



NDA 220358

NDA APPROVAL

Vanda Pharmaceuticals, Inc.
Attention: Gunter Birznieks
Senior Vice President, Business Development
2200 Pennsylvania Ave NW
Suite 300
Washington, DC 20037

Dear Gunter Birznieks:

Please refer to your new drug application (NDA) received February 21, 2025, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Bysanti (milsaperidone) tablets.

This NDA provides for the use of Bysanti (milsaperidone) tablets for the following indications:

- Treatment of schizophrenia in adults
- Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.¹ Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information) as well as annual reportable changes not included in the

¹ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.²

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *SPL Standard for Content of Labeling Technical Qs & As*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labeling for approved NDA 220358.**” Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Bysanti (milsaperidone) tablets shall be number of months specified in table below from the date of manufacture when stored at 20°C to 25°C.

Strength	50 cc HDPE bottle	23 cc HDPE bottle	Blister pack
1 mg	36 months	3 months	24 months
2 mg	24 months	Not applicable	24 months
4 mg	24 months	Not applicable	24 months
6 mg	24 months	24 months	24 months
8 mg	24 months	24 months	24 months
10 mg	24 months	Not applicable	Not applicable
12 mg	24 months	Not applicable	Not applicable

ADVISORY COMMITTEE

Your application for Bysanti was not referred to an FDA advisory committee because the application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of a disease.

² We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement in schizophrenia for ages 0 to less than 13 years because necessary studies are impossible or highly impracticable due to the very low incidence of schizophrenia diagnosed prior to age 13.

We are waiving the pediatric study requirement in bipolar I disorder for ages 0 to less than 10 years because necessary studies are impossible or highly impracticable due to very low incidence of bipolar I disorder diagnosed prior to age 10.

We are deferring submission of your pediatric studies in schizophrenia (ages 13 to less than 18 years) and in bipolar I disorder (ages 10 to less than 18 year) for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the FDCA. These required studies are listed below.

4968-1 Conduct an open-label study to assess the long-term safety in patients aged 10 to less than 13 years with bipolar I disorder.

Final Protocol Submission: 07/2025

Study Completion: 07/2030

Final Report Submission: 01/2031

4968-2 A long-term safety study in pediatric patients 13 to 17 years of age.

Final Protocol Submission: 06/2021

Study Completion: 06/2026

Final Report Submission: 11/2026

4968-3 Conduct a GLP juvenile animal study to assess the toxicology in juvenile rats to support clinical trials in the intended pediatric population ages 10 to less than 13 years.

Final Protocol Submission: 04/2024

Study Completion: 01/2026

Final Report Submission: 07/2026

- 4968-4 Conduct an open-label, multiple oral dose study to demonstrate the safety, tolerability, and pharmacokinetics in patients ages 10 to less than 13 years with manic or mixed episode associated with bipolar I disorder.

Final Protocol Submission: 07/2025

Study Completion: 07/2026

Final Report Submission: 01/2027

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.³

Submit the protocol(s) to your IND 153819, with a cross-reference letter to this NDA. Reports of these required pediatric postmarketing studies must be submitted as an NDA or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk associated with the presence of milsaperidone in human breast milk.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following study:

³ See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019)*.

<https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

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- 4968-5 Conduct a lactation study in lactating women who have received therapeutic doses of miltaperidone to assess concentrations of miltaperidone in breast milk using a validated assay. Assess the effects on the breastfed infant if available, based on study population.

The timetable you submitted on February 9, 2026, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 02/2027

Study Completion: 02/2029

Final Report Submission: 08/2029

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.⁴

Submit clinical protocol(s) to your IND 153819 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

REQUIRED POSTMARKETING PROTOCOL UNDER 505(o) , REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o), REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o).

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B(a)(1) of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B(a)(1) and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

⁴ See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019)*.

<https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

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PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs*.⁵

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.⁶ Information and Instructions for completing the form can be found at FDA.gov.⁷

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

POST APPROVAL FEEDBACK MEETING

New molecular entities qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standards for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise

⁵ For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/media/128163/download>.

⁶ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

⁷ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

official USP monographs. More information on the USP-NF is available on USP's website.⁸

If you have any questions, contact Shin-Ye (Sandy) Chang, Senior Project Manager, at shinye.chang@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Teresa Buracchio, MD,
Director
Office of Neuroscience
Office of New Drugs
Center for Drug Evaluation and
Research

ENCLOSURE(S):

- Content of Labeling
 - Prescribing Information
- Carton and Container Labeling

⁸ <https://www.uspnf.com/>

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TERESA J BURACCHIO
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