DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Christos Polymeropoulos
Senior Vice President, Medical Director
Vanda Pharmaceuticals, Inc.
2200 Pennsylvania Avenue NW, Suite 300E
Washington DC 20037

RE: NDA 220152
NEREUS™ (tradipitant) capsule, for oral use
MA 15

Dear Christos Polymeropoulos:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed the promotional communication, a direct-to-consumer (DTC) broadcast advertisement (NER0009) (TV ad) for NEREUS™ (tradipitant) capsule, for oral use (Nereus) submitted by Vanda Pharmaceuticals, Inc. (Vanda) under cover of Form FDA 2253. The FDA Bad Ad Program also received complaints regarding this TV ad for Nereus. The TV ad makes false or misleading representations about the safety and effectiveness of Nereus. In addition, the TV ad does not present the major statement relating to side effects and contraindications (major statement) in a clear, conspicuous, and neutral manner. Thus, the TV ad misbrands Nereus within the meaning of the Federal Food, Drug, and Cosmetic Act (FD&C) and makes its distribution a violation of the Act. 21 U.S.C. 352(n); 321(n); 331(a); 21 CFR 202.1(e)(1)(ii)(C), (e)(1)(ii)(E), (e)(5). These violations are concerning from a public health perspective because the promotional communication creates a misleading impression regarding the safety and effectiveness of Nereus.

The TV ad presents the main character, a man, aggressively driving a white convertible in an intense car chase with another black vehicle. The voiceover (VO) claims, “For the first time in over 40 years, Nereus is approved for the prevention of vomiting induced by motion in adults.” The visuals in the TV ad emphasize the speed at which the man is driving with depictions of intense skidding, swerving, and the car becoming airborne. Eventually the two cars become unexpectedly separated, the convertible stops on a bridge, and the man sees the other driver and passenger transfer to a waiting motorboat. The man subsequently reveals a hidden compartment in his convertible, removes and opens a small box, and swallows a white and black capsule, consistent with the dosage form and coloration of Nereus. In the context of a TV ad for the product, the impression created by this unidentified capsule is that the capsule is a dose of Nereus. The man then appears satisfied and confident with his decision to take the capsule, apparent from his facial expression. He then climbs down a ladder, jumps in a motorboat, and speeds off, driving the motorboat through a turbulent body of water.

The TV ad creates a misleading impression regarding the safety and effectiveness of Nereus for multiple reasons. First, in conjunction with initial claims of efficacy, the TV ad depicts the main character engaged in driving a car in a manner that could lead to vomiting induced by motion. He is then seen taking a drug capsule, presumably Nereus, immediately prior to jumping into a boat and speeding off. This creates the misleading impression that Nereus can be used either after or immediately prior to engaging in activities that could lead to vomiting induced by motion, when this has not been demonstrated. According to the INDICATIONS AND USAGE section of the FDA-approved full Prescribing Information (PI) (emphasis added), "NEREUS is indicated for the **prevention** of vomiting induced by motion in adults." Additionally, according to the CLINICAL STUDIES section of the PI, "The efficacy of NEREUS for the treatment of established nausea and vomiting was not evaluated in the studies." We are not aware of data that would support suggestions that the drug can be used to treat vomiting that has already been induced by existing motion.

Furthermore, the TV ad is misleading in respect to timing of administration, as the man is shown taking the capsule immediately prior to jumping on the boat, suggesting instant efficacy. However, according to the DOSAGE AND ADMINISTRATION section of the PI, Nereus is recommended to be administered "approximately 60 minutes before an event expected to cause vomiting induced by motion." Additionally, in the studies that supported approval, as described in the CLINICAL STUDIES section of the PI, subjects received the drug approximately 60 minutes prior to a boat trip. We are not aware of data that would support suggestions that the drug provides immediate efficacy as suggested in the TV ad.

Second, the TV ad is misleading because it minimizes the risks associated with Nereus by presenting visuals directly at odds with the information provided in the WARNINGS AND PRECAUTIONS section of the PI. Specifically, the driving style depicted requires acute mental awareness and an advanced state of alertness necessary to navigate the car and motorboat chase. However, according to the WARNINGS AND PRECAUTIONS section of the PI, "NEREUS may impair the mental and/or physical abilities required for driving a motor vehicle or operating heavy machinery." In clinical trials, somnolence and fatigue were reported in subjects who took a single dose of Nereus. This is especially concerning considering the manner in which the TV ad depicts motor vehicles being driven which creates the misleading impression that the impairment of mental and/or physical abilities is minimal and treatment with Nereus will not inhibit one's ability to drive, even at extreme levels. We note the TV ad includes the claim in the VO and SUPER, "Nereus may impair abilities required for driving a motor vehicle or operating heavy machinery." However, this is not sufficient to mitigate this misleading impression regarding the drug product's effects on the ability to drive or operate machinery, particularly given that the disclaimer occurs simultaneously with the depictions of extreme driving.

Human prescription DTC drug advertisements in television or radio format that state the name of the drug and its conditions of use must present the major statement in a clear, conspicuous, and neutral manner. Standards for achieving a clear, conspicuous and neutral manner of presentation are specified in FDA regulations. To satisfy the requirement for a clear, conspicuous, and neutral manner of presentation, among other things, the major statement in advertisements in television format must be presented concurrently using both

audio and text (dual modality) and the presentation must not include audio or visual elements alone or in combination that are likely to interfere with comprehension of the major statement.

The major statement in this advertisement is presented through audio and on-screen SUPERs over a duration of about 31 seconds (0:19-0:50), during which the verbatim complete transcript or verbatim key terms or phrases from the corresponding audio do not appear in dual modality, along with presentations where there is information in the SUPERs that is not from the corresponding audio. For example, starting at 0:41, the VO states, "Strong CYP3A4 inhibitors may increase Nereus levels and the risk of side effects. Tell your healthcare provider about all the medicines you're taking," whereas the SUPER displayed simultaneously states, "Medications that are strong CYP3A4 inhibitors may increase Nereus levels and the risk of side effects. Nereus has not been studied in people with severe kidney or liver impairment." Therefore, the TV ad fails to present the major statement concurrently using both audio and text (dual modality). Thus, the major statement is not presented in a clear, conspicuous, and neutral manner in accordance with 21 CFR 202.1(e)(1)(ii)(C).

Also, concurrently with the presentation of the major statement, the TV ad progresses through eleven dynamic scene changes featuring an engaging storyline. The visuals transition between wide panoramic vistas showing the vehicles race along a winding, cliffside road, to road-level angles depicting the extreme speed at which the vehicles are traveling, to close-ups of the characters illustrating their in-the-moment expressions. The riveting storyline, constant perspective changes, and quick scene cuts continue throughout the duration of the 31-second major statement. The presentation of these compelling and attention-grabbing visuals, all of which are unrelated to the risk message presented in the audio and on-screen SUPERs, directly competes for the consumer's attention and interferes with comprehension of the major statement. Thus, the major statement is not presented in a clear, conspicuous, and neutral manner in accordance with 21 CFR 202.1(e)(1)(ii)(E).

Conclusion and Requested Action

For the reasons described above, the TV ad misbrands Nereus within the meaning of the FD&C Act and makes its distribution violative. 21 U.S.C. 352(n); 321(n); 331(a); 21 CFR 202.1(e)(1)(ii)(C), (e)(1)(ii)(E), (e)(5).

This letter notifies you of our concerns and provides you with an opportunity to address them. OPDP requests that Vanda take immediate action to address any violations of the FD&C Act.

Please submit a written response to this letter within 15 working days from the date of receipt, addressing the concerns described in this letter, listing all promotional communications (with the 2253 submission date) for Nereus that contain representations like those described above, and explaining your plan for the discontinuation of such communications, or for ceasing distribution of Nereus.

If you believe that your products are not in violation of the FD&C Act, please include in your submission to us your reasoning and any supporting information for our consideration within 15 working days from the date of receipt of this letter.

The concerns discussed in this letter do not necessarily constitute an exhaustive list of potential violations. It is your responsibility to ensure compliance with each applicable requirement of the FD&C Act and FDA implementing regulations.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266**. A courtesy copy can be sent by facsimile to (301) 847-8444. Please refer to MA 15 in addition to the NDA number in all future correspondence relating to this particular matter. All correspondence should include a subject line that clearly identifies the submission as a Response to Untitled Letter. You are encouraged, but not required, to submit your response in eCTD format. All correspondence submitted in response to this letter should be placed under eCTD Heading 1.15.1.6. Additionally, the response submission should be coded as an Amendment to eCTD Sequence 0051 under NDA 220152. Questions related to the submission of your response letter should be emailed to CDER-OPDP-RPM@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Meeta Patel, Pharm.D.
Regulatory Review Officer
Division of Advertising & Promotion Review 2
Office of Prescription Drug Promotion

{See appended electronic signature page}

Adewale Adeleye, Pharm.D., M.B.A.
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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.

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