CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

220358Orig1s000

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	220358
PDUFA Goal Date	February 21, 2026
TTT #	2025-13361
Reviewer Name	Stephanie Olumba, PharmD, MPH, BCPS
Team Leader	Carolyn Tieu, PharmD, MPH
Division Director	Laura Zendel, PharmD
Review Completion Date	February 10, 2026
Subject	Evaluation of Need for a REMS
Established Name	Milsaperidone
Trade Name	Bysanti
Name of Applicant	Vanda Pharmaceuticals Inc.
Therapeutic Class	Atypical antipsychotic
Dosage Forms	1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg tablets
Dosing Regimen	<u>Schizophrenia</u> • Starting dosage: 1 mg orally twice daily • Recommended maintenance dosage: 6 mg to 12 mg orally twice daily <u>Bipolar I Disorder Manic or Mixed Episodes</u> • Starting dosage: 1 mg orally twice daily • Recommended maintenance dosage: 12 mg orally twice daily

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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) Bysanti (milsaperidone) is necessary to ensure the benefits outweigh its risks.

Vanda Pharmaceuticals (Applicant) submitted a New Drug Application (NDA) 220358 for Bysanti (milsaperidone) with the proposed indication for the treatment of schizophrenia in adults, and for the acute treatment of manic or mixed episodes associated with bipolar I disorder in adults. This application is under review in the Division of Psychiatry. Bysanti is an atypical antipsychotic. The efficacy and safety of Bysanti relies upon the Agency's previous findings of the effectiveness for Fanapt (iloperidone) for the same indication, as iloperidone and milsaperidone rapidly interconvert in vivo. The pharmacokinetic bioavailability studies demonstrated an adequate scientific bridge between Bysanti and Fanapt. The clinical review team concluded that this demonstrates substantial evidence of effectiveness.

The risks associated with Bysanti include increased mortality in elderly patients with dementia-related psychosis, the risk of cerebrovascular adverse reactions, including stroke, in elderly patients with dementia-related psychosis, QTc interval prolongation, neuroleptic malignant syndrome, tardive dyskinesia, metabolic changes, orthostatic hypotension and syncope, falls, and seizures. 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 Bysanti outweigh its risks. The safety profile is similar to that of Fanapt and other antipsychotics. Therefore, the likely prescribers are expected to be familiar with the monitoring and management of the risks associated with Bysanti. Labeling is expected to be sufficient to communicate the risks for Bysanti.

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) Bysanti (milsaperidone) is necessary to ensure the benefits outweigh its risks. Vanda Pharmaceuticals (Applicant) submitted a New Drug Application (NDA) 220358 for Bysanti with the proposed indication for the treatment of schizophrenia in adults, and for the acute treatment of manic or mixed episodes associated with bipolar I disorder in adults. This application is under review in the Division of Psychiatry (DP). The Applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Bysanti (milsaperidone), a new molecular entity[a], is proposed for the treatment of schizophrenia in adults and the acute treatment of manic or mixed episodes associated with bipolar I disorder in adults.

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity*

Bysanti is an atypical antipsychotic. Bysanti rapidly interconverts in vivo with Fanapt (iloperidone), NDA 022192. Fanapt is also an atypical antipsychotic approved for the same indication.[b] The mechanism of action for Bysanti is unknown, however, the efficacy of Bysanti could be mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 (5-HT_2) antagonism. Bysanti also has an in vitro receptor binding profile similar to Fanapt.[c]

Bysanti is supplied as 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg oral tablets. The proposed dosing regimen follows that of Fanapt, with a starting dosage is 1 mg twice daily, titrated to the recommended maintenance dosage of 6 mg to 12 mg twice daily for schizophrenia; and a starting dosage is 1 mg twice daily, titrated to the recommended maintenance dosage of 12 mg twice daily for bipolar I disorder manic or mixed episodes.[d] Bysanti is not currently approved in any jurisdiction.

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 220358 relevant to this review:

- **02/21/2025:** NDA 220358 submission received for the treatment of schizophrenia in adults and the acute treatment of manic or mixed episodes associated with bipolar I disorder in adults.
- **08/04/2025:** A Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that no major safety concerns have been identified at this time and there is currently no need for a REMS.

3. Therapeutic Context and Treatment Options[e]

3.1. Description of the Medical Condition

Schizophrenia

Schizophrenia is a severe mental illness characterized by recurrent or chronic psychosis that can lead to significant morbidity and mortality. Schizophrenia affects approximately 0.29% of the worldwide population, and an estimated prevalence of 0.25% to 0.64% in the US population (WHO, 2025; NIMH 2025).[f] The onset of schizophrenia is typically during late adolescence and twenties and tends to emerge later in women than in men (WHO, 2025). The clinical presentation of schizophrenia can include positive symptoms (i.e., delusions or hallucinations), negative symptoms (i.e., very limited speech, diminished

[b] See Fanapt (iloperidone) at https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/022192s024lbl.pdf.
[c] Vanda Pharmaceutical. Bysanti (Milsaperidone). NDA 220358. Draft Prescribing Information with Agency edits as of January 9, 2026.
[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*
[e] A GenAI tool (ELSA) was used in sections 3.1 and 3.2 to help proofread and edit for clarity and conciseness. The content has been reviewed, verified, and edited by Stephanie Olumba, PharmD, MPH, BCPS.
[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.*

emotional expression, or social withdrawal), cognitive impairments (i.e., impaired memory, attention, or verbal or visual learning), and mood and anxiety symptoms (WHO, 2022; Fischer and Buchanan, 2025).

Patients with schizophrenia have substantially higher mortality risk that exceeds that of the general population. The life expectancy of individuals with schizophrenia is estimated to be reduced by 15 to 20 years compared with the general population (Correll et al., 2022).[g] This premature mortality is associated with multiple factors, such as cardiovascular disease and suicide. Cardiovascular disease in schizophrenia is associated with medication side effects, lifestyle factors, and reduced access to preventive care. Furthermore, approximately 5% of individuals with schizophrenia commit suicide over their lifetime, and among all completed suicides, approximately 10% occur in individuals with schizophrenia (Fischer and Buchanan, 2025).

Bipolar I Disorder

Bipolar I disorder is a severe and chronic mood disorder with an estimated lifetime prevalence of 2.1% in the US population (Blanco et al., 2017).[h] The clinical presentation is characterized by manic episodes, hypomanic episodes, major depressive episodes, and episodes with mixed features (Ostacher, 2025). The onset of the first mood episode typically occurs in late adolescence to young adulthood, though it can also present at younger and older ages.

During manic episodes, patients may experience clinically significant elevations in mood, energy, and activity, along with symptoms of inflated self-esteem and grandiosity, racing thoughts, or decreased need for sleep (Ostacher, 2025). Hypomanic episodes present similarly to manic episodes but are less severe. Major depressive episodes can present with depressed mood, loss of interest or pleasure, decreased energy, and impaired memory and concentration. Episodes with mixed features include episodes of mania, hypomania, or major depression that are accompanied by significant symptoms of the opposite polarity (Ostacher, 2025).

Patients with bipolar disorder typically have at least one other psychiatric disorder. Comorbid psychiatric disorders can include anxiety disorders, attention deficit hyperactivity disorder (ADHD), and substance use disorders. Furthermore, bipolar disorder is associated with an increased risk of suicide.[i] It is estimated that individuals with bipolar disorders are approximately 20–30 times more likely to die by suicide compared with the general population (McIntyre et al., 2020).

[g] 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.*

[h] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[i] 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.*

3.2. Description of Current Treatment Options

Schizophrenia

Schizophrenia treatment options include pharmacological and nonpharmacological approaches. The American Psychiatric Association (APA) guidelines recommend that patients with schizophrenia be treated with an antipsychotic medication and monitored for effectiveness and side effects (APA, 2020). Antipsychotics medications are categorized into two classes: first-generation antipsychotics (also known as typical antipsychotics) and second-generation antipsychotics (also known as atypical antipsychotics). Examples of first-generation antipsychotics include haloperidol, chlorpromazine, and fluphenazine, while second-generation antipsychotics include olanzapine, risperidone, iloperidone, and paliperidone. Medication selection of an antipsychotic is typically individualized based on multiple factors, such as patient comorbidities, medication side effect profile, and patient preference.

Both antipsychotics classes are associated with serious risks, including increased risk of death and cerebrovascular adverse reactions in elderly patients with dementia-related psychosis, extrapyramidal symptoms, tardive dyskinesia, metabolic changes, hyperprolactinemia, and seizures. First-generation antipsychotics typically cause more extrapyramidal symptoms and tardive dyskinesia than second-generation antipsychotics (Jibson, 2025). The risk profile varies for each antipsychotic medication.

Currently, two FDA-approved antipsychotics have REMS programs. Zyprexa Relprevv (olanzapine pamoate) was approved in 2009 with a REMS to mitigate the risk of Post-Injection Delirium/Sedation Syndrome.[j] Adasuve (loxapine) was approved in 2012 with a REMS to mitigate the risk of bronchospasm.[k] Both are used in schizophrenia. Additionally, clozapine, which is used for treatment resistant schizophrenia, previously had a REMS to mitigate the risk of severe neutropenia. However, FDA removed the clozapine REMS effective June 13, 2025, after determining the REMS was no longer necessary to ensure the benefits outweigh the risk.[l]

Furthermore, nonpharmacological treatment options serve as adjunctive therapies to antipsychotic medications and include psychosocial interventions, such as cognitive-behavioral therapy (CBT), social skills training, and supportive psychotherapy. Electroconvulsive therapy has also been utilized in cases of treatment-resistant schizophrenia.

[j] Approval Letter for Zyprexa Relprevv (olanzapine) extended-release injection. NDA 022173. December 11, 2009. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2009/022173s000ltr.pdf

[k] Approval Letter for Adasuve (loxapine) inhalation powder. NDA 22549. December 21, 2012. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/022549Orig1s000ltr.pdf

[l] See Drug Safety Communication: FDA removes risk evaluation and mitigation strategy (REMS) program for the antipsychotic drug Clozapine, dated August 27, 2025, available at https://www.fda.gov/drugs/drug-safety-and-availability/fda-removes-risk-evaluation-and-mitigation-strategy-rems-program-antipsychotic-drug-clozapine

Bipolar I Disorder

Pharmacological treatments used for bipolar I disorder are mood stabilizers and antipsychotics. FDA-approved mood stabilizers used for bipolar I disorder include lithium, divalproex, and carbamazepine extended-release. Antipsychotics used for bipolar I disorder are primarily second-generation antipsychotics and include risperidone, quetiapine, olanzapine, iloperidone, and ziprasidone. Medication selection will be based on multiple factors, such as patient comorbidities, side effect profiles, patient preference and response, and cost considerations. Furthermore, psychosocial interventions such as psychoeducation and CBT, have been used as adjuncts to pharmacotherapy for the treatment of bipolar I disorder (Marzani, 2021).

4. Benefit Assessment

The efficacy of Bysanti for the treatment of schizophrenia in adults and the acute treatment of manic or mixed episodes associated with bipolar I disorder in adults relies upon the Agency's previous findings of the effectiveness for Fanapt (iloperidone), and the scientific bridge between Fanapt and Bysanti using pharmacokinetic data. The pharmacokinetic comparative bioavailability studies VP-VHX-896-1101 (single dose crossover of 3 mg in healthy subjects) and VP-VHX-896-1103 (steady-state crossover at 12 mg twice daily in subjects with schizophrenia or bipolar 1 disorder) demonstrated an adequate scientific bridge between Bysanti and Fanapt.

The clinical review team concluded that this demonstrates substantial evidence of effectiveness for the proposed indication for the treatment of schizophrenia in adults and the acute treatment of manic or mixed episodes associated with bipolar I disorder in adults. [m] Refer to the Multi- Disciplinary Review and Evaluation for more information.[n]

5. Risk Assessment & Safe-Use Conditions

The safety population included 86 subjects that were exposed to at least one dose of Bysanti in the four phase 1 studies (Study VP-VHX-896-1101, Study VP-VHX-896-1102, Study VP-VHX-896-1103, and Study VP-VYV-683M-1201). There were no deaths reported in any of the four phase 1 studies. One serious adverse event (SAE) of fall (leading to able fracture and hospitalization) occurred in Study VP-VHX-896-1103. The SAE was considered unrelated to Bysanti.

Given the adequate scientific bridge between Bysanti and Fanapt, the safety profile and proposed label for Bysanti will be similar to that of Fanapt. Fanapt is not approved with a REMS. The proposed label[o] for Bysanti will include a Boxed Warning for increased mortality in elderly patients with dementia-related

[m] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

[n] Food and Drug Administration. Center for Drug Evaluation and Research. Division of Psychiatry. Multi-Disciplinary Review: Bysanti (milsaperidone), NDA 220358 Draft as of January 9, 2026.

[o] Vanda Pharmaceutical. Bysanti (Milsaperidone). NDA 220358. Draft Prescribing Information with Agency edits as of January 9, 2026.

psychosis.[p] Additionally, the Warnings and Precautions will include information on the risk of cerebrovascular adverse reactions, including stroke, in elderly patients with dementia-related psychosis, QTc interval prolongation, neuroleptic malignant syndrome, tardive dyskinesia, metabolic changes, orthostatic hypotension and syncope, falls, and seizures.

6. Expected Postmarket Use

Schizophrenia and bipolar I disorder are typically diagnosed in inpatient and outpatient settings. The likely prescribers will be psychiatric healthcare providers, such as psychiatrists, who are expected to be familiar with managing the risks of antipsychotics. If approved, Bysanti will likely be dispensed from inpatient and outpatient pharmacy settings and will primarily be administered by the patient or caregiver for chronic treatment. Based on the anticipated medication use process, monitoring for the risks 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 Bysanti 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 Bysanti outweigh the risks. FDA expects labeling to be sufficient to communicate the risks associated with Bysanti.

The efficacy and safety of Bysanti relies upon the Agency's previous findings of safety and effectiveness for Fanapt (iloperidone) for the same indication, and the pharmacokinetic comparative bioavailability studies that demonstrated an adequate scientific bridge between Bysanti and Fanapt. The clinical review team concluded that substantial evidence of effectiveness has been established.

The safety profile for Bysanti will be similar to that of Fanapt. Fanapt is not approved with a REMS. The proposed label for Bysanti will include a Boxed Warning for increased mortality in elderly patients with dementia-related psychosis. The Warnings and Precautions will include information on the risk of cerebrovascular adverse reactions in elderly patients with dementia-related psychosis, QTc interval prolongation, neuroleptic malignant syndrome, tardive dyskinesia, metabolic changes, orthostatic hypotension and syncope, falls, and seizures. These risks are known to Fanapt and other antipsychotics. The likely prescribers are expected to be familiar with the monitoring and management of these risks. Therefore, we do not anticipate that additional mitigation strategies beyond labeling would be necessary to ensure the benefits of Bysanti outweigh the risks.

[p] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

8. Risk Management Activities Proposed by the Applicant

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

9. Conclusion & Recommendations

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

10. References

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