CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205677Orig1s000

<u>SUMMARY REVIEW</u>

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Eric Bastings, MD
Subject	Division Director Summary Review
NDA/BLA # Supplement #	205,677
Applicant Name	Vanda Pharmaceuticals
Date of Submission	May 31, 2013
PDUFA Goal Date	January 30, 2014
Proprietary Name / Established (USAN) Name	Hetlioz (tasimelteon)
Dosage Forms / Strength	20 mg capsule
Proposed Indication(s)	Non-24 hour sleep wake disorder in blind patients
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	Names of discipline reviewers
Medical Officer Review	Devanand Jillapalli, M.D.
Statistical Review	Jingyu (Julia) Luan, Ph.D.
Pharmacology Toxicology Review	Melissa Banks-Muckenfuss, Ph.D.
CMC Review	Rao Kambhampati, Ph.D.
Biopharmaceutics	Kareen Riviere, Ph.D.
Clinical Pharmacology Review	Jagan Parepally, Ph.D.
OSI	Antoine El-Hage, Ph.D.
CDTL Review	Ronald Farkas, M.D., Ph.D.
OSE/DRISK	Nyedra W. Booker, Pharm.D., M.P.H.
OSE/DMEPA	Julie Neshiewat, Pharm.D., BCPS
CSS	Katherine Bonson, Ph.D.
OPDP	Melinda McLawhorn, Pharm.D., BCPS
Biopharmaceutics	Kareen Riviere, Ph.D.
Carcinogenicity statistics	Steve Thomson
DMPP	LaShawn Griffiths, MSHS-PH, BSN, RN
QT review	Moh Jee Ng

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OPDP=Office of Prescription Drug Promotion
CSS=Controlled Substance Staff
DMPP=Division of Medical Policy Programs
DRISK=Division of Risk Management

1. Introduction

Vanda Pharmaceuticals submitted NDA 205,677 to support marketing of tasimelteon, a melatonin agonist, for the treatment of Non-24 hour sleep-wake disorder (Non-24) in totally blind patients. This is a novel indication, for which no drug is currently approved.

Non-24 hour sleep-wake disorder is characterized by a mismatch between the timing of the sleep-wake cycle and the 24-hour day because of a lack of environmental light input in completely blind individuals. As the individual "biological clock" runs longer than 24 hours in most people, the absence of light input creates a cyclical misalignment of sleep and wakefulness with the 24-hour day.

2. Background

As discussed by Dr. Jillapalli and Dr. Farkas, there was extensive interaction with the applicant during the drug development program, as there is no precedent for regulatory approval of a drug for this indication. No agreement could be reached with the applicant about the primary endpoints to be used in pivotal efficacy studies. The applicant insisted on using as primary endpoint an unvalidated surrogate ("entrainment"), based on measures of the melatonin biomarker. The division, however, considered that showing a benefit on clinical endpoints was feasible, and did not accept the applicant's proposal. The applicant nevertheless decided to conduct the two pivotal efficacy studies using "entrainment" as primary endpoint. The studies, however, also included endpoints that the division had prospectively identified as the most important measures of clinical benefit in Non-24: assessments of the duration of nighttime sleep and daytime naps. While the applicant defined these clinical endpoints as secondary, the division considered them as the true primary endpoints for the pivotal studies. As discussed by Dr. Farkas, the division expected the applicant to show that tasimelteon had an effect on the circadian disruption of sleep/wakefulness, and not just that it increased sleep time in an aspecific manner.

3. CMC/Biopharmaceutics

I concur with the conclusions reached by Dr. Kambhampati and Dr. Riviere regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 30 months when stored at controlled room temperature. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by Dr. Banks-Muckenfuss that there are no outstanding nonclinical issues that preclude approval.

5. Clinical Pharmacology

I concur with the conclusions reached by Dr. Parepally that there are no outstanding clinical pharmacology issues that preclude approval. CYP1A2 and CYP3A4 are the major isozymes involved in the metabolism of tasimelteon, and strong inducers and inhibitors of these isoenzymes have marked effects on tasimelteon plasma levels, i.e., a 90% reduction for the former, and a 650% increase for the latter. These interactions will be addressed in labeling.

6. Clinical Microbiology

N/A.

7. Clinical/Statistical-Efficacy

The applicant conducted two placebo-controlled trials of tasimelteon in Non-24: Study 3201 and Study 3203. As discussed above, and in the clinical and statistical reviews, the applicant's proposed surrogate primary endpoint was not accepted by the division, and only clinical endpoints were considered by the review team in their determination of tasimelteon efficacy.

Study 3201

Study 3201 was a parallel-group placebo-controlled study in which 84 totally blind subjects with Non-24 were randomized 1:1 to 20 mg tasimelteon or placebo, at a time when the patient's circadian rhythm was thought to be coming into alignment with the 24-hour day (as measured by urinary melatonin biomarker). The primary efficacy endpoint was defined as the proportion of patients who were entrained (as defined based on melatonin measurements). As second biomarker-based measure, the "Non-24 Clinical Response Scale[1]" was to be tested in a step-down approach. Nominal p values for both of these biomarker-based measures were under 0.05, but again, these were not considered to assess tasimelteon efficacy. Instead, the review team focused on clinical endpoints, which were as follows:
- Nighttime total sleep time (nTST)
- Lower Quartile of nTST (LQ-nTST): worst quarter of sleep during nighttime (nights with lowest sleep time)
- Daytime total sleep duration (dTSD)

---

[1] This endpoint combined a responder analysis of 4 of the above endpoints: LQ-nTST $\geq$ 45 minutes increase, UQ-dTSD $\geq$ 45 minutes decrease, MoST $\geq$ 30 minutes increase and a standard deviation $\leq$ 2 hours during the double-masked phase, and $\leq$ 2.0 score on CGI-C from the average of Day 112 and Day 183 compared to baseline.

- Upper quartile of dTSD (UQ-dTSD): worst quarter of sleep during daytime (days with highest sleep time)
- Clinical Global Impression of Change (CGI-C)
- Midpoint of Sleep Timing (MoST).

As discussed by Dr. Farkas, the division found the LQ-nTST and the UQ-dTSD to be the most relevant measures, because they were best adapted to a cyclical disorder such as Non-24. The nTSTwas expected to be less sensitive to benefit, because nTST is expected to be normal when patients are in alignment with their biological clock. The same concept applied to dTSD. The MoST was not considered as a good endpoint, because of interpretability issues, as described in the clinical review and in the CDTL memo. For these reasons, the team's attention focused primarily on the LQ-nTST and the UQ-dTSD.

In Study 3201, the contrasts for tasimelteon vs. placebo were nominally significant for UQ-dTSD, MoST, CGIC and dTSD, and marginally significant for LQ-nTST (Table 1). The contrast for nTST did not reach nominally significant difference.

Table 1: Clinical endpoints results in Study 3201 (copied from table 14, statistical review)

Endpoints	Placebo	Tasimelteon	P-value
LQ-nTST	0.37	0.83	0.0510
UQ-dTSD	-0.36	-0.81	0.0118
MoST	0.25	0.54	0.0366
CGIC[1]	3.34	2.63	0.0080
nTST	0.35	0.60	0.1149
dTSD	-0.18	-0.36	0.0166

Study 3203
Study 3203 was a randomized withdrawal placebo-controlled study designed to evaluate the long-term maintenance effect and safety of 20 mg of tasimelteon versus placebo in patients with Non-24. Twenty patients were randomized 1:1 to receive tasimelteon (20 mg/day) or placebo during the randomized withdrawal phase, which took place after about 11 weeks of treatment. The applicant's proposed primary endpoint was the proportion of non-entrainment of the circadian melatonin rhythm as measured by urinary melatonin metabolite aMT6s. As in Study 3201, the division was not in agreement with that biomarker-based endpoint, and the assessment of efficacy by the review team was instead based on clinical endpoints.

The biomarker-based primary endpoint showed a statistically significant benefit favoring tasimelteon. As in Study 3201, the contrasts for tasimelteon vs. placebo were nominally significant for UQ-dTSD, MoST, CGIC and dTSD. The contrast was also nominally significant for LQ-nTST (Table 2). The contrast for nTST did not reach nominal significance.

Table 2: Clinical endpoints results in Study 3203 (copied from table 20, statistical review)

Endpoint	ANCOVA without Site	Permutation ANCOVA				
		Seed=3203	Seed=11	Seed=14	Seed=2013	Seed=100000
LQ-nTST	0.0233	0.0226	0.0227	0.0234	0.0237	0.0235
UQ-dTSD	0.0266	0.0069	0.0064	0.0074	0.0070	0.0067
MoST	0.0108	0.0063	0.0067	0.0075	0.0068	0.0064
nTST	0.1315	0.1532	0.1530	0.1546	0.1548	0.1523
dTSD	0.0547	0.0224	0.0229	0.0234	0.0224	0.0235

As discussed by Dr. Farkas, additional analyses based on a graphic representation of the sleep diary data for each individual subject in Studies 3201 and 3203, and for study 3201, based on within-patient difference in nTST between maximum alignment (in-phase period of cycle) and maximum misalignment (out-of-phase period in cycle) also favored tasimelteon.

8. Safety

Dr. Farkas and Dr. Jillapalli note that 1346 subjects received at least one dose of tasimelteon, including 621 subjects who received at least one dose of tasimelteon 20 mg. Among 183 patients with Non-24 who received at least one dose of tasimelteon 20 mg, 111 patients were treated for at least 6 months, and 44 patients were treated for at least one year. While these numbers are below the typical ICH recommendations for the size of safety database (E1), I agree with Dr. Farkas and Dr. Jillapalli that the database is adequate for an orphan indication such as Non-24.

The safety experience was overall benign. An increased incidence of mild alanine aminotransferase elevations was not associated with a suggestion for a potential for serious drug-induced liver injury. At a dose 15 times the maximum recommended dose, tasimelteon does not prolong QTc to any clinically relevant extent.

9. Advisory Committee Meeting

The Peripheral and Central Nervous System Drugs Advisory Committee met on November 14, 2013, to discuss tasimelteon. The following is a summary of the committee's votes and recommendations.

Efficacy

1) No drugs are currently FDA approved for Non-24 Hour Sleep-Wake Disorder (Non-24). Please discuss the appropriateness of Non-24 as an indication for FDA approval of drug therapies.

   a. **DISCUSSION:** Are the intended population and diagnostic criteria reasonable?

Committee Discussion: The committee agreed that the intended population and diagnostic criteria was reasonable.

b. **DISCUSSION:** Are there any other concerns with the way the condition is defined or represented?

Committee Discussion: The committee did not express any other concerns with the way the condition is defined or represented.

c. **DISCUSSION:** Are you satisfied that Non-24 is a bona fide sleep disorder with consequences for patients?

Committee Discussion: The committee expressed that the Open Public Hearing speakers illustrated the strongest evidence that Non-24 is a bona fide sleep disorder with consequences for patients.

d. **DISCUSSION:** Is Non-24 appropriate as an indication for an FDA-approved drug therapy?

Vote: YES = 10   NO = 1   ABSTAIN = 0

Committee Discussion: The committee agreed that Non-24 is an appropriate indication for an FDA-approved drug therapy. The committee member who voted "NO" stated that he pressed the wrong button and meant to cast a "Yes" vote.

2) The clinical endpoints used in the efficacy studies supporting the new drug application (NDA) for tasimelteon in Non-24 are novel, and have not been used to support the approval of other drugs.

a. **DISCUSSION:** Please discuss the appropriateness of the clinical endpoints (those that sought to measure directly how patients feel or function), specifically, Lower Quartile of Nighttime Total Sleep Time (LQ-nTST), Upper Quartile of Daytime Total Sleep Duration (UQ-dTSD), and Clinical Global Impression of Change (CGI-C).

Committee Discussion: The committee agreed that the study designs were very novel, unique and appropriate for this indication.

b. **VOTE:** Are the clinical endpoints used in the tasimelteon development program appropriate to support an indication in Non-24?

Vote: YES = 10   NO = 1   ABSTAIN = 0

Committee Discussion: The majority of the committee agreed that the clinical endpoints used in the tasimelteon development program were appropriate to support an indication in Non-24. One panel member noted that the Lower Quartile of Nighttime Total Sleep Time (LQ-nTST), Upper Quartile of Daytime Total Sleep Duration (UQ-dTSD) were the best endpoints. A few of the panel members recommended including additional parameters, such as entrainment measures, daytime

function measures, and psychomotor vigilance test (PVT), to strengthen the power of future studies. The committee member who voted "'No" stated that the scale was very unnecessarily complex and not likely to be reproducible.

3) Please discuss the evidence of efficacy presented

    a. **DISCUSSION:** Are there any concerns with the design, conduct or analysis of the efficacy trials?

    Committee Discussion: The majority of the committee did not have concerns with the design, conduct or analysis of the efficacy trials. Many of the committee members conveyed that the study design was appropriate.

    b. **VOTE:** Has substantial evidence of efficacy been presented for tasimelteon in Non-24?

    Vote: YES = 10   NO = 0   ABSTAIN = 1

    Committee Discussion: The majority of the committee agreed that substantial evidence of efficacy was presented for tasimelteon in Non-24. Many of the committee members also conveyed that the study design was clever and appropriate for both trials. One panel member stated that the results were robust and illustrated efficacy. The committee member who abstained stated that the drug product failed on its primary endpoint and succeeded the subsequent compound endpoint, making it difficult to determine if the drug is effective.

Safety

4) **DISCUSSION**: Please discuss the safety evidence presented for tasimelteon.

    Committee Discussion: The majority of the committee agreed that the safety data was compelling.

5) **VOTE:** Has the safety of tasimelteon in Non-24 been adequately addressed?

    Vote: YES = 11   NO = 0   ABSTAIN = 0

    Committee Discussion: The committee agreed that the safety profile of tasimelteon in Non-24 was adequately addressed. Several committee members commented that tasimelteon had a low percentage of adverse events because the targeted population was small. One panel member stated that the safety profile may increase for non-responders as physicians increase the dose for response.

10.   Pediatrics

Because this product has orphan designation, PREA is not triggered.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

The CSS team does not recommend tasimelteon for scheduling under the Controlled Substances Act because there are no signs that the drug produces abuse potential or physical dependence in animal and humans.

The DRISK team agrees that there are no serious risks identified at this time to warrant a REMS.

12. Labeling

There are no other unresolved labeling issues.

A unique feature of labeling is that some information is presented in Braille. The applicant was asked to conduct a Braille label comprehension study. Dr. Neshiewat, from DMEPA, found the results of the study acceptable.

OSI inspected four clinical investigator sites. Dr. El-Hage notes the inspections revealed no regulatory violations, and the final classifications for these inspections are noted as "No Action Indicated". Overall, the data submitted from these four sites are considered acceptable by OSI in support of the pending application.

13. Decision/Action/Risk Benefit Assessment

I recommend approval of tasimelteon.

Even though no agreement was reached with the applicant regarding the primary endpoints to be used in pivotal efficacy studies, and the applicant opted to use biomarker-based endpoints that the division did not agree with, tasimelteon produced consistently positive results in both studies on the endpoints assessing aspects of the disease that the division had prospectively identified, during the development program, as the most clinically relevant for this new indication: the duration of nighttime sleep, as assessed by the "Lower Quartile of Nighttime total sleep time", and the duration of daytime naps, as assessed by the "Upper quartile of Daytime total sleep duration". In this setting, I find it reasonable to not use the primary endpoints selected by the applicant (which, of note, significantly favored tasimelteon in both studies), and only consider the clinical endpoints of interest. These clearly support efficacy of the product. In addition, the positive effects on these

endpoints are supported by significant contrasts on the "Clinical Global Impression of Change" in both studies.

There is no safety concern with the product. The safety database is somewhat smaller than typically expected for a new molecular entity, but I find it reasonable for this drug class and for this indication.

I recommend no Postmarketing Risk Evaluation and Mitigation Strategies for this product.

I recommend no Postmarketing Requirements or Commitments.

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

/s/

ERIC P BASTINGS

01/23/2014