information/search-fda-guidance-documents. Persons unable to download an electronic copy of ''Laser-Assisted In Situ Keratomileusis (LASIK) Lasers—Patient Labeling Recommendations'' may send an email request to *CDRH-Guidance@fda.hhs.gov* to receive an electronic copy of the document. Please use the document number 16053 and complete title to identify the guidance you are requesting.

Dated: October 4, 2022.

Lauren K. Roth,

Associate Commissioner for Policy.

[FR Doc. 2022–21971 Filed 10–7–22; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2022–N–2390]

Proposal To Refuse To Approve a New Drug Application Supplement for HETLIOZ (Tasimelteon); Opportunity for a Hearing

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Director of the Center for Drug Evaluation and Research (Center Director) at the Food and Drug Administration (FDA or Agency) is proposing to refuse to approve a supplemental new drug application (sNDA) submitted by Vanda Pharmaceuticals, Inc. (Vanda), for HETLIOZ (tasimelteon) capsules, 20 milligrams (mg), in its present form. This notice summarizes the grounds for the Center Director's proposal and offers Vanda an opportunity to request a hearing on the matter.

DATES: Either electronic or written requests for a hearing must be submitted by November 10, 2022; submit data, information, and analyses in support of the hearing and any other comments by December 12, 2022.

ADDRESSES: You may submit hearing requests, documents in support of the hearing, and any other comments as follows. Please note that late, untimely filed requests and documents will not be considered. The *https://www.regulations.gov* electronic filing system will accept hearing requests until 11:59 p.m. Eastern Time at the end of November 10, 2022, and will accept documents in support of the hearing and any other comments until 11:59 p.m. Eastern Time at the end of December 12, 2022. 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 No. FDA–2022–N–2390 for ''Proposal To Refuse To Approve a New Drug Application Supplement for HETLIOZ (Tasimelteon); Opportunity for a Hearing.'' Received comments, those filed in a timely manner (see **ADDRESSES**), 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.govinfo.gov/content/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, found in brackets in the heading of this document, 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.

FOR FURTHER INFORMATION CONTACT: Kaetochi Okemgbo, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6224, Silver Spring, MD 20993, 301–796–1546, *Kaetochi.Okemgbo@fda.hhs.gov.*

SUPPLEMENTARY INFORMATION:

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 (Ref. 1). Jet lag disorder is characterized by daytime fatigue, general malaise, memory difficulties, difficulty staying alert, problems with concentration and decision-making, and gastrointestinal symptoms (*e.g.,* constipation or diarrhea) (Ref. 1). Although symptoms of jet lag are common, all of the following criteria must be met for a diagnosis of jet lag disorder:

(1) 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.

(2) There is associated impairment of daytime function, general malaise, or somatic symptoms (*e.g.,* gastrointestinal disturbance) within 1 to 2 days after travel.

(3) The sleep disturbance is not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder (Ref. 1).

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: (1) 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 (2) an associated impairment of daytime function, general malaise, or somatic symptoms within 1 to 2 days after travel, as those symptoms are described in the diagnostic criteria for a diagnosis of jet lag disorder.[1]

On August 16, 2019, the former Division of Psychiatry Products, Office of Drug Evaluation I (Division),[2] 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 1 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) 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.[3]

(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 1 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 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 Ref. 2).

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

[1] In contrast, when appropriate, clinically meaningful evidence that a drug has an effect on certain symptoms of a multisymptom 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.

[2] This division is now the Division of Psychiatry within the Office of Neuroscience in the Office of New Drugs (OND) of FDA's Center for Drug Evaluation and Research (CDER).

[3] 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).

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, 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 (OND), 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.

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).[4]

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) (21 CFR 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).

Paper submissions under this notice of opportunity for a hearing should be filed in one copy, except for those submitted as ''Confidential Submissions'' (see ''Written/Paper Submissions'' and ''Instructions'' in **ADDRESSES**). 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 is issued under section 505(c)(1)(B) of the FD&C Act and §§ 314.110(b)(3) and 314.200.

III. References

The following references marked with an asterisk (*) are on display at the Dockets Management Staff (see **ADDRESSES**) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they also are available electronically at *https://www.regulations.gov.* References without asterisks are not on public display at *https://www.regulations.gov* because they have copyright restriction. Some may be available at the website address, if listed. References without asterisks are available for viewing only at the Dockets Management Staff. FDA has verified the website addresses, as of the date this document publishes in the **Federal Register**, but websites are subject to change over time.

1. Sateia, M., ''Jet Lag Disorder,'' *International Classification of Sleep Disorders,* 3rd ed., Illinois: American Academy of Sleep Medicine, pp. 220–224, 2014.

* 2. FDA Guidance for Industry and Review Staff, ''Formal Dispute Resolution: Sponsor Appeals Above the Division Level,'' November 2017, (available at *https://www.fda.gov/media/126910/download*), accessed August 30, 2022.

Dated: October 4, 2022.

Jacqueline Corrigan-Curay,

Principal Deputy Center Director, Center for Drug Evaluation and Research.

[FR Doc. 2022–21932 Filed 10–7–22; 8:45 am]

BILLING CODE 4164–01–P

[4] 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.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Meeting of the Presidential Advisory Council on HIV/AIDS

AGENCY: Department of Health and Human Services, Office of the Secretary, Office of the Assistant Secretary for Health.