U.S. FOOD & DRUG ADMINISTRATION

SENT VIA CERTIFIED MAIL AND E-MAIL

Vanda Pharmaceuticals, Inc.
[redacted]
2200 Pennsylvania Ave., NW, Suite 300E
Washington, DC 20037

Re: Proposal To Refuse To Approve a New Drug Application Supplement for Hetlioz (tasimelteon); Opportunity for a Hearing

Dear [redacted]:

This letter responds to your letter dated June 30, 2022, and sent July 1, 2022, addressed to Elizabeth Jungman, Associate Director for Policy and Director of the Office of Regulatory Policy, on behalf of Vanda Pharmaceuticals, Inc. (Vanda), requesting an opportunity for a hearing on the question of whether there are grounds for denying approval of Vanda's supplemental new drug application (sNDA) for Hetlioz (tasimelteon) capsules, 20 milligrams (mg) (sNDA 205677-004). The Director of the Center for Drug Evaluation and Research (Center Director) at the Food and Drug Administration (FDA or the Agency) is proposing to refuse to approve sNDA 205677-004 in its present form. This notice of opportunity for hearing (NOOH) summarizes the grounds for the Center Director's proposal and offers Vanda an opportunity to request a hearing on the matter.

In accordance with § 314.200(a)(2) (21 CFR 314.200(a)(2)), FDA intends to publish a version of this NOOH in the *Federal Register*. If you wish to withdraw your request for an NOOH before it publishes in the *Federal Register*, contact Kaetochi Okemgbo at kaetochi.okemgbo@fda.hhs.gov within 7 calendar days of the date of this letter.

I. PROPOSAL TO REFUSE TO APPROVE sNDA 205677-004

FDA approved new drug application (NDA) 205677 for Hetlioz (tasimelteon) for treatment of non-24-hour sleep-wake disorder on January 31, 2014. On October 16, 2018, Vanda submitted sNDA 205677-004 for Hetlioz (tasimelteon) capsule, 20 mg, as an efficacy supplement proposing to add a new indication for the treatment of jet lag disorder. Jet lag disorder is recognized by the International Classification of Sleep Disorders as a circadian rhythm sleep-wake disorder resulting from a mismatch between an individual's internal circadian clock and the local time, most frequently occurring in response to rapid travel across time zones.[1] Jet lag disorder is characterized by daytime fatigue, general malaise, memory difficulties, difficulty

[1] Sateia M. Jet lag disorder. International Classification of Sleep Disorders, 3rd ed., Illinois: American Academy of Sleep Medicine, 2014: 220–224.

staying alert, problems with concentration and decision-making, and gastrointestinal symptoms (e.g., constipation or diarrhea).[2] Although symptoms of jet lag are common, all of the following criteria must be met for a diagnosis of jet lag disorder:

A. There is a complaint of insomnia or excessive daytime sleepiness, accompanied by a reduction of total sleep time, associated with transmeridian jet travel across at least two time zones.
B. There is associated impairment of daytime function, general malaise, or somatic symptoms (e.g., gastrointestinal disturbance) within one to two days after travel.
C. The sleep disturbance is not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.[3]

Therefore, substantial evidence of efficacy of tasimelteon for the treatment of jet lag disorder would include sufficient evidence to show that the drug will have an effect on (a) insomnia or excessive daytime sleepiness, accompanied by a reduction of total sleep time, associated with transmeridian jet travel across at least two time zones; and (b) an associated impairment of daytime function, general malaise, or somatic symptoms within one to two days after travel, as those symptoms are described in the diagnostic criteria for a diagnosis of jet lag disorder.[4]

On August 16, 2019, the former Division of Psychiatry Products, Office of Drug Evaluation I (Division)[5] issued a complete response letter to Vanda under § 314.110(a) (21 CFR 314.110(a)) stating that sNDA 205677-004 could not be approved in its present form because the application does not provide substantial evidence of efficacy for tasimelteon for the treatment of jet lag disorder. The complete response letter described the specific deficiencies that led to this determination and, where possible, recommended ways that Vanda might remedy these deficiencies. The following is a summary of these deficiencies:

(1) There was inadequate justification for the primary endpoints for the pivotal clinical trials, Study VP-VEC-162-3101 (Study 3101) and VP-VEC-162-3107 (Study 3107). The primary endpoint in Study 3101 was latency to persistent sleep as measured by polysomnogram. Latency to persistent sleep is defined as the length of time that elapsed between lights out and the point of 10 minutes of solid (persistent) sleep. The primary endpoint in Study 3107 was total sleep time in the first two thirds of the night as measured by polysomnogram. Both latency to persistent sleep and total sleep time in the first two thirds of the night provide objective assessments of sleep on one night after a sleep advance cycle, but the supplement did not demonstrate how these primary endpoints assess the fundamental sleep disturbances associated with jet lag disorder.

---

[2] Id.
[3] Id. at 220.
[4] In contrast, when appropriate, clinically meaningful evidence that a drug has an effect on certain symptoms of a multi-symptom condition such as jet lag disorder may support an indication limited to those particular symptoms. Because Vanda did not propose such an indication in its sNDA, FDA did not consider whether the data show substantial evidence of effectiveness for a more limited use.
[5] This division is now the Division of Psychiatry within the Office of Neuroscience in the Office of New Drugs (OND) of the FDA's Center for Drug Evaluation and Research (CDER).

(2) The clinical trials did not prespecify type I error control for subjective endpoints. Additionally, there was insufficient support for the relevance of the exploratory subjective endpoints to the diagnosis of jet lag disorder. Subjective endpoints can be important to FDA's analysis of whether objective endpoints are clinically meaningful.[6]

(3) Studies 3101 and 3107 each focused on only one jet lag-related symptom and one direction of travel in healthy subjects. Other important aspects required for a diagnosis of the disorder (i.e. associated impairment of daytime function, general malaise, or somatic symptoms (e.g., gastrointestinal disturbance)), were not evaluated in these studies.

(4) Studies 3101 and 3107 did not include sufficient data, such as baseline polysomnograms, to determine each individual's reaction to the sleep advance within the protocol or the effects of the drug.

(5) There are inadequate data to demonstrate effectiveness of the drug when administered according to the dosing and administration information in the proposed labeling, i.e., for "one or more nights depending on the number of time zones traveled and the duration of the stay." Studies 3101 and 3107 were single dose studies that did not demonstrate the effectiveness of repeat dosing of tasimelteon for jet lag disorder.

(6) There are inadequate data to inform a recommendation on the optimal night to dose the drug, and whether dosing on multiple nights is more effective than dosing on a single night.

(7) There are inadequate data to characterize the use of the study drug with a sleep-delay cycle (westward travel as outgoing or incoming). The only data presented simulate eastward travel by sleep advance.

(8) The assessment of next-day functioning appears to be based on the driving study (Study VP-VEC-162-1201) and a subjective assessment of sleepiness, i.e., the Karolinska Sleepiness Scale. The Karolinska Sleepiness Scale is not fit-for-purpose for the proposed indication, and the driving study, which enrolled healthy subjects without sleep advance, does not assess the range of functional impairments associated with jet lag disorder. Thus, the assessment of next-day functioning is inadequate.

These deficiencies preclude a finding of substantial evidence of effectiveness for the treatment of jet lag disorder. The complete response letter stated that to address the deficiencies, Vanda should conduct at least one additional adequate and well-controlled study. FDA encouraged Vanda to meet with the Division to discuss and reach agreement on the design of a study or studies that would address the deficiencies. The complete response letter stated that Vanda is required either to resubmit the application, fully addressing all deficiencies listed in the letter, or

[6] Here, irrespective of subjective endpoints, the supplement failed to demonstrate that the objective endpoints used in Study 3101 and Study 3107 were clinically meaningful for the reasons discussed in deficiency (1).

take other actions available under § 314.110 (i.e., withdraw the application or request an opportunity for a hearing). Applicable regulations, including 21 CFR 10.75, also provide a mechanism for applicants to obtain formal review of one or more decisions reflected in a complete response letter (see FDA's guidance for industry and review staff *Formal Dispute Resolution: Sponsor Appeals Above the Division Level* (November 2017)).[7]

On January 3, 2020, Vanda submitted a formal dispute resolution request (FDRR) concerning the complete response letter. Dr. Billy Dunn, then-Acting Director of the Office of Neuroscience, denied the FDRR by correspondence dated August 4, 2020, based on his determination that the application did not provide substantial evidence of effectiveness for tasimelteon for treatment of jet lag disorder. In addition to the bases provided in the complete response letter, Dr. Dunn noted that only one study relied upon by Vanda to support the approval of the supplement, Study VP-VEC-162-2102 (Study 2102), evaluated individuals with a history of jet lag disorder. The other studies were conducted in healthy individuals with no evidence of experiencing jet lag disorder. Dr. Dunn evaluated Study 2102 and the other study submitted by Vanda as supportive evidence, Study VP-VEC-162-2101 (Study 2101), and concluded that they were small phase 2 studies with design and methodological limitations. He also noted that jet lag disorder presents a series of complaints and symptoms beyond sleep disturbances and daytime sleepiness, and the sleep disturbances of jet lag disorder typically persist over several days. Because Studies 3101 and 3107 lacked robust assessment of important additional endpoints that might have been able to address these characteristics of jet lag disorder, Dr. Dunn concluded the data submitted do not support a finding of substantial evidence of effectiveness of tasimelteon for treatment of jet lag disorder. He also denied Vanda's requests (1) for the Division to consider a narrower indication for treatment of insomnia and daytime sleepiness in jet lag disorder, because that request was raised after the complete response letter and therefore was outside the scope of the dispute resolution process; and (2) for FDA to convene an Advisory Committee to answer the question of whether the supplement had provided substantial evidence of effectiveness, because he found no scientific questions that would have been appropriate for consideration by an Advisory Committee.

Vanda submitted another FDRR on September 2, 2020, for review of the Office of Neuroscience denial. Dr. Mary Thanh Hai, then-Acting Deputy Director of the Office of New Drugs, denied the second FDRR on behalf of OND by correspondence dated October 21, 2020, based on her determination that the application did not provide substantial evidence of effectiveness for tasimelteon for treatment of jet lag disorder. Dr. Thanh Hai noted that the regulatory history of this development program revealed very clear advice from FDA on the study population and recommended endpoints for clinical trials to support a marketing application for the treatment of jet lag disorder. She also agreed with Dr. Dunn's denial of Vanda's requests regarding a narrower indication and convening an Advisory Committee.

On July 1, 2022, Vanda submitted a request for an opportunity for a hearing under § 314.110(b)(3) on whether there are grounds under section 505(d) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(d)) for denying approval of sNDA 205677-004.

[7] Available at https://www.fda.gov/media/126910/download. FDA updates guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

II. NOTICE OF OPPORTUNITY FOR A HEARING

For the reasons stated above and as explained in further detail in the August 16, 2019, complete response letter and the August 4, 2020, and October 21, 2020, FDRR denials, notice is given to Vanda and all other interested persons that the Center Director proposes to issue an order refusing to approve sNDA 205677-004 on the grounds that the application fails to meet the criteria for approval under section 505(d) of the FD&C Act because there is a lack of substantial evidence that the drug is effective for treatment of jet lag disorder (section 505(d)(5) of the FD&C Act).[8]

Vanda may request a hearing before the Commissioner of Food and Drugs (the Commissioner) on the Center Director's proposal to refuse to approve sNDA 205677-004. Pursuant to § 314.200(c)(1), if Vanda decides to seek a hearing, it must file: (1) a written notice of participation and request for a hearing on or before 30 days after the notice is published in the *Federal Register*, and (2) the studies, data, information, and analyses relied upon to justify a hearing, as specified in § 314.200, on or before 60 days after the date the notice is published in the *Federal Register*.

As stated in § 314.200(g), a request for a hearing may not rest upon mere allegations or denials but must present specific facts showing that there is a genuine and substantial issue of fact that requires a hearing to resolve. We note in this regard that because CDER proposes to refuse to approve sNDA 205677-004 based on the multiple deficiencies summarized above, any hearing request from Vanda must address all of those deficiencies. Failure to request a hearing within the time provided and in the manner required by § 314.200 constitutes a waiver of the opportunity to request a hearing. If a hearing request is not properly submitted, FDA will issue a notice refusing to approve sNDA 205677-004.

The Commissioner will grant a hearing if there exists a genuine and substantial issue of fact or if the Commissioner concludes that a hearing would otherwise be in the public interest (§ 314.200(g)(6)). If a hearing is granted, it will be conducted according to the procedures provided in 21 CFR parts 10 through 16 (21 CFR 314.201).

You may submit hearing requests, documents in support of the hearing, and any other comments as follows. Please note that late, untimely filed documents will not be considered. Electronic requests for a hearing must be submitted on or before 30 days after the date the notice is published in the *Federal Register*; electronic documents in support of the hearing and any other comments must be submitted on or before 60 days after the date the notice is published in the *Federal Register*. The https://www.regulations.gov electronic filing system will accept hearing requests until 11:59 p.m. Eastern Time at the end of the day that is 30 days after the date the notice is published in the *Federal Register*, and will accept documents in support of the hearing

[8] Section 505(d)(5) of the FD&C Act provides that FDA shall refuse to approve an NDA supplement if "there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof[.]" For the reasons explained in this notice, CDER has concluded that the data and information submitted in the supplement do not show that the drug is effective for the proposed conditions of use.

and any other comments until 11:59 p.m. Eastern Time at the end of the day that is 60 days after the date the notice is published in the *Federal Register*. Documents received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are received on or before these dates.

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to https://www.regulations.gov will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on https://www.regulations.gov.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the docket number for "Proposal To Refuse To Approve a New Drug Application Supplement for Hetlioz (tasimelteon); Opportunity for a Hearing." This number can be found in the version of this notice that will publish in the *Federal Register*. Received comments, those filed in a timely manner, will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at https://www.regulations.gov or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The

second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on https://www.regulations.gov. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: https://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to https://www.regulations.gov and insert the docket number, which can be found in the version of this notice that will publish in the *Federal Register*, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

Except for data and information prohibited from public disclosure under 21 U.S.C. 331(j) or 18 U.S.C. 1905, submissions may be seen in the Dockets Management Staff Office between 9 a.m. and 4 p.m., Monday through Friday, and on the internet at https://www.regulations.gov. This notice of opportunity for a hearing is issued under section 505(c)(1)(B) of the FD&C Act and §§ 314.110(b)(3) and 314.200 in FDA regulations. If you have questions, please contact Kaetochi Okemgbo at kaetochi.okemgbo@fda.hhs.gov.

Sincerely,

Douglas C. Throckmorton -S

Digitally signed by Douglas C. Throckmorton -S
Date: 2022.08.25 22:14:49 -04'00'

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research