NDA 220152

NDA APPROVAL

Vanda Pharmaceuticals Inc.
Attention: Vasilios Polymeropoulos, M.D.
Vice President, Medical Director
2200 Pennsylvania Ave NW
Suite 300 E
Washington, D.C. 20037

Dear Dr. Polymeropoulos:

Please refer to your new drug application (NDA) received December 30, 2024, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Nereus (tradipitant) capsules.

This NDA provides for the use of Nereus (tradipitant) capsules for prevention of vomiting induced by motion 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 with minor editorial revisions listed below and reflected in the enclosed labeling.

- Removed (b) (4) information in Section 17 PATIENT COUNSELING INFORMATION for consistency with Section 8.1 *Pregnancy*.

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 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]

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[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.

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 carton and container labeling submitted on December 29, 2025, 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 220152**." 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 Nereus (tradipitant) capsules shall be 48 months from the date of manufacture when stored at 20°C to 25°C.

ADVISORY COMMITTEE

Your application for Nereus was not referred to an FDA advisory committee because the application did not raise questions regarding the benefit-risk analysis that warranted convening an advisory committee.

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 for ages 0 to less than 2 years because necessary studies are impossible or highly impracticable. This is because vomiting induced by motion is not common in infants and children under two years of age.

We are deferring submission of your pediatric studies for ages 2 to less than 18 years 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 Federal Food, Drug, and Cosmetic Act 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 Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

4946-1 Conduct a clinical trial to evaluate the pharmacokinetics and safety of an age-appropriate formulation of tradipitant in pediatric patients 2 to < 18 years of age with a history of motion sickness.

Final Protocol Submission: 06/2026
Study Completion: 12/2026
Final Report Submission: 03/2027

4946-2 Conduct a randomized, double-blind, placebo-controlled clinical trial to evaluate the safety and efficacy of tradipitant in pediatric patients 2 to < 18 years of age with a history of motion sickness.

Final Protocol Submission: 01/2027
Study Completion: 01/2028
Final Report Submission: 06/2028

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 141315, 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 Federal Food, Drug, and Cosmetic Act (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 identify an unexpected serious risk of adverse maternal, fetal, and infant outcomes resulting from the use of tradipitant capsules during pregnancy, or to identify an unexpected serious

[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.

risk of the potential presence of tradipitant in human breast milk resulting in effects on the breastfed infant.

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 these serious risk(s).

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

4946-3 Collect data from a prospective pregnancy exposure registry, preferably a disease-based multiproduct pregnancy registry, using a cohort analysis that compares the maternal, fetal, and infant outcomes of women exposed to tradipitant regardless of indication during pregnancy with unexposed comparator population(s) in a timely manner. Align the study protocol with protocol(s) outside the U.S. to reach the target sample size. The registry should identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortion, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes described in the protocol will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

The timetable you submitted on December 22, 2025, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	06/2026
Final Protocol Submission:	12/2026
Study Completion:	12/2036
Final Report Submission:	06/2037

4946-4 Conduct a retrospective pregnancy cohort study using claims or electronic health record data with medical chart validation that is adequately powered to assess major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births in individuals exposed to tradipitant during pregnancy compared to appropriate comparator population(s).

The timetable you submitted on December 22, 2025, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 06/2026
Final Protocol Submission: 12/2026
Study Completion: 12/2032
Final Report Submission: 12/2033

4946-5 Perform a lactation study (milk only or mother-infant pair study) in lactating women who have received tradipitant to measure concentrations of tradipitant and its major metabolites 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 December 22, 2025, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 06/2026
Final Protocol Submission: 12/2026
Study Completion: 12/2028
Final Report Submission: 06/2029

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 141315 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).**

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312.

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.

[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.

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.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4946-6 Conduct a clinical pharmacology study to evaluate the effects of hepatic impairment on the pharmacokinetics of tradipitant and its major metabolites compared to subjects with normal hepatic function.

The timetable you submitted on December 22, 2025, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 06/2026
Final Protocol Submission: 12/2026
Study Completion: 12/2027
Final Report Submission: 06/2028

4946-7 Conduct a clinical pharmacology study to evaluate the effects of severe renal impairment on the pharmacokinetics of tradipitant and its major metabolites compared to subjects with normal renal function

The timetable you submitted on December 22, 2025, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 06/2026
Final Protocol Submission: 12/2026
Study Completion: 12/2027
Final Report Submission: 06/2028

4946-8 Conduct in vitro assessment(s) to evaluate the contribution of all major CYP enzymes to the overall metabolism of tradipitant and its active metabolites, and to assess the relative contribution of specific CYP enzymes to tradipitant metabolism. The in vitro study results will determine the need for subsequent clinical drug-drug interaction study(ies).

The timetable you submitted on December 22, 2025, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 06/2026
Final Protocol Submission: 10/2026
Study Completion: 04/2027
Final Report Submission: 10/2027

4946-9 Conduct a study to evaluate the effects of tradipitant on QT intervals in the fed state.

Final Protocol Submission: 02/2026
Trial Completion: 02/2027
Final Report Submission: 08/2027

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 141315 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," **or** "**Postmarketing Commitment Correspondence**."

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]

[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

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

If you have any questions, contact Mary Chung, Regulatory Project Manager, at (301) 796-0260 or Mary.Chung@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Nikolay Nikolov, M.D.
Director
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
    - Prescribing Information

[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/

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