4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2022-N-2390]

Vanda Pharmaceuticals, Inc.; Grant of Hearing Request Regarding a Proposal to Refuse to Approve a Supplemental New Drug Application for HETLIOZ (Tasimelteon)

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA or the Agency) is announcing a formal evidentiary public hearing on the proposal to refuse to approve the supplemental new drug application (sNDA) 205677-004, submitted by Vanda Pharmaceuticals Inc. (Vanda) for HETLIOZ (tasimelteon) capsules, 20 milligrams (mg), to treat jet lag disorder. On October 11, 2022, the Director of FDA's Center for Drug Evaluation and Research (CDER) published a notice of opportunity for hearing on a proposal to refuse to approve sNDA 205677-004. Vanda submitted a timely request for hearing on that proposal. This notice of hearing provides factual and legal information concerning CDER's proposal to refuse to approve sNDA 205677-004 and identifies the factual issues that will be the subject of the evidentiary hearing.

DATES: A prehearing conference will be held on [INSERT DATE 45 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*], beginning at 10 a.m. Eastern Daylight Time. Any person wishing to participate in this hearing shall submit a written notice of participation by [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Disclosure of data and information as required by 21 CFR 12.85(b) must be made by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: You may submit a written notice of participation and data and information

required under 21 CFR 12.85 by either of the following methods:

Electronic Submissions

Submit electronically in the following way:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting information. Information submitted electronically, including attachments, to https://www.regulations.gov will be posted to the docket unchanged. Because your information will be made public, you are solely responsible for ensuring that your information 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 information, that information will be posted on https://www.regulations.gov.
- If you want to submit any information with confidential information that you do not wish to be made available to the public, submit the information as a written/paper submission and in the manner detailed (see "Written/Paper Submission" 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 submissions sent to the Dockets Management Staff, FDA will post your submission, as well as any attachments, except for the 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 "Vanda Pharmaceuticals, Inc.; Grant of Hearing Request Regarding a Proposal to Refuse to

Approve a Supplemental New Drug Application for HETLIOZ (Tasimelteon)." Received submissions 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 make a submission with confidential information that you do not wish to be made publicly available, send your submissions 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 any decisions on this matter. 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 submissions 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 information 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.

DAB E-File: Beginning on the date of this notice, parties to the hearing and participants

should make submissions related to this hearing to Departmental Appeals Board electronic filing system (DAB E-File) at: https://dab.efile.hhs.gov/, except insofar as they are submitting initial notices of participation or disclosing data and information pursuant to 21 CFR 12.85. Submissions to DAB E-File by parties and participants must conform to the Case Development Order (Ref. 1) and other orders issued by the presiding officer. Although certain regulations in 21 CFR part 12 require submissions for hearing matters to be filed with the Dockets Management Staff, FDA will deem a submission made by a party or participant to DAB E-File that conforms to the presiding officer's orders and this notice to satisfy any such applicable requirement and will make the submission available on the docket (see "Docket"). Non-parties and non-participants should continue to make submissions through Dockets Management Staff, as detailed in "Electronic Submissions" and "Written/Paper Submissions." The record will continue to be accessible at https://www.regulations.gov or through the Dockets Management Staff, between 9 a.m. and 4 p.m., Monday through Friday.

FOR FURTHER INFORMATION CONTACT: Karen Fikes, Office of Scientific Integrity, Food and Drug Administration, 10903 New Hampshire Avenue, Bldg. 1, Rm. 4218, Silver Spring, MD 20993, 301-796-9603.

SUPPLEMENTARY INFORMATION:

I. Background

On January 31, 2014, FDA approved new drug application 205677 for HETLIOZ (tasimelteon) for treatment of non-24-hour sleep-wake disorder, a circadian-rhythm disorder that disproportionately afflicts individuals who are totally blind. On October 16, 2018, Vanda submitted sNDA 205677-004, which seeks approval of HETLIOZ (tasimelteon) to treat jet lag disorder. On August 16, 2019, in accordance with 21 CFR 314.10(a), CDER issued a complete response letter notifying Vanda of its determination that sNDA 205677-004 is not approvable in its current form.

On June 30, 2022, Vanda requested an opportunity for a hearing under 21 CFR

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 for the treatment of jet lag disorder. On August 29, 2022, by registered mail, CDER notified Vanda of an opportunity for hearing on a proposal to refuse to approve sNDA 205677-004. On October 11, 2022, FDA published a notice of opportunity for hearing on the proposal to refuse approval (NOOH) in the *Federal Register* (87 FR 61337). On November 10, 2022, Vanda filed a notice of participation and requested a hearing and, on December 12, 2022, submitted information, data, and analyses in support of that request. On June 12, 2023, CDER submitted a proposed order denying Vanda's request for a hearing and refusing to approve the sNDA. On August 11, 2023, Vanda responded to CDER's proposed order. On September 8, 2023, CDER submitted a reply, which included a revised proposed order.

After considering the parties' submissions, FDA issued a decision on March 1, 2024, denying Vanda's request for a hearing and refusing to approve sNDA 205677-004. The United States Court of Appeals for the District of Columbia Circuit subsequently set aside FDA's denial of Vanda's requested hearing and remanded the matter for further proceedings consistent with its opinion (*Vanda Pharms., Inc. v. FDA*, 150 F.4th 563 (D.C. Cir. 2025)). At the request of CDER and Vanda, FDA's Office of the Commissioner later held the matter in abeyance until February 6, 2026. By letter dated March 2, 2026, the Office of the Commissioner granted Vanda's hearing request.

II. Presiding Officer

The Office of the Commissioner hereby appoints Administrative Law Judge Keith W. Sickendick, at the Department of Health and Human Services' Departmental Appeals Board, to serve as presiding officer under 21 CFR 12.60 and to conduct the hearing in accordance with authority prescribed in 21 CFR 12.70.

III. Statutory Grounds for the Hearing

In the NOOH published on October 11, 2022, CDER proposed to refuse to approve

sNDA 205677-004 under section 505(d)(5) of the FD&C Act (21 U.S.C. 355(d)(5)) because the application lacks "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."

Vanda has the burden of proof in this proceeding. See 21 CFR 12.87(d) (putting the burden of proof on the hearing participant requesting approval of a drug application).

IV. Factual Issues for the Hearing

The central factual issue for the hearing is whether Vanda has provided substantial evidence that HETLIOZ (tasimelteon) is effective for treatment of jet lag disorder. As noted by CDER, the decision by the Court of Appeals for the D.C. Circuit included two key holdings that limit the factual scope of the hearing with respect to that central issue. First, the Court upheld FDA's previous conclusion that the question for any hearing on this matter would be whether there is substantial evidence of effectiveness for the indication in the sNDA's proposed labeling—as opposed to any narrower or modified indication that Vanda might now propose, such as treatment of insomnia related to jet lag disorder (*Vanda*, 150 F.4th at 578-79). Second, the Court held that FDA "reasonably determined" that approval of the proposed indication for HETLIOZ (tasimelteon)—treatment of jet lag disorder—requires establishing an effect on both sleep and next-day impairment (Id. at 577 (finding that Vanda has an "obligation to prove [effectiveness regarding] the second symptom of jet lag, next-day impairment" and that it is not adequate to "show only that tasimelteon can remedy sleep-disturbance symptoms")).

On May 15, 2026, pursuant to 21 CFR 12.85(a)(4), CDER submitted to the Dockets Management Staff, *inter alia*, a narrative position statement that, consistent with the deficiencies listed in the NOOH and the decision by the Court of Appeals for the D.C. Circuit, identifies eight specific issues for the hearing:

1. Whether Vanda failed to demonstrate that the primary endpoints in Studies 2102, 3101, and 3107 were appropriate to assess effectiveness of tasimelteon for the treatment of jet lag disorder.
2. Whether Vanda failed to demonstrate that the secondary endpoints in Studies

2102, 3101, and 3107 were appropriate to assess effectiveness of tasimelteon for the treatment of jet lag disorder.

3. Whether the sNDA provides sufficient evidence of an effect on symptoms that are integral to jet lag disorder, such that effectiveness could be established for the proposed indication—treatment of jet lag disorder.
4. Whether Vanda's analysis of the secondary endpoints in Studies 2102, 3101, and 3107 lacks the statistical rigor to reliably support conclusions about the effectiveness of tasimelteon for the treatment of jet lag disorder.
5. Whether the interpretability of Studies 3101 and 3107 is impaired by the failure to include sufficient data (e.g., via collecting baseline polysomnograms or other methods) to determine whether subjects experienced a sleep disturbance after undergoing a phase advance in the laboratory setting.
6. Whether Vanda failed to provide adequate data to demonstrate effectiveness of the drug when administered according to the dosing and administration information in the proposed labeling.
7. Whether Vanda's assessment of next-day functioning was inadequate.
8. Whether Vanda's application lacks adequate data to characterize the use of tasimelteon to treat jet lag disorder associated with westward travel (CDER's Narrative Position Statement, 5-6).

The presiding officer may further revise the factual issues for the hearing under 21 CFR 12.35(b).

V. Parties to the Hearing

The parties to the hearing will be FDA's CDER and Vanda. Other interested persons shall be permitted to participate as nonparty participants as provided by 21 CFR 12.45 and 12.89.

VI. Disclosure of Information by CDER, Vanda, and Other Hearing Participants

In accordance with 21 CFR 12.85(a), CDER has filed with the Dockets Management Staff a narrative statement setting forth its position on the issues of the hearing and a summary of the types of evidence to be introduced in support of its position in the hearing, together with copies of data and information contained in the Center's files that relate to the issues to be resolved at the hearing. Hearing participants other than CDER, including Vanda, shall disclose data and information and submit their narrative statements pursuant to 21 CFR 12.85(b) to the Dockets Management Staff (see "Addresses") on or before [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*], or within another period of time set by the presiding officer. Interested persons may also examine the data on the drug subject to this hearing notice (with the exception of any data identified as confidential pursuant to the

provisions of 21 CFR 10.20(j)) via https://www.regulations.gov or at the Dockets Management Staff, between 9 a.m. and 4 p.m., Monday through Friday (see "Addresses").

VII. Prehearing Conference

The prehearing conference will be held on [INSERT DATE 45 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*], beginning at 10:00 a.m. Eastern Daylight Time, by videoconference with instructions to be provided. The hearing will be held on a date to be set at the prehearing conference. Written notices of participation shall be filed with the Dockets Management Staff no later than [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. All participants are required both to attend the prehearing conference and to be prepared to comply with the provisions of 21 CFR 12.92.

VIII. Conclusion

In accordance with the foregoing, under section 505 the FD&C Act (21 U.S.C. 355) and under authority delegated to me, I order that a formal evidentiary public hearing be held on the issues set out in this notice. The hearing will be open to the public by visiting the HHS Live Streaming page at www.hhs.gov/live. A direct link for the hearing will be visible on the HHS Live Streaming page once a hearing date has been set by the presiding officer after the prehearing conference. Interested persons are encouraged to monitor the docket for any updated links for public access.

IX. References

1. U.S. Department of Health and Human Services, Departmental Appeals Board, Civil Remedies Division, Vanda Pharmaceuticals, Inc. Supplemental New Drug Application for Hetlioz (Tasimelteon), C-26-457, Case Development Order [Civil Remedies Division Procedures, March 28, 2016], [INSERT DATE DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

Grace R. Graham,

Deputy Commissioner for Policy, Legislation, and International Affairs.

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