

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205677Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

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

**Risk Evaluation and Mitigation Strategy (REMS) Memo**

Date: October 22, 2013

Reviewer(s): Nyedra W. Booker, Pharm.D., M.P.H., Risk Management Analyst, Division of Risk Management (DRISK)

Team Leader: Kendra Worthy, Pharm.D., DRISK

Division Director: Claudia Manzo, Pharm.D., DRISK

Drug Name(s): tasimelteon

Therapeutic Class: Circadian Regulator (first in class)

Dosage and Route: 20 mg oral capsules

Indication(s): Treatment of Non-24-hour disorder in blind individuals with no light perception

Application Type/Number: NDA 205-677

Applicant/sponsor: Vanda Pharmaceuticals, Inc.

OSE RCM #: 2013-1559

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## 1 INTRODUCTION

This review documents the Division of Risk Management (DRISK) evaluation of the NDA 205-677 for tasimelteon, an NME, to assess the need for a Risk Evaluation and Mitigation Strategy.

Tasimelteon is the first circadian regulator in clinical development for the treatment of Non-24-hour disorder in blind patients with no light perception (total blindness). Non-24-hour disorder (Non-24) is also referred to as:

- Circadian rhythm sleep disorder-non-entrained type
- Non-24-hour circadian rhythm disorder
- Circadian rhythm sleep disorder- free-running type
- Free running disorder (FRD)
- Non-24-hour sleep-wake disorder
- Hypnnychthemeral disorder

The recommended dose of tasimelteon is 20 mg per day taken (b) (4) prior to bedtime, preferably at the same time every night. The draft label states that tasimelteon can be taken (b) (4) without food.

## 2 MATERIALS REVIEWED

- Clinical Overview, Vanda Pharmaceuticals Inc., dated May 31, 2013
- NDA 225-677 Tasimelteon Mid-Cycle Meeting Clinical Review-slides (D. Jillapalli), dated September 12, 2013
- NDA 225-677 Tasimelteon Mid-Cycle Meeting Clinical Pharmacology Review-slides (J. Parepally), dated September 12, 2013

## 3 OVERVIEW OF CLINICAL PROGRAM

Tasimelteon is a circadian regulator that resets the body's master clock in the suprachiasmatic nucleus (SCN) of the hypothalamus by binding to melatonin MT<sub>1</sub> and MT<sub>2</sub> receptors, with an approximate 2-4x greater affinity for MT<sub>2</sub>. The clinical program for tasimelteon included over 1,300 patients and healthy volunteers. The trials were designed to demonstrate the drug's safety and effectiveness as a circadian regulator to treat Non-24-hour disorder<sup>1</sup> in patients with total blindness, and as a circadian regulator in healthy individuals<sup>2</sup>.

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<sup>1</sup> Study criterion for diagnosis of Non-24 was determined based on the following: 1) history (within the past 3 months) of difficulty sleeping at night (difficulty with sleep initiation or maintenance), difficulty awakening in the morning, or daytime sleepiness and, 2) demonstration of progressive delay of aMT6s acrophase time.

<sup>2</sup> Vanda Pharmaceuticals, Inc. Pharmacovigilance Plan (NDA 205677).

## Safety and Efficacy Trials

### *Efficacy*

Tasimelteon's effectiveness as a circadian regulator in the treatment of Non-24 in totally blind individuals was established through two randomized, double-blind, placebo-controlled, parallel-group trials plus a parallel-group trial in healthy volunteers:

- 26-week randomized, open-label study (with an open-label extension)  
Non-24 patients (N=84) with non-entrained melatonin circadian rhythms (circadian period ( $\tau$ ) length  $\geq 24.25$ hrs) at baseline and a sleep-wake complaint were randomized to receive 20 mg tasimelteon or placebo one hour before bedtime at the same time daily for a 6-month treatment period. Entrainment of urinary aMT6s (a major metabolite of melatonin) and cortisol was measured at screening, then during weeks 2 through 5 of the study.
- 20-24 week randomized withdrawal trial  
Non-24 patients from the open-label study who responded to tasimelteon treatment as measured by aMT6s and  $\tau \leq 24.1$  hours (N=20), were included in this study. The study was designed to evaluate tasimelteon's maintenance effect after long-term use. Patients were randomized to receive 20 mg tasimelteon or placebo daily (one hour before bedtime) for approximately 12 weeks. Those achieving melatonin circadian rhythm entrainment during the run-in phase were subsequently randomized to receive continued treatment with 20 mg tasimelteon or placebo for an additional 8 weeks.
- 3-day study involving healthy volunteers (N=39) using tasimelteon (10, 20, 50 and 100 mg) or placebo oral capsules once daily. This study was conducted to assess tasimelteon's efficacy as a circadian regulator.

Primary efficacy endpoints: 1) entrainment of circadian rhythms (measured by aMT6s) and 2) clinical response (measured by demonstration of entrainment of aMT6s and a Non-24 Clinical Response Scale (N24CRS)<sup>3</sup> score  $\geq 3$ ) were both achieved in the randomized, controlled trial. Significantly more tasimelteon-treated patients achieved more frequent entrainment compared to placebo ( $p=0.0171$ ), and more tasimelteon-treated patients achieved entrainment associated with significant clinical improvement, as measured by N24CRS scores ( $p=0.0028$ ). The secondary endpoint "entrainment of the cortisol rhythm" was also achieved ( $p=0.0313$ ).

Statistical significance was achieved in the randomized withdrawal trial for the primary endpoint "maintenance of effect of tasimelteon to entrain circadian rhythms" in Non-24 patients, as measured by urinary aMT6s ( $p=0.0026$ ), and the secondary endpoint "maintenance of entrainment of the cortisol rhythm" ( $p=0.0118$ ).

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<sup>3</sup> Non-24 Clinical Response Scale (N24CRS) is a composite scale of endpoints for measuring clinical improvement in nighttime sleep, daytime sleep duration, sleep timing and global functioning.

## Safety

Tasimelteon's safety was established based on a pooled analysis of available safety data across all clinical trials [a total of 23 clinical studies: safety, efficacy, pharmacokinetic (PK), pharmacodynamic (PD) and "thorough QT" to assess effects on QT interval].

Long-term safety was established in a 6 month open-label extension of the 26-week randomized/26-week open-label trial, and in the following two open label studies:

- 52 weeks followed by a 3 year optional sub-study involving (N=140; "planned") totally blind subjects with Non-24 disorder using tasimelteon 20 mg oral capsules once daily.
- 2-year study involving (N=200; "planned") totally blind subjects with Non-24 disorder using tasimelteon 20 mg oral capsules once daily.

The most frequently reported adverse events (AEs) in all subjects (tasimelteon and placebo-treated) included headache, "vivid or unusual dreams", somnolence, nasopharyngitis, urinary tract infections and increases in alanine aminotransferase (ALT). Events were typically reported within the first 30 days post-treatment initiation. Headache and "vivid or unusual dreams" were the two AEs reported with higher frequency in tasimelteon-treated subjects to an extent that was "clinically meaningful" according to the sponsor.

The discontinuation rate (overall and *adverse-events specific*) between the tasimelteon and placebo groups was comparable [tasimelteon (7.1% and 2.5%); placebo (6.9% and 2.3%)]. Significantly more tasimelteon-treated subjects, however, experienced AEs in the "Nervous Systems Disorders" and "Psychiatric Disorders" system-organ classes (SOCs) as compared to the placebo group.

## Agency Findings

In March 2007, the Agency requested that all manufacturers of sleep disorder (sedative-hypnotic) drug products strengthen their product labeling (including the development of patient Medication Guides) to include stronger language concerning potential risks including severe allergic reactions and complex sleep-related behaviors such as sleep-driving.<sup>4</sup>

A Medication Guide was not included in the sponsor's original submission. The Agency notified the sponsor on June 20, 2013 that a Medication Guide (using approved sedative-hypnotics as a model) would be required, and the sponsor subsequently proposed a Medication Guide to be available in (b) (4)

Clinical reviewer Dr. Devanand Jilapalli discussed the clinical program for tasimelteon during the Mid-cycle meeting and concluded that no major safety issues had been identified thus far. Clinical pharmacology reviewer Dr. Jagan Parepally presented study findings related to the effect of intrinsic factors (e.g., age, gender, renal and hepatic function) on tasimelteon's exposure. According to Dr. Parepally, tasimelteon plasma

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<sup>4</sup> FDA NEWS RELEASE. FDA Requests Label Change for All Sleep Disorder Drug Products. March 14, 2007.

concentration (as measured by C<sub>max</sub> and AUC) increased 2 fold in the elderly compared to adults, and the AUC by 43% and 90% in patients with mild and moderate hepatic impairment respectively. The preliminary recommendation was to reduce the tasimelteon dose to 10 mg for the elderly and patients with moderate hepatic impairment.

At the time of this review, a Peripheral and Central Nervous System Drugs (PCNS) Advisory Committee meeting has been scheduled for November 14, 2013.

#### **4 DISCUSSION**

Non-24 hour disorder is a condition that affects approximately 100,000 individuals in the U.S. Non-24 is characterized by a sleep-wake cycle that lacks synchronization to the 24-hour environment, which can occur when “synchronizing input” such as the environment’s light-dark cycle has been compromised. Blind patients who have diminished or complete absence of light perception are at significantly increased risk for Non-24, and more than 50% are believed to have the condition.<sup>56</sup> Patients with Non-24 often experience significant impairment in social and occupational functioning.

There are no sleep disorder (sedative-hypnotic) drugs currently approved to treat Non-24 hour disorder. In addition, none of the approved sleep disorder drugs have REMS program requirements.

Tasimelteon appears to demonstrate clinical benefit in Non-24 hour disorder patients with total blindness, and the adverse event profile thus far is favorable according to the clinical review team. There are no serious risks identified at this time to warrant a REMS. Adverse events of concern will be addressed in the labeling.

#### **5 CONCLUSION**

DRISK believes that a REMS for tasimelteon is not necessary at this time to ensure the benefits outweigh the risks. The inclusion of a Medication Guide and the sponsor’s proposal for labeling and routine pharmacovigilance are reasonable. Should DNP identify additional safety information that warrants risk mitigation measures, please send a consult to DRISK.

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<sup>5</sup> Harrison’s Principles of Internal Medicine (18e)/Harrison’s Online. Chapter 27 (Sleep Disorders).

<sup>6</sup> Zee PC, Attarian H, Videnovic A. Circadian Rhythm Abnormalities. American Academy of Neurology (Continuum Review Article) 2013; 199(1):132-147.

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/s/  
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