CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214517Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABELS AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 30, 2020
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 214517
Product Name and Strength:	Hetlioz LQ (tasimelteon) oral suspension, 4 mg/mL
Applicant/Sponsor Name:	Vanda Pharmaceuticals Inc. (Vanda)
OSE RCM #:	2020-1149 -1
DMEPA Safety Evaluator:	Loretta Holmes, BSN, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on November 24, 2020 for Hetlioz LQ. The Division of Psychiatry (DP) requested that we review the revised container labels and carton labeling for Hetlioz LQ (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous labels and labeling review[a] and in follow-up email correspondence with the Applicant.

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Holmes, L. Labels Labeling Packaging Review for Hetlioz LQ (NDA 214517) and Hetlioz (NDA 205677/S-007). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Oct 30. RCM No.: 2020-1149 and 2020-1151.

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/s/

LORETTA HOLMES
11/30/2020 10:09:45 AM

SEVAN H KOLEJIAN
11/30/2020 01:03:05 PM

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

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

Memorandum

Date: November 19, 2020

To: Latrice Wilson, Regulatory Project Manager
Division of Psychiatry (DP)

Kim Updegraff, Associate Director for Labeling, DP

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

CC: Aline Moukhtara, Team Leader, OPDP

Subject: OPDP Labeling Comments for HETLIOZ® (tasimelteon) capsules, for oral use; oral suspension

NDA: 205677 s7; 214517

In response to DP's consult request dated July 6, 2020, OPDP has reviewed the proposed product labeling (PI), Instructions for Use (IFU), and carton and container labeling for HETLIOZ® (tasimelteon) capsules, for oral use; oral suspension (Hetlioz).

PI and IFU: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DP (Latrice Wilson) on November 10, 2020, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed IFU will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted on November 17, 2020, and we do not have any comments.

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

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/s/

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

PATIENT LABELING REVIEW

Date:	November 19, 2020
To:	Latrice M. Wilson, PharmD, RAC Regulatory Project Manager **Division of Psychiatry (DP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Ruth Mayrosh, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Dhara Shah, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Instructions for Use (IFU)
Drug Name (established name), Dosage Form and Route:	HETLIOZ LQ (tasimelteon) oral suspension
Application Type/Number:	NDA 214517
Applicant:	Vanda Pharmaceuticals Inc.

1 INTRODUCTION

On June 1, 2020, Vanda Pharmaceuticals Inc. resubmitted for the Agency's review an original New Drug Application (NDA) for HETLIOZ LQ (tasimelteon) oral suspension in response to the Agency's Refuse to File letter dated March 12, 2020. The purpose of this submission is to provide a suspension formulation of HETLIOZ (tasimelteon) for the treatment of nighttime sleep disturbances in Smith-Magenis Syndrome (SMS) in pediatric patients 3 to 15 years of age.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Psychiatry (DP) on October 6, 2020 and July 6, 2020, for DMPP and OPDP to review the Applicant's proposed Instructions for Use (IFU) for HETLIOZ LQ (tasimelteon) oral suspension.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed October 30, 2020.

2 MATERIAL REVIEWED

- Draft HETLIOZ LQ (tasimelteon) oral suspension IFU received on October 15, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 12, 2020.
- Draft HETLIOZ LQ (tasimelteon) oral suspension Prescribing Information (PI) received on June 1, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 12, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the IFU the target reading level is at or below an 8th grade level.

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

In our collaborative review of the IFU we:

- simplified wording and clarified concepts where possible
- ensured that the IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The IFU is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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LASHAWN M GRIFFITHS
11/19/2020 12:30:44 PM

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

Pharmacovigilance Memorandum

Date:	November 3, 2020
Reviewer:	Kelly Harbourt, PharmD, BCCCP Division of Pharmacovigilance I (DPV I)
Team Leader:	Vicky Chan, PharmD, BCPS DPV I
Division Director:	Cindy Kortepeter, PharmD DPV I
Product Name:	Hetlioz (tasimelteon)
Subject:	Postmarket Safety Update
Application Type/Number:	NDA 214517, NDA 205677/S-7
Applicant/Sponsor:	Vanda Pharmaceuticals, Inc.
OSE RCM #:	2020-1848

1 INTRODUCTION

The Division of Psychiatry (DP) consulted the Division of Pharmacovigilance I (DPV I) to provide input from postmarket adverse event reports to anticipate safety concerns (e.g., urinary tract infections [UTIs], respiratory tract infections) from the use of tasimelteon in patients with Smith Magenis Syndrome (SMS). DP was also interested in the characteristics of postmarket reports in pediatric patients.

Tasimelteon (Hetlioz) is a melatonin receptor agonist approved on January 31, 2014 for the treatment of Non-24-Hour Sleep-Wake Disorder (Non-24). On January 21, 2020, the applicant submitted an efficacy supplement (SUPP-7) requesting a new indication be added to labeling: treatment of sleep disorder in SMS. At the same time, the applicant submitted NDA 214517 which provides for a suspension formulation of tasimelteon for the treatment of sleep disorder in SMS in pediatric patients.

DPV completed a Postmarket Drug Safety Surveillance Summary (PDSSS) in April 2019 **(See Section 4)**.[1] In response to this consult, DPV performed an updated search of the FDA Adverse Events Reporting System (FAERS) and disproportionality assessment for selected adverse events in Empirica Signal. The purpose of this memorandum is to describe findings from these updated searches. The contents of this memorandum were also included in the Integrated Review of the new drug application (NDA) described above.

2 METHODS AND MATERIALS

2.1 FAERS

DPV searched the FAERS database with the strategy described in **Table 1**.

Table 1. FAERS Search Strategy*	
Date of search	August 19, 2020
Time period of search	January 15, 2019† – August 18, 2020
Search type	Product-Manufacturer Reporting Summary
Product terms	Tasimelteon
MedDRA search terms (Version 22.1)	All adverse events
* See Appendix A for a description of the FAERS database. † Update from Postmarket Drug Safety Surveillance Summary (PDSSS) completed on April 1, 2019 (data lock date January 14, 2019)	

2.2 DATA MINING (EMPIRICA SIGNAL)

DPV also used the Empirica Signal software with the strategy described in **Table 2** to perform disproportionality analyses on FAERS data and to identify patterns of associations or unexpected

occurrences (i.e., "potential signals") for three specific Preferred Terms: *Respiratory tract infection, Upper respiratory tract infection,* and *Urinary tract infection,* as requested by DP. If a drug-event combination has a score (EB05) of ≥ 2, this score indicates 95% confidence that a drug-event combination appears at least twice the expected rate when considering all other drugs and events in the database. Data mining scores do not, by themselves, demonstrate causal associations; rather, they can serve as a signal for further investigation.

Table 2. Data Mining Search Strategy*	
Data refresh date	As of August 22, 2020
Product terms	Tasimelteon
Empirica Signal run name	PAI (S)
MedDRA search strategy (Version 22.1)	Preferred Terms: *Respiratory tract infection, Upper respiratory tract infection,* and *Urinary tract infection*
* See Appendix A for description of Data Mining of FAERS using Empirica Signal. PAI (S) = Product Active Ingredient (Suspect), MedDRA = Medical Dictionary for Regulatory Activities	

3 RESULTS

3.1 FAERS SEARCH RESULTS

Our updated FAERS search retrieved 1,141 reports, bringing the total number of reports for tasimelteon in FAERS to 3,300 from approval through August 18, 2020. **Table 3** describes the characteristics of the adverse event reports for tasimelteon received by the FDA between January 15, 2019 and August 18, 2020. Report counts may include duplicate reports for the same patient from multiple reporters (e.g., manufacturer, family member, physician, pharmacist, nurse), miscoded reports, or unrelated reports. Reported outcomes for this section are the coded outcomes submitted to FDA; causality and the role of the product in the coded outcome have not been determined for all reports (see **Appendix A** for FAERS limitations).

Table 3. Descriptive Characteristics of FAERS Reports with Tasimelteon, All Reports Received by FDA from January 15, 2019 through August 18, 2020* **N=1,141†**		
Sex (n=1,133)	Male Female	432 701
Age, years (n=181)	7 to <18 18 to <65 ≥ 65	1 110 70
Country	United States Foreign	1,135 6
Report type	Expedited Periodic	187 954
Serious outcomes‡ (n=189)	Death Hospitalization Disability	53 79 1

Table 3. Descriptive Characteristics of FAERS Reports with Tasimelteon, All Reports Received by FDA from January 15, 2019 through August 18, 2020* N=1,141†		
	Other serious	72

* Update from Postmarket Drug Safety Surveillance Summary (PDSSS) completed on April 1, 2019 (data lock date January 14, 2020)
† May include duplicates.
‡ For the purposes of this document, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention and other serious important medical events. A report may have one or more outcome.

3.2 DATA MINING RESULTS

Our updated screen of Empirica Signal revealed the data mining scores shown in **Table 4**. Although none of the EB05 scores were higher than 2, DPV performed a manual review of the cases reporting *Respiratory tract infection, Upper respiratory tract infection,* and *Urinary tract infection* to determine causality.

Table 4. Disproportionality Assessment for Tasimelteon and Adverse Events of Interest				
Preferred Term*	**N**	**EB05**	**EBGM**	**EB95**
Respiratory tract infection	12	1.31	2.15	3.35
Upper respiratory tract infection	19	1.37	2.02	2.89
Urinary tract infection	46	1.23	1.58	2.00
*DP specifically requested that DPV evaluate these three PTs using data mining.				

4 REVIEWER'S COMMENTS

Safety Signals from April 2019 PDSSS
Upon completion of the PDSSS for tasimelteon in April 2019, DPV identified three Newly Identified Safety Signals (NISS) that required further workup:

- Seizures (No signal upon further review described in Melatonin Receptor Agonists and Seizures Pharmacovigilance Memo)[2]
- Somnambulism (Monitoring)
- Suicidal ideation and behavior (Monitoring)

DPV identified three cases of completed suicide in FAERS through January 14, 2019 as described in the April 2019 PDSSS. We did not identify additional cases of completed suicide in the updated search. Two of the three cases lacked sufficient information for assessment regarding underlying psychiatric co-morbidities and temporal association. One case occurred in a patient with underlying schizoaffective disorder and post-traumatic stress disorder prior to the

use of tasimelteon. The remaining case (FAERS #14226934) occurred in a 54-year-old female who was hit by a train in a suspected suicide per the patient's spouse. This event occurred approximately three weeks after initiating therapy with tasimelteon. The report stated that the patient's spouse inquired about "whether tasimelteon was associated with suicidal ideations or tendencies." The report did not provide the patient's medical history or concomitant medications.

DP reviewed the safety of tasimelteon in their clinical review[3] prior to initial approval of tasimelteon and concluded that it was not associated with suicidality as assessed by the Columbia Suicide Severity Rating Scale. Of note, ramelteon, another melatonin receptor agonist, is labeled for worsening of depression (including suicidal ideation and completed suicides) in the WARNINGS AND PRECAUTIONS section.[4]

Respiratory Tract Infections, Upper Respiratory Tract Infection, Urinary Tract Infection

Upon review of the cases reporting *Respiratory tract infection, Upper respiratory tract infection,* and *Urinary tract infection,* DPV found that most reports lacked sufficient information to assess for causality, such as time to onset of the adverse event, dates of administration of tasimelteon, and presence or absence of underlying risk factors for respiratory tract infections, upper respiratory tract infections, or UTIs. These adverse events occur frequently in the general population and in those with SMS; therefore, determining relatedness of these adverse events to a drug based on spontaneous adverse event reports is very difficult.

DPV identified one non-serious case of recurrent UTIs with positive dechallenge and rechallenge described below. Despite identification of this case, DPV did not identify a convincing causal relationship between tasimelteon and the development of UTIs.

> **FAERS #16578642**: A 44-year old female patient with a history of blindness in both eyes was treated with tasimelteon 20 mg once daily on unknown dates (first shipment date one month prior to report) for Circadian rhythm disorder free-run type. The patient reportedly discontinued use of tasimelteon because she "had too many urinary tract infections." It was noted in the report that the patient's healthcare provider discontinued tasimelteon, the symptoms of recurrent UTIs resolved, and when the patient tried tasimelteon again, the UTIs recurred. This was noted in the case as a positive dechallenge and positive rechallenge. Concomitant medications included an unknown blood pressure medication that caused "kidney issues" in the past and no other medications specified.
>
> *Reviewer's comment: This medically confirmed case describes a temporal relationship between tasimelteon and the occurrence (and reoccurrence) of UTIs. Although this case also describes positive dechallenge and rechallenge, this reviewer assessed this case as possible because there is a lack of information regarding time to onset of UTI as well as timing between UTIs with respect to the discontinuation and resumption of tasimelteon.*

DPV did not identify any cases of respiratory tract infections or upper respiratory tract infections that were related to tasimelteon. All reports were confounded by concomitant medications indicated for respiratory symptoms/seasonal allergies or lacked sufficient information to assess causality, such as dates of therapy and time to onset of AE.

Pediatric Reports

We retrieved a total of 10 reports in patients less than 18 years of age from FAERS for tasimelteon, only one of which was received by the FDA since January 15, 2019. These 10 pediatric adverse event reports occurred in patients between the ages of 12 and 17, the majority of whom were female (n=7). Of these 10 reports, one patient died for a reason unrelated to tasimelteon (progression of malignant astrocytoma). The remaining nine reports were non-serious and reported PTs including, but not limited to: *Abdominal discomfort, Constipation, Diarrhea, Dyssomnia, Fatigue, Headache, Product prescribing error,* and *Urticaria.*

DPV did not identify any postmarketing safety issues that would affect the review of NDA 205677/S-7 or NDA 214517 and will continue routine pharmacovigilance for tasimelteon.

5 REFERENCES

[1] Harbourt, K. Hetlioz (tasimelteon) NDA 205677: OSE Postmarket Drug Safety Surveillance Summary, April 1, 2019. RCM 2018-1775, DARRTS Ref ID: 4412498.
[2] Harbourt, K. Melatonin Receptor Agonists and Seizures Pharmacovigilance Memorandum, June 3, 2019. RCM 2019-874, DARRTS Ref ID: 4442574.
[3] Jillapalli, D. NDA 205677: Hetlioz. REV-Clinical-21 (Primary Review). November 29, 2013.
[4] Rozerem [Package Insert]. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; December 2018 (Accessed September 16, 2020).

6 APPENDICES

6.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

FAERS is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

Data Mining of FAERS using Empirica Signal

Empirica Signal refers to the software that OSE uses to perform data mining analyses while using the Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm. “Data mining” refers to the use of computer algorithms to identify patterns of associations or unexpected occurrences (i.e., “potential signals”) in large databases. These potential signals can then be evaluated for intervention as appropriate. In OSE, the FDA Adverse Event Reporting System (FAERS) database is utilized for data mining. MGPS analyzes the records in FAERS and then quantifies reported drug-event associations by producing a set of values or scores that indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting of an event for a particular drug relative to all other drugs and events in FAERS. MGPS also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05 and EB95, respectively. Because EBGM scores are based on FAERS data, limitations relating to FAERS data also apply to data mining-derived data. Further, drug and event causality cannot be inferred from EBGM scores.

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/s/

KELLY M HARBOURT
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11/03/2020 02:09:40 PM

CINDY M KORTEPETER
11/03/2020 02:54:33 PM

M E M O R A N D U M

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

Date: November 2, 2020

To: Tiffany Farchione, M.D., Director (Acting)
Division of Psychiatry

Through: Dominic Chiapperino, Ph.D., Director
Controlled Substance Staff

From: Chad J. Reissig, Ph.D., Supervisory Pharmacologist
Controlled Substance Staff

Subject: Tasimelteon, NDAs 214517 and 205677/S-7
Hetlioz 4 mg/mL suspension (NDA 214517) and 20 mg capsules
Indication(s): Treatment of sleep disorder in Smith-Magenis Syndrome in pediatric patients and adults
Sponsor: Vanda Pharmaceuticlas
PDUFA Goal Date:

Materials Reviewed: Previous CSS review of tasimelteon by K. Bonson (November 26, 2013)
Abuse-related preclinical and clinical data in NDA 214517

Table of Contents

I. EXECUTIVE SUMMARY

1. Background

This memorandum responds to a consult request by the Division of Psychiatry to evaluate a New Drug Application (NDA) for the use of a (new) suspension formulation of tasimelteon (Hetlioz) for the treatment of sleep disorder in Smith-Magenis Syndrome (SMS) in pediatric patients (3+ years old) (NDA 214517). The Sponsor has also submitted an efficacy supplement to NDA 205677 (approved January 31, 2014) for use of the previously approved capsule formulation of tasimelteon in the treatment of sleep disorder in SMS in adults. NDA 214517 is cross-referenced to NDA 205677.

Tasimelteon and its major metabolites have affinity and activity at melatonin receptors (MT1 and MT2). Tasimelteon was approved as Hetlioz in 2014 in 20 mg capsules for the treatment of Non-24-hour sleep-wake disorder (non-24). The CSS review noted that tasimelteon did not have affinity for CNS receptor sites associated with abuse, did not produce abuse-related signals in toxicology studies, was not self-administered, did not produce abuse-related adverse events in clinical studies, and did not produce signs or symptoms associated with withdrawal or dependence (K. Bonson, review in DARRTS 2014). Based on these results, tasimelteon was not recommended for scheduling under the Controlled Substances Act (CSA).

According to the Sponsor "Smith-Magenis syndrome (SMS) is a rare (1 in 15,000 to 25,000 births), clinically recognizable syndrome that results from an interstitial deletion of chromosome 17p11.2 and, in rare cases, from a retinoic acid induced 1 (RAI1) gene mutation. SMS is characterized by a distinct pattern of minor craniofacial and skeletal anomalies, language delays, psychomotor and growth retardation, and a striking neurobehavioral phenotype that includes disrupted sleep."

2. Conclusions

- Based on the receptor binding profile, preclinical assessment of CNS activity, and adverse event profile in clinical trials, tasimelteon does not appear to present a potential for abuse and should not be scheduled under the Controlled Substances Act.

3. Recommendations

Based on our findings as captured in the Conclusions section, we recommend the following:

1. CSS does not recommend scheduling of tasimelteon under the Controlled Substances Act (CSA).

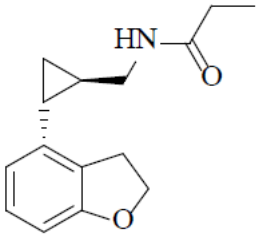
2. Because tasimelteon does not have an abuse potential, section 9 Drug Abuse and Dependence is not necessary in the drug product labeling.

II. DISCUSSION

1. Chemistry

1.1 Substance Information

According to the Sponsor, tasimelteon is a white to yellow opaque oral suspension. The molecular formula is $C_{15}H_{19}NO_2$ and the structure of tasimelteaon appears below:



Tasimelteon

2. Nonclinical Pharmacology

2.1 Receptor Binding and Functional Assays

No new receptor binding studies were performed in either NDA. The original CSS review noted that:

> "Binding of tasimelteon to the abuse-related CNS sites was low (< 10 micromolar). The only sites that showed high affinity for tasimelteon were two melatonin sites (MT1 and MT2), with respective Ki values of 0.3 nM and 0.07 nM.
>
> Similarly, the tested metabolites of tasimelteon showed no significant affinity (< 10 micromolar) for any sites other than MT1 and MT2. The respective Ki values for each major metabolite at the MT1 and MT2 sites are as follows: M9 (1,180 nM and 72 nM), M11 (250 nM and 3 nM), M12 (136 nM and 11 nM), M13 (4 nM and 0.9 nM), M14 (103 nM and 4 nM)."

2.2 Findings from Safety Pharmacology and Toxicology Studies

A single, new rodent safety/toxicology study was performed (study TAJ0026). In the study three groups of ten male and ten female rats (n=20/group) received tasimelteon doses of 50, 150, or 450 mg/kg/day in a volume of 2.5 mL/kg for ten weeks. These animals were compared to a control group receiving polyethylene glyocol. These animals were sacrificed after 10 weeks when they were 91 days old. A second set of four groups of animals with 20 male and 20 female (n=20/group) received vehicle, or tasimelteon doses of 50, 150, or 450 mg/kg/day, followed by a four week recovery phase. According to the Sponsor, during the study, avariety of data were collected including clinical observations, body weight, food consumption, limb measurements, sexual maturation, neurobehavioural examinations, haematology (peripheral blood), blood chemistry, urinalysis, toxicokinetics, oestrous cycles, organ weights, sperm analysis, litter data, bone density measurements, macropathology and micropathology investigations.

After ten weeks, the Sponsor observed signs of toxicity after 150 mg/kg/day in males and after 450 mg/kg/day in females manifesting as "a delay in the attainment of balano pre-putial separation and an increased incidence of minimal/slight centrilobular hypertrophy in the liver." The Sponsor also noted abnormalities in femur developments, and delays in puberty in males. Based on these data the Sponsor concluded the no observed adverse effect level (NOAEL) to be 450 mg/kg/day.

2.3 Abuse-related Animal Studies

The Sponsor did not perform any new abuse related animal studies. Prior abuse related studies submitted to NDA 205677 that were previously reviewed included a rodent self administration study and drug drug discrimination study. The results of the self administration study did not find tasimelteon to be a reinforcer, evidenced by the inability of tasimelteon to maintain self administration at levels significantly greater than placebo. Likewise, the drug discrimination data suggests that tasimelteon does not generalize to midazolam in midazolam trained animals. Although the drug discrimination data are expected given the dissimilar pharmacological effects between tasimelteon and midazolam, the data suggest that tasimelteon produces an interoceptive cue that is distinct from benzodiazepine sedatives.

3. Clinical Pharmacology

The Sponsor conducted one pharmacokinetic (PK) study with the tasimelteon (study VP-VEC-162-4201).

According to the Sponsor, new PK parameters for the tasimelteon oral suspension were not predicted due to the "sparseness of data." Instead, the data were used as inputs for PK modeling based on adult data. The Sponsor found that apparent clearance of tasimelteon in children was similar to adults in kids weighing > 28 kg.

4. Clinical Studies

Clinical studies were performed to assess the efficacy and PK of tasimelteon in adults and pediatric patients with SMS. There was one study examining the PK and safety of the oral suspension of tasimelteon (VP-VEC-162-4201) and another examining the efficacy of tasimelteon in subjects with Smith Magenis Syndrome (both pediatric patients and adults).

Study VP-VEC-162-4201 (PK): Open Label Study to Investigate the Pharmacokinetics and Safety of Tasimelteon in Children and Adolescents

According to the Sponsor, the objectives of this study were to determine a pediatric dose of tasimleteon using adult AUC values. Other goals were to characterize the PK of orally administered tasimelteon, its metabolites, and to determine its overall safety and tolerability. The study was an open-label, single dose, non-controlled study to evaluate the PK and safety of tasimelteon in blind children 3 to <18 years of age with either Circadian Rhythm Sleep-Wake Disorder (CRSWD), Non-24-Hour Sleep Wake Disorder (Non 24), and/or who are diagnosed with a Neurodevelopmental Disorder per the DSM-V including (but not limited to) Autism Spectrum Disorder (ASD) and Smith-Magenis Syndrome (SMS) with a nighttime sleep complaint. Twenty four subjects (n=24) completed the study. Dosing was weight-based and subjects received a single dose of either 6, 12, 16, or 20 mg. Twenty-five treatment-emergent adverse events (TEAEs) were reported across 14 (56.0%) subjects. Irritability was experienced by two subjects (8.3%). No other abuse-related AEs occurred.

Study VP-VEC-162-2401: A Double Blind, Randomized, two-period Crossover Study Evaluating the Effects of Tasimelteon vs. Placebo on Sleep Disturbances of Individuals with Smith-Magenis Syndrome (SMS)

According to the Sponsor, this was an open label efficacy and double blind, randomized, two-period crossover study evaluating the effects of tasimelteon on sleep distubances in both adult and pediatric patients. The first phase of the study was an open label treatment phase. The second phase was a randomized cross over treatment phase, followed by an open label extension phase. The randomization arm included treatment with tasimelteon and placebo in a cross over study design with each treatment separated by a one week washout period. The primary endpoints of the randomized cross over phase of the study were the average of 50% worst daily diary sleep quality (DDSQ50) and the average of 50% worst daily diary total nighttime sleep time (DDTST50). Primary outcome measures included measures on the daily diary sleep quality (DDSQ) daily diary total nighttime sleep time (DDTST50). Both pediatric subjects and adults were enrolled (age range: 3-65 years). Adults were administered a single 20 mg capsule of tasimelteon and pediatric patients received the 4 mg/mL liquid suspension. Tasimelteon or placebo was administered nightly, an our before bedtime.

During the treatment phase, seven subjects (n=7, 26.9%) experienced a TEAE while on placebo and six subjects (n=6, 24.0%) experienced a TEAA while on tasimelteon. Few of the reported adverse events were abuse-related. There was one AE of “emotional disorder” while receiving tasimelteon, and one report of somnolence in a subject receiving tasimelteon during the open label portion of the study. There were no reports of euphoria or euphoric mood. Overall, the AE profile does not suggest a signal of abuse in this study.

The clinical studies were performed in blind pediatric subjects with neurodevelopmental disorders (Study VP-VEC-162-4201) and in adults with SMS (Study VP-VEC-162-2401). Each of these subject populations represent relatively severe behavioral phenotypes and/or adolescent subjects. The validity and predictability of AE analyses in these populations is unknown. In addition, the PK study was not placebo controlled. Despite these limitations, abuse-related AEs were extremely rare, with no mentions of euphoric mood. Overall, the abuse-related AE profile does not suggest a signal of abuse associated with tasimelteon.

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM TO FILE

Version Date:	October 23, 2020
From:	Ethan D. Hausman, MD, Medical Officer Division of Pediatric and Maternal Health (DPMH)
Through:	Shetarra Walker, MD, MSCR, Acting Medical Team Leader, DPMH John J. Alexander, MD, MPH, Deputy Director DPMH
NDA Number:	205,677 and 214,517
Sponsor:	Vanda Pharmaceuticals Inc.
Drug:	Hetlioz (tasimelteon)
Current Indication:	Treatment of non-24-hour sleep-wake disorder (Non-24)
Proposed Indication:	Treatment of sleep disorder in Smith-Magenis Syndrome (SMS) in pediatric patients
Dosage Form and Route of Administration:	20 mg capsule, oral (PO) administration (approved) 4 mg/mL Suspension, PO administration (under development)
Proposed Regimen (SMS):	Adults: 20 mg before bedtime Children: >28 kg, 20 mg PO at bedtime; ≤28 kg, 0.7 mg/kg before bedtime
Division Consult Request:	The Division of Psychiatry products (DP) requests DPMH assistance for labeling of this product for the newly proposed indication.

Background

On January 31, 2014, FDA approved the capsule formulation of Hetlioz for treatment of adults with Non-24. As of the most recent labeling update of October 7, 2020, section 8.4 states that safety and effectiveness for treatment of Non-24 in pediatric patients are not established.

Tasimelteon received orphan drug designation for treatment of Non-24 on January 9, 2010 and received orphan designation for treatment of sleep wake disorder in SMS on April 30, 2010. Tasimelteon does not have a pediatric Written Request and no pediatric study requirements have been issued.

The following summary is taken from the Online Mendelian Inheritance in Man website (OMIM, entry #: 182,290) except where noted. SMS is a rare disorder with a prevalence of between 1 in 15,000 to 1 in 25,000. SMS in most patients appears to be attributed to non-inherited genetic abnormalities of the RAI1 gene at chromosome 17 band p11.2.[1] The genetic abnormality most commonly arises from *de novo* mutations during male or female gametogenesis (not strictly inherited) or during early embryonic development. Some cases have been attributed to balanced translocations and transmission in this case is expected to be autosomal dominant. Clinical signs include neurocognitive issues (mild to moderate intellectual disability, speech and motor delay), distinctive facies, sleep disturbances, behavioral problems, and skeletal and dental abnormalities. Virtually all patients have inversion of 24-hour pattern of melatonin secretion with melatonin elevations occuring in the morning rather than at night, which is thought to be directly related to the sleep disturbance.[2] There are no approved drug or biologic treatments for SMS.

The sponsor's development plan focuses on improving disordered sleep in these patients via the putative action of tasimelteon in the melatonin pathway.

To support the NDA, the Applicant submitted a single, two-part clinical trial in 25 adult and pediatric patients ages 3 years and older. In Part 1, 11 patients received tasimelteon one hour prior to bedtime for up to 189 weeks. In Part 2, 25 patients received tasimelteon or placebo every night one hour prior to bedtime for 4 weeks followed by a 1-week washout period, and then 4 weeks treatment with the opposite therapy. The 11 patients in the 3 to 15-year age group received a suspension formulation (to be marketed) and the 14 patients in the older group (16 to 65 years old) received the previously marketed capsule formulation.

The Applicant submitted the clinical data without having performed the previously recommended bioequivalence (BE) study intended to establish comparability between the two formulations. The Applicant stated that establishing study sites for enrollment of healthy adults in a BE study has been difficult due to extenuating circumstances related to

[1] Boudreau EA, Johnson KP, Jackman AR, et al. Review of Disrupted Sleep Patterns in Smith-Magenis Syndrome and Normal Melatonin Secretion in a Patient with an Atypical Interstitial 17p11.2 Deletion. Am J Med Genet A. 2009 Jul; 149A(7): 1382–1391.
[2] Potocki L, Glaze D, Tan DX, Park SS, Kashork CD, Shaffer LG, Reiter RJ, Lupski JR. Circadian rhythm abnormalities of melatonin in Smith-Magenis syndrome. J Med Genet. 2000; 37(6):428–433

the COVID-19 pandemic; further, the Applicant does not plan to perform a BE study and intends for the efficacy of the two formulations to be assessed separately.

At the September 1, 2020 team meeting, DP and the Statistics reviewers stated that the trend toward positive effect in the proposed clinical endpoints and adverse events, which appeared generally mild to moderate in severity, were both balanced across the age groups. Additionally, Clinical Pharmacology stated that the PK profiles were generally similar across the two groups. Clinical Pharmacology stated that the application could be approved without the BE study without setting new FDA precedent.

Labeling Review

Comments in this review are taken from draft labeling as of July 13, 2020. DPMH labeling comments and recommendations focus on sections 1 (Indications and Usage), 2 (Dosage and Administration), 5 (Warnings and Precautions), and 8.4 (Pediatric Usage). Tasimelteon has no contraindications (section 4 of labeling).

For this review, text which DPMH recommends deleting is noted by ~~strike out~~, and text which DPMH recommends adding is noted in **bold red**. The reader is directed to the final negotiated label which may reflect changes not discussed in this document (e.g., agreed upon trade name of the drug), and to the approval letter which will include the text of any required postmarket studies.

The comments below were provided to DP on October 6, 2020.

1 Indication

Reviewer comment: At the October 6, 2020 labeling meeting, DN, Clinical Pharmacology, and DPMH discussed the indication and formulations and that the following language is appropriate and reflects the single indication for the oral suspension (in patients 3 to 15 years) and the two indications for the capsule (in patients 16 years and older).

1.1 Non-24-Hour Sleep-Wake Disorder (Non-24)

HETLIOZ capsules are indicated for the treatment of Non-24-Hour Sleep-Wake Disorder in adults.

1.2 Nighttime Sleep Disturbances in Smith-Magenis Syndrome (SMS)

HETLIOZ capsules are indicated for the treatment of nighttime sleep disturbances in SMS in patients 16 years and older.

HETLIOZ oral suspension is indicated for the treatment of nighttime sleep disturbances in SMS in pediatric patients 3 to 15 years.

Reviewer comment: DN concluded that the pathophysiology of SMS is such that sleep disorder is necessarily related to the biochemical defect and that sleep disorder is present in virtually all patients necessitating the phrase "… in SMS" rather than (b) (4)

2.2 Nighttime (b) (4) Sleep Disturbances (b) (4) in Smith-Magenis Syndrome (SMS)

Patients 16 years and older (Capsules)

The recommended dosage of HETLIOZ in adults is 20 mg one hour before bedtime, at

the same time every night.

Pediatric Patients 3 years to 15 years of age (b) (4)

The recommended dosage of HETLIOZ in pediatric patients is based on body weight (see Table 1). Administer HETLIOZ one hour before bedtime, at the same time every night.

Table 1: Recommended Dosage of HETLIOZ for the Treatment of Nighttime Sleep Disturbances in Smith-Magenis Syndrome (SMS) in Pediatric Patients 3 Years to 15 Years of Age

Body Weight	**Daily Dose (oral suspension)**
≤28 kg	0.7 mg/kg one hour before bedtime
>28 kg	20 mg one hour before bedtime

Reviewer comment: The above language was agreed upon at the October 6, 2020 labeling meeting. If the sponsor undertakes a BE study and comparability of the two formulations is established the originally proposed language would be appropriate.

5 WARNINGS AND PRECAUTIONS

5.1 Somnolence

After taking HETLIOZ, patients should limit their activity to preparing for going to bed. HETLIOZ can potentially impair the performance of activities requiring complete mental alertness.

Reviewer comment: There are no changes to labeled Warnings and Precautions.

8.4 Pediatric Use

Reviewer comment: At the October 6, 2020 labeling meeting DP, Clinical Pharmacology, and DPMH agreed to the following revisions for section 8.4. The revision to the proposed language for SMS reflects the conditions of study (a single, placebo-controlled study of children and adults).

Safety and effectiveness **of Hetlioz for the treatment of Non-24** in pediatric patients have not been established.

Safety and effectiveness **of Hetlioz for the treatment of nighttime sleep disturbances in Smith-Magenis Syndrome (SMS)** (b) (4) -have been established in **pediatric patients** (b) (4) 3 years and older. **Use is based on a placebo-controlled crossover study of pediatric and adult patients** *[see Clinical Studies (14.2)]*

Reviewer comment: The Toxicology reviewer stated the juvenile toxicology data are under review and juvenile toxicology labeling language for section 8.4 is pending. DPMH will participate in those labeling discussions and the reader is directed to the final labeling for additional details.

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

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

Date of This Review:	October 30, 2020
Requesting Office or Division:	Division of Psychiatry Products (DP)
Application Type and Number:	NDA 214517 and NDA 205677/S-007
Product Name and Strength:	Hetlioz LQ[a](tasimelteon) oral suspension, 4 mg/mL (NDA 214517) Hetlioz (tasimelteon) capsules, 20 mg (NDA 205677/S-007)
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Rx
Applicant/Sponsor Name:	Vanda Pharmaceuticals Inc. (Vanda)
FDA Received Date:	June 1, 2020
OSE RCM #:	2020-1149 and 2020-1151
DMEPA Safety Evaluator:	Loretta Holmes, BSN, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

[a] The proposed proprietary name, Hetlioz LQ, submitted on August 28, 2020 for NDA 214517 is currently under review.

1 PURPOSE OF REVIEW

Vanda resubmitted (after a previous Refuse-To-File action) supplement NDA 205677/S-007 for Hetlioz (tasimelteon) capsules and new NDA 214517 for Hetlioz LQ[b] oral suspension for tasimelteon's use for the treatment of the sleep disorder in Smith-Magenis Syndrome (SMS). Subsequently, the Division of Psychiatry Products (DP) requested that we review the proposed container label and carton labeling for tasimelteon oral suspension and the proposed Prescribing Information (PI), shared PI for both NDAs, for areas that may lead to medication errors.

2 REGULATORY HISTORY

Hetlioz (tasimelteon) capsules (NDA 205677), approved on January 31, 2014, is a currently marketed product indicated for the treatment of Non-24-Hour Sleep-Wake Disorder (Non-24) in adults.

3 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

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

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 FINDINGS AND RECOMMENDATIONS

We reviewed the working draft of the Prescribing Information (PI), current as of October 22, 2020, as well as physical samples of the packaging components (i.e., proposed bottles, bottle adapter, cap, and oral dosing syringe). We note that the proposed Hetlioz LQ carton contains a bottle containing Hetlioz LQ, a press-in bottle adapter, and a 5 mL oral dosing syringe. The

[b] The proposed proprietary name, Hetlioz LQ, submitted on August 28, 2020 for NDA 214517 is currently under review.

graduations on the oral dosing syringe support measurement of the proposed Hetlioz LQ doses. Our review of the packaging components did not identify any areas of vulnerability that may lead to medication errors. Therefore, we have no comments on the PI or packaging components at this time.

Our review of the proposed container labels and carton labeling identified areas of needed improvement. Table 2, below, includes the identified medication error issues with the submitted Hetlioz LQ container labels and carton labeling, DMEPA's rationale for concern, and the proposed recommendation to minimize the risk for medication error. We note that the container labels are peel-back labels so there is a "top" segment of the label and a "base" inside segment of the label (what is seen when the top label is pulled back).

Table 2: Identified Issues and Recommendations for Vanda (entire table to be conveyed to Applicant)

Top Container Labels and Carton Labeling			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	A (b) (4) font is used for the NDC number, Rx only statement, net quantity statement, etc. The (b) (4) font lacks sufficient contrast against the "lavender" background.	The (b) (4) font is difficult to see.	Consider the use of a different font color, background color, both, or other means in order to improve contrast and readability.
2.	The established name does not appear to be at least ½ the size of the proprietary name.	The size of the established name does not appear to comply with 21 CFR 201.10(g)(2).	Ensure the established name is at least ½ the size of the proprietary name as required per 21 CFR 201.10(g)(2).
3.	The NDC number is represented by a placeholder (i.e., 43068-XXX-XX).	We are unable to evaluate the actual NDC number.	Replace the NDC number placeholder with the actual NDC number.
4.	The statement of strength is adjacent to the dosage form statement.	The statement of strength lacks prominence in its current location.	Increase the size of the statement of strength and relocate it to a position below the dosage form statement.
5.	The statement "For Oral Use Only" is not present.	Post-marketing experience has indicated that wrong route of administration errors have occurred when oral liquid products have been inadvertently administered as injections.	Because this product is an oral suspension (liquid), and the product is supplied with a dosing syringe, we recommend adding the statement "For Oral Use Only" to the Principal Display

			Panel (PDP) to minimize the risk of wrong route of administration errors.
Base (inside label) Container Labels and Carton Labeling			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	(b) (4)	(b) (4)	Delete the statement (b) (4) Relocate the statement "See package insert for full prescription information" so that it follows the word "Dosage". Additionally, change the word "(b) (4)" to "prescribing" and for consistency with the Prescribing Information, precede the word "Dosage" with the word "Recommended" (i.e., "Recommended Dosage").
2.	The statement "Use within (b) (4) weeks after first opening of the bottle" lacks prominence.	Due to its lack of prominence, the statement may be overlooked.	Use a bold font for the statement.
3.	There is no place allotted for users to write in the date of first opening of the bottle.	Lack of an allotted space to write in the date of first opening of the bottle may lead to use beyond (b) (4) weeks.	Follow the "Use within (b) (4) weeks after first opening of the bottle" statement with the following statement: "Date of first opening __/__/__. Discard unused portion (b) (4) weeks after first opening" or use similar verbiage.
4.	Under "Preparation instructions" there is no statement that refers the user to the Instructions for Use (IFU).	The full instructions for use of the product are included in the IFU.	Follow the last statement under "Preparation instructions" with the following sentence: "See the Instructions for Use" in bold font.

5.	The heading "Preparation instructions" does not indicate who the instructions are for.	It is not clear whether the "Preparation instructions" are intended for the pharmacist/dispenser or the patient/caregiver.	Revise the heading so that it clearly indicates who the instructions are for.
Top Container Labels			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	We note that you intend to include Braille on the labels.	It is unclear why Braille is needed on the labels.	Please provide the rationale for using Braille on the labels.
2.	The expiration date format is not shown.	We are unable to evaluate the expiration date format.	Provide the proposed expiration date format.
3.	(b) (4)		
4.	There is no linear barcode on the labels.	The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label whenever possible.	Add the linear barcode to the label per 21 CFR 201.25(c)(2).
Carton Labeling			
1.	The carton contents are not clearly identified with a heading.	The lack of a heading may make it difficult to easily locate the carton contents information.	Precede the carton contents information with a heading (e.g., "Contents: An oral dosing syringe…") or use a similar heading. Ensure the heading is prominent by using a bold font, underling, or other means. Additionally, consider moving the information from its current location at the bottom

			portion of the back panel to the top of the back panel.

5 CONCLUSION

Our evaluation of the proposed container labels and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Applicant. We ask that the Division convey Table 2 in its entirety to the Applicant so that recommendations are implemented prior to approval of this new NDA and NDA supplement.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Hetlioz and Hetlioz LQ that Vanda submitted on June 1, 2020 and September 15, 2020 and draft updates to the Prescribing Information by the Division.

<table>
<tr><th colspan="2">Table 3. Relevant Product Information for Hetlioz and Hetlioz LQ (shared Prescribing Information)</th></tr>
<tr><td>Initial Approval Date</td><td>Hetlioz, NDA 205677, approved on January 31, 2014
Hetlioz LQ, NDA 214517, pending</td></tr>
<tr><td>Active Ingredient</td><td>tasimelteon</td></tr>
<tr><td>Indication</td><td>Non-24-Hour Sleep-Wake Disorder (Non-24)
The Sleep Disorder in Smith-Magenis Syndrome (SMS)</td></tr>
<tr><td>Route of Administration</td><td>Oral</td></tr>
<tr><td>Dosage Form</td><td>Hetlioz (capsules); Hetlioz LQ (oral suspension)</td></tr>
<tr><td>Strength</td><td>20 mg (capsules); 4 mg/mL (oral suspension)</td></tr>
<tr><td>Dose and Frequency</td><td>Non-24-Hour Sleep-Wake Disorder (Non-24)
<u>Adults (Capsules)</u>
The recommended dosage of is 20 mg one hour before bedtime, at the same time every night.
Nighttime Sleep Disturbances in Smith-Magenis Syndrome (SMS)
<u>Patients 16 years and older (Capsules)</u>
The recommended dosage of in adults is 20 mg one hour before bedtime, at the same time every night.
<u>Pediatric Patients 3 years to 15 years of age (Oral Suspension)</u>
The recommended dosage in pediatric patients is based on body weight (see Table 1). Administer one hour before bedtime, at the same time every night.
Table 1: Recommended Dosage for the Treatment of Nighttime Sleep Disturbances in Smith-Magenis Syndrome (SMS) in Pediatric Patients 3 Years to 15 Years of Age
<table>
<tr><th><u>Body Weight</u></th><th><u>Daily Dose (oral suspension)</u></th></tr>
<tr><td><u>≤28 kg</u></td><td>0.7 mg/kg one hour before bedtime</td></tr>
<tr><td><u>>28 kg</u></td><td>20 mg one hour before bedtime</td></tr>
</table>
</td></tr>
<tr><td>How Supplied</td><td><u>Capsules:</u> Bottles of 30 capsules
<u>Oral Suspension</u>: Bottles of 48 mL or (b) (4) mL, a press-in bottle adapter, and a 5 mL oral dosing syringe</td></tr>
</table>

Storage	<u>Capsules</u> Store at controlled room temperature, 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature]. Protect from exposure to light and moisture. <u>Suspension</u> Store oral suspension at refrigerated temperature 5°C (41°F); excursions permitted to 2°C to 8°C (36°F t o 46°F). (b) (4)
Container Closure	Child resistant cap

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On October 23, 2020, we searched the L:drive and AIMS using the term, Hetlioz, to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified one previous review that informs this current review:

Neshiewat, J. Label, Labeling and Packaging Review for Tasimelteon (NDA 205677). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 Sep 26. RCM No.: 2013-1436.

APPENDIX C. ISMP NEWSLETTERS

C.1 Methods

On October 23, 2020, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below.

Table 6. ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care, Community, and Nursing
Search Strategy and Terms	Match Exact Word or Phrase: Hetlioz

C.2 Results

Our search did not retrieve any articles.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Hetlioz and Hetlioz LQ labels and labeling submitted by Vanda on June 1, 2020 and September 15, 2020.

- Container labels received on September 15, 2020
- Carton labeling received on September 15, 2020
- Prescribing Information (Image not shown) received on June 1, 2020

We also reviewed physical samples of the bottles, bottle adapter, oral dosing syringe, and bottle cap provided by the Applicant.

F.2 Labels and Labeling Images (not to scale)

Container Label ((b) (4) mL bottle)

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

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Clinical Inspection Summary

Date	10/29/2020
From	Christian Shenouda, M.D., Medical Officer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Valentina Mantua, MD/PhD, Clinical Reviewer Mike Davis, MD/PhD, Clinical Team Leader Latrice Wilson, Regulatory Project Manager Division of Psychiatry (DP)
NDA	214517
Applicant	Vanda Pharmaceuticals Inc.
Drug	Tasimelteon (Hetlioz)
NME	No
Proposed Indication(s)	The treatment of sleep disorder in Smith-Magenis Syndrome
Consultation Request Date	6/25/2020
Summary Goal Date	10/30/2020
Action Goal Date	12/1/2020
PDUFA Date	12/1/2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical investigators Drs. Helene Emsellem and Daniel Norman were inspected in support of this NDA. Based on the results of these inspections, Protocol VP-VEC-162-2401 appears to have been conducted adequately, and the data generated by these clinical investigators in support of the respective indication appear to be reliable.

II. BACKGROUND

Smith-Magenis syndrome (SMS) is a rare (1/15,000 – 25,000 births) developmental disorder that results from an interstitial deletion of human chromosome 17p11.2, and in rare cases from a point mutation in the *RAI1* gene. Patients with SMS present with a number of physical, mental, and behavioral problems, including a severe sleep disorder associated with significant disruption in the lives of patients and their families.

Tasimelteon is a melatonin agonist, currently approved for the treatment of patients with Non-24 Hour Sleep Wake Disorder. The medication is administered every evening 1 hour before bedtime in either a single 20mg capsule or a 4mg/mL suspension. The Division of Psychiatry (DP) requested two clinical investigator inspections for the pivotal study for this NDA, Protocol VP-VEC-162-240, which is briefly summarized below.

Protocol VP-VEC-162-2401

Title: "A Double-Blind, Randomized, Two-Period Crossover Study Evaluating the Effects of Tasimelteon vs. Placebo on Sleep Disturbances of Individuals with Smith-Magenis Syndrome (SMS)"

Subjects: 26 subjects

Sites: 4 domestic sites

Study Initiation and Completion Date: 10/16/2015 to 11/19/2018

Summary:
This was a double-blind, randomized, crossover study with 3 phases: a 4-week screening period, a 9-week treatment period, and a 180-week open label extension period. All enrolled subjects completed a 4-week screening. Thereafter, subjects could be enrolled into the crossover study with an open label extension or go straight into an open label arm of the study. The 9-week treatment (crossover) phase consisted of a 4-week intervention with the study drug or placebo, a 1-week washout period, followed by a 4-week period in which subjects were given the assignment not supplied prior to the washout. Thereafter, these subjects continued onto the open-label extension phase of the trial. A subset of patients not eligible to be enrolled in the main part of the study were enrolled into an open-label arm after screening and did not participate in the cross-over or open-label extension parts of the study.

During the study, subjects or their caregivers (for pediatric subjects) were provided with electronic diaries to collect sleep data on a daily basis, including total number of hours slept, number of awakenings, and daytime naps. Study visits for this study were performed either at the study site or as home visits at the discretion of the Sponsor.

The main inclusion criteria were confirmed diagnosis of SMS via genetic testing, aged 3-65, and ongoing sleep disturbance. The main exclusion criteria were impaired liver function, previous night shift work in the last month, and recent use of the study drug or melatonin (within 30 days). Actual inclusion/exclusion criteria were more extensive than those listed above.

The primary efficacy outcome was improvement in nighttime sleep as measured by the average of 50% worst daily diary sleep quality (DDSQ50) and the average of 50% worst daily diary total sleep time (DDTST50) during the double-blind phase (not including the washout period). These outcome measures were derived from sleep data recorded by subjects or their caregivers in the electronic diary in the form of the daily post-sleep questionnaire (PSQ). Secondary endpoints included actigraphy to assess number of nighttime awakenings and length of awakenings as well as the Clinician Global Impression of Change (CGI-C).

Rationale for Site Selection
The following clinical investigators (CIs) were chosen for inspection primarily based on numbers of enrolled subjects, site efficacy, protocol deviations, and prior inspectional history.

Note
The review division was concerned regarding a lack of variability in some of the sleep data for certain subjects, raising the question whether that data was collected contemporaneously. This issue is addressed in the inspection results.

III. INSPECTION RESULTS

1. Helene Emsellem, MD
Site #101
The Center for Sleep and Wake Disorders
5454 Wisconsin Avenue; Suite 1725
Chevy Chase, Maryland 20815
Inspection dates: 9/8/2020-9/14/2020

At this site for protocol Protocol VP-VEC-162-2401, 21 subjects were screened and 17 were enrolled (7 were enrolled into the treatment arm, and 10 were enrolled in the open-label arm). All seven subjects completed the treatment arm of the study.

Records reviewed included, but were not limited to, informed consent forms (ICFs), regulatory binders, IRB/sponsor correspondence, subject files, drug accountability, and electronic source data. Eight subject records were reviewed during the inspection, i.e., all 7 subjects who were enrolled in the treatment phase of the protocol and one subject who was later classified as a screen fail.

The FDA field investigator was given access to the web portal to verify the electronic diary sleep data. The primary efficacy endpoint data were verifiable for all seven subjects who completed the treatment phase of the study. There was an instance in which a subject reported multiple daytime naps in a single day, and the time and duration of the events were erroneously transcribed (i.e., naps were recorded at 4 and 5pm for 10 and 20 minutes, respectively, but the listing for 4pm recorded 20 minutes and 5pm showed 10 minutes). However, the daily totals were consistent, and no other discrepancies were noted. Actigraphy data was verified in 8 subjects, with no discrepancies identified.

The inspection showed that time stamps revealed that all the electronic diary sleep data were logged on the day or the day after the event.

There was no evidence of underreporting of adverse events (AEs). There were four SAEs recorded at the site, and all were reported to the sponsor within the specified timeframe (24 hours). Two of the SAEs (Subject #s (b) (6) and (b) (6)) occurred during the open-label arm period of the study and were, in the judgement of the CI, unrelated to the study medication (finger infection and dental infection, respectively). Two occurred during double blind treatment period in

patients assigned to the treatment arm (Subject #s (b) (6) and (b) (6)) and consisted of a tonic clonic seizure and sepsis post-cystoscopy, respectively. The tonic clonic seizure occurred when the subject was assigned to receive placebo, and the sepsis event occurred when the subject was taking the active medication.

2. Daniel Norman, MD
Site #102
Santa Monica Clinical Trials
1301 Twentieth Street, Suite 370
Santa Monica, California 90404
Inspection dates: 8/26/2020 – 9/2/2020

At this site for protocol Protocol VP-VEC-162-2401, 25 subjects were screened and 24 were enrolled. There were 13 subjects who were enrolled into the treatment arm, all of whom were taking part in the open-label extension phase of the study at the time of the inspection. There were 11 subjects who were enrolled directly into the open-label arm of the study.

Records reviewed during the inspection included, but were not limited to, study protocol and amendments, regulatory binders and IRB correspondence, subject files, financial disclosures, monitoring visits, staff training logs, delegation of authority log, ICFs, inclusion/exclusion criteria, concomitant medications, investigational product administration, drug accountability, and adverse events.

The FDA field investigator was given access to the web portal to verify the electronic diary sleep data (i.e., the daily post sleep questionnaire). The primary efficacy endpoint data was verifiable for all 13 subjects who completed the treatment phase of the study. Actigraphy data for all subjects was also verified.

Time stamps revealed that all the electronic diary sleep data was not entered more than 3 days after the event.

There was no evidence of underreporting of AEs. There were three SAEs reported in two subjects (Subject # (b) (6), with enteritis and subsequent levofloxacin-induced hepatitis, and Subject # (b) (6) with an anaphylactic reaction to food). The enteritis and levofloxacin-induced hepatitis occurred when the subject was in the screening phase and prior to the treatment being initiated. The anaphylactic food reaction occurred when the subject was on the active medication. The FDA field investigator noted that the SAEs of enteritis and levofloxacin-induced hepatitis were not reported to the sponsor in a timely fashion (i.e., not until months after the events occurred). However, there was no evidence of underreporting of AEs, and these three SAEs were included in the NDA submission.

The inspection noted instances of lack documentation for three enrolled subjects who were receiving medications that would affect wakefulness (methylphenidate and/or trazadone. They were Subject #s (b) (6) and (b) (6) (both of whom were assigned to the cross-over arm) and Subject # (b) (6) (in the open-label arm). In the investigator written response dated 9/22/2020, Dr. Norman submitted documentation that these medications were in fact reported to and cleared by the sponsor prior to subject enrollment. He stated that he had trouble finding

this documentation during the inspection as he was reportedly not made aware of the finding until late on the last day of the inspection, when the 483 was issued.

{See appended electronic signature page}

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/s/

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