CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

220152Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	220152
PDUFA Goal Date	December 30, 2025
TTT #	2025-12434
Reviewer Name	Brian Caruth, Pharm.D., BCPS
Team Leader	Yasmeen Abou-Sayed, Pharm.D.
Associate Division Director	Suzanne Robottom, Pharm.D.
Review Completion Date	December 29, 2025
Subject	Evaluation of Need for a REMS
Established Name	Tradipitant
Trade Name	Nereus
Name of Applicant	Vanda Pharmaceuticals, Inc. (Vanda)
Therapeutic Class	Substance P/neurokinin-1 (NK-1) receptor antagonist
Dosage Form	Oral capsule
Dosing Regimen	85 mg or 170 mg orally as a single dose approximately 60 minutes before the event expected to cause vomiting induced by motion

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Nereus (tradipitant) is necessary to ensure the benefits outweigh its risks. Vanda Pharmaceuticals, Inc. submitted a New Drug Application (NDA) 220152 for tradipitant with the proposed indication for the acute prevention of vomiting induced by motion in adults. During the course of the review, the Division of Gastroenterology (DG) revised the indication to the prevention of vomiting induced by motion in adults

This application is under review in the Division of Gastroenterology (DG). Data from the two phase 3 studies (Study VP-VLY-686-3401 and Study VP-VLY-686-3404), demonstrated a statistically significant reduction in the proportion of subjects who vomited in the 170 mg tradipitant group and the 85 mg tradipitant group compared to placebo. The review team concluded that this demonstrates substantial evidence of effectiveness.

The risks associated with tradipitant include somnolence, headache, and fatigue. The Applicant did not submit a proposed REMS or risk management plan with this application. DRM has determined that a REMS is not needed to ensure the benefits of tradipitant outweigh its risks. The higher rates of somnolence and fatigue in subjects receiving tradipitant compared to placebo may affect a patients' ability to drive or operate machinery. Monitoring for somnolence and fatigue is expected to be a collaborative effort between the prescriber and the patient or patient's caregiver. In addition, the effects on the ability to drive or operate machinery will be addressed in the Warnings and Precautions section of the label.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Nereus (tradipitant) is necessary to ensure the benefits outweigh its risks. Vanda Pharmaceuticals, Inc. submitted a New Drug Application (NDA) 220152 for tradipitant with the proposed indication for the acute prevention of vomiting induced by motion in adults. This application is under review in the Division of Gastroenterology (DG). The Applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Tradipitant, a new molecular entity[a] (NME), is a substance P/neurokinin-1 (NK-1) receptor antagonist proposed for the acute prevention of vomiting induced by motion in adults. NK-1 receptors located in the area postrema, nucleus tractus solitarius, and visceral afferent nerves mediate the emetic effects of substance P.[b] NK-1 receptor antagonism blocks the binding of substance P preventing the transmission of emetic signals.

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*
[b] Ibrahim MA, et al. Antiemetic Neurokinin-1 Receptor Blockers. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470394/

Tradipitant is proposed to be available as 85 mg capsules. The recommended dose is 85 mg or 170 mg orally as a single dose approximately 60 minutes before the event expected to cause vomiting induced by motion. Tradipitant should be administered without food. The maximum dosage in a 24-hour period is 170 mg. Currently available data does not support unlimited intermittent use of tradipitant, and labeling will include a statement that the safety of more than 90 doses has not been established in clinical trials.[c] Tradipitant is not currently approved in any jurisdiction.

2.2. Regulatory History

The following is a summary of the regulatory history for 220152 relevant to this review:

- 10/02/2018: IND 141315 submitted for tradipitant.
- 02/28/2023: The Agency informed the Applicant that they should conduct a 6-month toxicity study in a nonrodent species to assess the risk of cumulative toxicity following repeated short-term exposures to tradipitant.
- 12/23/2024: FDA issued a partial clinical hold for Trial 3403 citing insufficient information to assess risks to human subjects beyond 90 dosing days.
- 12/30/2024: NDA 220152 submission for the acute prevention of vomiting induced by motion in adults received.
- 07/23/2025: A Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that the data submitted may not be adequate to characterize the safety of tradipitant.
- 10/15/2025: A Late-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for tradipitant.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Motion sickness is a syndrome of nausea and vomiting, pallor, sweating, headache, dizziness, malaise, increased salivation, apathy, drowsiness, belching, hyperventilation, and stomach awareness. Symptoms can be provoked by externally imposed motion, or implied self motion from a moving visual field.[d] Symptoms typically subside after 36 to 72 hours of continuous exposure, but they can recur upon returning to the pre-exposure environment.[e] There is enormous variability in susceptibility to motion sickness, as it may be produced with minimal provocation in some individuals but can be difficult to elicit in others. In general, females (especially during pregnancy), children older than two years of age, and migraine sufferers are more susceptible to motion sickness.[f]

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[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*
[d] Murdin L, Golding J, Bronstein A. Managing motion sickness. BMJ. 2011;343:d7430. doi:10.1136/bmj.d7430
[e] Section 505-1 (a) of the FD&C Act: *FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.*
[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

3.2. Description of Current Treatment Options

Treatment of acute motion sickness is often ineffective. Therefore, treatment options for the management of motion sickness are generally consistent with an emphasis on prevention. Commonly used FDA-approved treatment options for the prevention of motion sickness include dimenhydrinate, meclizine, and scopolamine. Some first-generation antihistamines (diphenhydramine and chlorpheniramine) have also been used as off-label treatment options. Transdermal scopolamine is a prescription drug that may be beneficial if prolonged exposure to motion is expected due to an extended duration of action. Adverse effects associated with antihistamines include sedation, blurred vision, and dry mouth. Nonsedating antihistamines (cetirizine, loratadine, fexofenadine) do not appear to be effective for the treatment of motion sickness[g] and ondansetron is not effective in the prevention of motion sickness.[h] Non-pharmacologic interventions for the prevention of motion sickness includes environmental modifications, use of acupressure bands, and ginger. Available data for non-pharmacologic options is limited and the benefit is uncertain. While various treatment options for the prevention of motion sickness are available, the likelihood of experiencing motion sickness must be balanced with potential adverse effects, and a lack of specific or highly active therapies to treat and prevent motion sickness represent an unmet medical need.

4. Benefit Assessment

The efficacy of tradipitant for the prevention of vomiting induced by motion in adults was evaluated in two phase 3 studies (Study VP-VLY-686-3401 [NCT04327661] and Study VP-VLY-686-3404 [NCT05903924]) conducted at multiple sites throughout the US. Both studies evaluated a single dose of either 170 mg or 85 mg of tradipitant administered approximately 60 minutes before a planned vehicle travel event via a boat. All subjects were ≥ 18 years of age and had a history of motion sickness. Subjects with a nausea-inducing disorder other than motion sickness were excluded from the studies. The primary efficacy endpoint for both studies was the percentage of subjects with vomiting during the trip in the tradipitant 170 mg group as assessed by the vomiting assessment (VA) 1-item questionnaire to objectively measure the incidence of emesis. A secondary efficacy endpoint for both studies was the percentage of subjects who vomited in the tradipitant 85 mg group. Table 1 summarizes studies VP-VLY-686-3401 and VP-VLY-686-3404.

Table 1: Summary of Studies Contributing to the Efficacy Data of Tradipitant

Study	Total Subjects	Subjects (Randomized Group)	Tradipitant 170 mg Group (Risk Difference [95% CI])	Tradipitant 85 mg Group (Risk Difference 95% CI)
Phase 3 Studies				
VP-VLY-686-3401	366	123 (85 mg) 121 (170 mg) 122 (placebo)	-25.9% [-37.1%, -14.7%] p < 0.0001	-24.9% [-36.0%, -13.9%] p < 0.0001
VP-VLY-686-3404	316	104 (85 mg) 106 (170 mg) 106 (placebo)	-27.4% [-38.3%, -16.5%] p < 0.0001	-19.5% [-31.3%, -7.6%] p < 0.0025

[g] Cheung BS, Heskin R, Hofer KD. Failure of cetirizine and fexofenadine to prevent motion sickness. Ann Pharmacotherapy. 2003;37(2):173-177. doi:10.1177/106002800303700201

[h] Hershkovitz D, et al. Ondansetron for the prevention of seasickness in susceptible sailors: an evaluation at sea. Aviat Space Environ Med. 2009;80(7):643-646. doi:10.3357/asem.2365.2009

The primary efficacy endpoint for both studies was met. A secondary efficacy endpoint for both studies, the percentage of subjects who vomited in the tradipitant 85 mg group, was also met. There were no statistically significant differences in the tradipitant groups compared to placebo for endpoints related to the prevention of nausea. The review team concluded that substantial evidence of effectiveness supported the benefit of tradipitant for the prevention of vomiting induced by motion. This determination relied on the statistically significant results of studies VP-VLY-686-3401 and VP-VLY-686-3404.[i]

5. Risk Assessment & Safe-Use Conditions

The primary safety review of tradipitant relies on data from studies VP-VLY-686-3401 and VP-VLY-686-3404, as well as one single dose, placebo-controlled phase 2 study (study 2401) that evaluated a 170 mg dose of tradipitant, one phase 3 open-label, repeat-dose study (study 3403) that evaluated either 170 mg or 85 mg of tradipitant, and studies for indications other than the prevention of vomiting induced by motion (gastroparesis, social anxiety disorder, irritable bowel disease, alcohol use disorder, and atopic dermatitis).

The most common adverse events in subjects who received tradipitant were somnolence, headache, and fatigue. These adverse events occurred in ≥ 5% of subjects who received tradipitant (85 mg or 170 mg dose) and greater than placebo in the single dose studies (VP-VLY-686-3401, VP-VLY-686-3404, and 2401). In the single dose studies, there were no serious treatment emergent adverse events or deaths. In the repeat dose study, subjects in the 170 mg dose group experienced serious adverse events and adverse events leading to discontinuation at a higher rate compared to subjects in the 85 mg dose group. In addition, the higher rates of somnolence and fatigue in subjects receiving tradipitant compared to placebo may affect a patients' ability to drive or operate machinery. The effects on the ability to drive or operate machinery will be addressed in the Warnings and Precautions section of the label.

Safety data from the phase 3 open-label, repeat-dose study (study 3403) was limited by several factors, including but not limited to, infrequent exposure that was limited to a maximum of 90 doses over 12 months, variability in the timing of tradipitant administration, type and duration of travel event, infrequent safety assessment, and lack of a comparator. The common adverse events reported in study 3403 were similar to the adverse event rates in the placebo-controlled studies and no new safety signals were identified. The majority of subjects used tradipitant for 30 days or fewer (69.6% for the 85 mg dose group and 68% for the 170 mg dose group).

A chronic toxicity study in a nonrodent species was not conducted and insufficient data were provided to demonstrate that such a study is not warranted. There is also insufficient evidence to support that intermittent dosing of tradipitant results in different cumulative toxicity than scheduled dosing of tradipitant. There were no randomized, placebo-controlled studies assessing safety of multiple doses of tradipitant for the prevention of vomiting induced by motion and there were only 74 subjects with additional co-morbidities who completed a randomized, placebo-controlled 12-week study of tradipitant (85 mg twice daily) for a different indication.

[i] Food and Drug Administration. Center for Drug Evaluation and Research. Division of Gastroenterology. Integrated Review: Tradipitant, NDA 220152. Draft as of December 5, 2025.

The review team determined there are insufficient data to support unlimited use of tradipitant over a lifetime. To address these findings, labeling will include a statement that the safety of more than 90 doses has not been established in clinical trials. Tradipitant may be used by women of reproductive potential, and it is not known whether tradipitant may affect maternal, fetal, and infant outcomes. Postmarketing requirements (PMR) will be issued to collect data from a prospective pregnancy exposure registry using a cohort analysis to assess maternal, fetal, and infant outcomes of women exposed to tradipitant and to conduct a retrospective pregnancy cohort study and lactation study in lactating women who have received tradipitant.

To evaluate the effects of tradipitant in subjects with hepatic impairment or severe renal impairment, postmarketing commitments (PMC) will be issued to conduct pharmacology studies to evaluate the effects of hepatic impairment and severe renal impairment on the pharmacokinetics of tradipitant and its major metabolites. Additional PMCs include an in vitro assessment to evaluate the contribution of all major cytochrome (CYP) enzymes to the overall metabolism of tradipitant and its active metabolites and a study to evaluate the effects of tradipitant on QT intervals in the fed state.

6. Expected Postmarket Use

Patients with motion sickness or a previous history of motion sickness are typically evaluated in ambulatory care settings such as urgent care clinics, telemedicine visits, or physician offices. Patients with motion sickness or a previous history of motion sickness may otherwise be healthy. The likely prescribers will be primary care providers, such as internal medicine practitioners including nurse practitioners and physician assistants, and family physicians. If approved, tradipitant will likely be dispensed from retail pharmacy settings and primarily be self-administered by the patient at home or prior to a precipitating event for short term treatment. Based on the anticipated medication use process, counseling about and monitoring for somnolence and fatigue should be a collaborative effort between the prescriber and the patient or patient's caregiver. No concerning care gaps have been identified within the intended scope of practice. Labeling is sufficient to ensure the safe use of tradipitant in the expected postmarket setting.

7. Discussion of the Need for a REMS

Based on the efficacy and safety information currently available, FDA determined that a REMS is not necessary to ensure the benefits of tradipitant outweigh the risks.

Vomiting induced by motion is a specific symptom of the heterogenous condition of motion sickness. Otherwise, healthy individuals may be susceptible to motion sickness, and while symptoms typically subside after 36 to 72 hours of continuous exposure, they can recur upon returning to the pre-exposure environment. Multiple pharmacologic treatment options are approved for the prevention of motion sickness; however, they are associated with sedation, blurred vision, and dry mouth. There remains a need for preventative treatment options for motion sickness.

Data from the two phase 3 studies (Study VP-VLY-686-3401 and Study VP-VLY-686-3404), demonstrated a statistically significant reduction in the proportion of subjects who vomited in the 170 mg tradipitant group and the 85 mg tradipitant group compared to placebo. There were no statistically significant

differences in the tradipitant groups compared to placebo related to the prevention of nausea. The most common adverse events in subjects who received tradipitant were somnolence, headache, and fatigue. There were no serious treatment emergent adverse events or deaths.

Labeling will address safe-use limitations due to insufficient data to support unlimited use of tradipitant over a lifetime and the higher rates of somnolence and fatigue in subjects receiving tradipitant compared to placebo. The Dosage and Administration section of labeling will include information regarding the maximum dosage of 170 mg of tradipitant in a 24-hour period and a statement that the safety of more than 90 doses has not been established in clinical trials. The effects on the ability to drive or operate machine will be addressed in the Warnings and Precautions section of the label. At the time of this review, the label for tradipitant does not contain a Boxed Warning and has no Contraindications. Labeling is sufficient to ensure that the benefits of tradipitant in the target population outweigh the risks. Postmarketing requirements (PMR) and postmarketing commitments (PMC) will be issued in the Action letter to gather additional information about the safe and optimal use of tradipitant. Therefore, this reviewer is not recommending a REMS for tradipitant therapy.

8. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for tradipitant beyond routine pharmacovigilance and labeling.

9. Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for tradipitant to ensure the benefits outweigh the risks. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

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/s/

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