>

3. REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LCM AGENDA

1. Introductory Comments – Ronald Farkas, MD, PhD, and Cathleen Michaloski, BSN, MPH
Welcome, Introductions, Ground rules, Objectives of the Meeting.
2. Discussion of Substantive Review Issues – 45 minutes
Each issue will be introduced by FDA and followed by a discussion (see above).
3. Outstanding Information Requests – 10 minutes
Cigarette smoking analysis - request sent via email October 18, 2013.
4. Discussion of Upcoming Advisory Committee Meeting – 20 minutes
 - a. Key topics that FDA expects the Committee to address
 - b. Potential overlap in presentations
5. Review Plans – 10 minutes
6. Wrap-up and Action Items – 5minutes

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

/s/

CATHLEEN B MICHALOSKI
10/22/2013

ERIC P BASTINGS
10/22/2013