New Drug Overview

Bysanti (milsaperidone)

PDL Category: Antipsychotics- Atypicals

Introduction

Disease Background:

- Schizophrenia is a persistent psychiatric condition described by a combination of positive symptoms (for instance hallucinations, delusions, and disorganized speech) as well as negative symptoms (for instance social withdrawal, flattened affect, and no motivation), and associated with general impairment in cognitive function (*Kovacevich et al 2025*).
  - It is the most frequent psychotic illness or disease, with a global lifetime prevalence between 0.3% to 0.7% and a prevalence in the United States of approximately 0.6% to 1.9%.
  - Schizophrenia is diagnosed clinically by having at least one positive symptom and either one negative symptom or grossly disorganized or catatonic conduct for at least 6 months. Symptoms have to be substantially disabling to one's social and occupational functioning. Mania or depression episodes cannot happen at the same time with active-phase symptoms (or only present for a minority of the time).
- Bipolar Disorder (BP) is a mood disorder described as having recurrent episodes of unusually and continually elevated, expansive, or irritable mood, and fluctuating or interweaving episodes of major depression (*Zimmerman et al 2025*).
  - Mood episodes are associated with changes in activity or energy and linked with cognitive, physical, and behavioral symptoms.
    - Bipolar I disorder is described as having at least one episode of mania or mixed episode, with or without psychosis and/or major depression.
    - Bipolar II disorder is described as having at least one episode of major depression and 1 hypomanic episode (not mania or mixed episode).
      - Worldwide, it is estimated that bipolar I and II are reported in >1% of the population.
- Bysanti was FDA approved in 2026.

Pharmacology/Usage

- Bysanti (milsaperidone) is an atypical antipsychotic that is in the piperidinyl-benzisoxazole derivative chemical class.
  - The mechanism of action of milsaperidone in the treatment of schizophrenia in adults and the acute treatment of manic or mixed episodes associated with bipolar I disorder in adults is unknown. However, the efficacy of milsaperidone in these conditions could be mediated through a combination of dopamine type 2 (D2) and serotonin type 2 (5-HT2) antagonism.
  - Milsaperidone and iloperidone rapidly interconvert in vivo. Milsaperidone has an in vitro receptor binding profile similar to iloperidone.

Indications

Table 1. Food and Drug Administration Approved Indications

Indication	Bysanti (milsaperidone)
• For the treatment of schizophrenia in adults. • For the acute treatment of manic or mixed episodes associated with bipolar I disorder in adults.	√

(Prescribing information: Bysanti 2026)

- Information on indications, mechanism of action, pharmacokinetics, dosing, safety, and clinical efficacy summary has been obtained from the prescribing information for the individual products, except where noted otherwise.

Dosing and administration

Table 2. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Bysanti (milsaperidone)	Tablets: 1mg, 2mg, 4mg, 6mg, 8mg, 10mg, and 12mg.	PO	*Schizophrenia*: 6mg to 12mg BID as the recommended maintenance dosage, after 7 days of titration. -Patients with schizophrenia may either 1.) follow the recommended titration schedule, OR 2.) starting on day 5, continue 6mg BID dosing. As needed, titrate subsequent doses based on tolerability and response within the recommended maintenance dosing range of 6mg to 12mg BID. *Bipolar I Disorder*: 12mg BID as the recommended maintenance dosage, after 5 days of titration.	• Titrate Bysanti to reduce the risk of orthostatic hypotension. • Administer with or without food. • If patients miss more than 3 days of treatment, restart the titration schedule. • Dose adjustments are not required with mild hepatic impairment but consider a lower maintenance dosage in patients with moderate hepatic impairment. Bysanti is not recommended in patients with severe hepatic impairment. • The recommended dosage in CYP2D6 poor metabolizers is lower than the recommended dosage in the overall population.

See the current prescribing information for full details.

Clinical Efficacy Summary

- The efficacy of Bysanti in the treatment of schizophrenia in adults has been established from adequate and well-controlled studies of iloperidone tablets (referred to as “iloperidone” [iloperidone and milsaperidone rapidly interconvert in vivo]) in adults with schizophrenia. The studies included in the Bysanti prescribing information display the efficacy results of iloperidone in these adequate and well-controlled studies.
- The efficacy of Bysanti in the acute treatment of manic or mixed episodes associated with bipolar I disorder has been established from an adequate and well-controlled study of iloperidone tablets (referred to as “iloperidone” [iloperidone and milsaperidone rapidly interconvert in vivo]) in adults with manic or mixed episodes associated with bipolar I disorder.

The studies included in the Bysanti prescribing information display the efficacy results of iloperidone in this adequate and well-controlled study.

Clinical guidelines

- There are currently no published guidelines addressing the use of Bysanti.
- **Veterans Affairs (VA)/Department of Defense (DoD) Clinical Practice Guideline for Management of bipolar disorder** (*VA/DoD 2023*).
  - Recommendations on pharmacotherapy for acute mania includes:
    - Lithium or quetiapine are suggested as monotherapy for acute mania.
      - If lithium or quetiapine are not selected per patient preference and characteristics, olanzapine, paliperidone, or risperidone are suggested as monotherapy for acute mania.
      - If lithium, quetiapine, olanzapine, paliperidone, or risperidone are not selected per patient preference and characteristic, aripiprazole, asenapine, carbamazepine, cariprazine, haloperidol, valproate, or ziprasidone are suggested as monotherapy for acute mania.
    - Lithium or valproate combined with haloperidol, asenapine, quetiapine, olanzapine, or risperidone are suggested for acute mania symptoms in patients with an unsatisfactory response or a breakthrough episode on monotherapy.
    - Brexpiprazole, topiramate, or lamotrigine are suggested against as monotherapy for acute mania.
    - There is not sufficient evidence to recommend for or against other first-generation antipsychotics or second-generation antipsychotics, gabapentin, oxcarbazepine, or benzodiazepines as monotherapy or in combination for acute mania.
  - Recommendations on pharmacotherapy for acute bipolar depression includes:
    - Monotherapy with quetiapine is recommended for acute bipolar depression.
      - If quetiapine is not selected per patient preference and characteristics, it is suggested to use cariprazine, lumateperone, lurasidone, or olanzapine as monotherapy.
- **Veterans Affairs (VA)/Department of Defense (DoD) Clinical Practice Guideline for Management of first-episode psychosis and schizophrenia** (*VA/DoD 2023*).
  - Recommendations regarding pharmacologic interventions for psychosis include:
    - Antipsychotic interventions other than clozapine are recommended for treatment of an acute episode in patients with schizophrenia or first-episode psychosis who have previously responded to antipsychotic treatments. The decision on which antipsychotic medication to use should be individualized.
    - Antipsychotic medication is recommended for maintenance treatment of schizophrenia to prevent relapse and hospitalization in patients with schizophrenia who have responded to treatment. The decision on which antipsychotic to use should be individualized.
    - A trial of another antipsychotic agent is suggested in patients with schizophrenia who do not respond to (or tolerate) an adequate trial of an antipsychotic treatment. The decision on which antipsychotic to use should be individualized.
    - Long-acting injectable antipsychotics are suggested for improving adherence in patients with schizophrenia.
    - Clozapine is recommended for treatment-resistance schizophrenia.
- **The American Psychiatric Association (APA) Practice Guideline for the treatment of patients with schizophrenia** (*Keepers et al 2020*).
  - Recommendations regarding pharmacotherapy include:
    - An antipsychotic medication is recommended to treat schizophrenia and the patient be monitored for effectiveness and adverse effects.
    - It is recommended to continue to treat with an antipsychotic medication if symptoms have improved. In addition, it is suggested to continue to treat with the same antipsychotic medication if symptoms have improved.

- Clozapine is recommended for treatment-resistant schizophrenia or if the risk of suicide attempts or suicide continues to be significant despite other treatments in patients with schizophrenia.
- It is suggested to treat with a long-acting injectable antipsychotic medication if the patient prefers such treatment or if there is a history of poor adherence.

Safety summary

- **Contraindications:**
  - In individuals with a known hypersensitivity reaction to milsaperidone or the inactive ingredients of the product.

- **Box Warning:**
  - Bysanti has a box warning regarding increased mortality in elderly patients with dementia-related psychosis.
    - Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Bysanti is not approved for the treatment of patients with dementia-related psychosis.

- **Warnings and precautions:**
  - In placebo-controlled trials in elderly patients with dementia-related psychosis treated with risperidone, aripiprazole, or olanzapine had a higher incidence of stroke and transient ischemic attack, including fatal stroke compared to those treated with placebo.
    - Bysanti is not approved for the treatment of patients with dementia-related psychosis.
  - In a QTc study, the use of iloperidone (iloperidone and milsaperidone rapidly interconvert in vivo) was associated with QTc interval prolongation, especially with concomitant use of a CYP2D6 inhibitor or a CYP3A4 inhibitor. No cases of torsade de pointes or other severe cardiac arrhythmias were observed in the iloperidone studies.
    - Certain circumstances may increase the risk of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval.
    - The concomitant use of Bysanti should be avoided with other drugs that prolong the QTc interval, including Class IA antiarrhythmics or Class III antiarrhythmics, antipsychotic drugs that prolong the QTc interval, antibiotics that prolong the QTc interval, or any other class of drugs known to prolong the QTc interval.
    - Avoid Bysanti in other patients with significant risk of developing torsade de pointes, including those with congenital long QT syndrome, recent MI, ischemic cardiomyopathy, unstable angina, bradyarrhythmia's, uncontrolled hypertension, high degree atrioventricular block, severe aortic stenosis, or uncontrolled hypothyroidism.
    - Patients being considered for Bysanti treatment who are at risk for significant electrolyte disturbances should have baseline serum potassium and magnesium measurements with periodic monitoring because hypokalemia (and/or hypomagnesemia) may increase the risk of QTc interval prolongation and arrhythmia.
    - Discontinue Bysanti in patients who are found to have persistent QTc measurements >500msec.
  - Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex, has been reported in association with administration of antipsychotic drugs, including iloperidone (iloperidone and milsaperidone rapidly interconvert in vivo).
    - If NMS is suspected, immediately discontinue Bysanti and provide intensive symptomatic treatment and monitoring.
  - Tardive dyskinesia may develop in patients treated with antipsychotics drugs, including Bysanti.
    - In patients who require chronic antipsychotic drug treatment, use the lowest dosage and shortest duration of treatment producing a satisfactory clinical response.
    - Periodically reassess the need for continued treatment.
  - Atypical antipsychotic drugs have caused metabolic changes (eg, hyperglycemia, dyslipidemia, and body weight gain) that may increase cardiovascular/cerebrovascular risk.

- Bysanti can induce orthostatic hypotension associated with dizziness, tachycardia, and syncope.
  - Orthostatic vital signs should be monitored in patients who are vulnerable to hypotension, patients with known cardiovascular disease, and patients with cerebrovascular disease.
- Antipsychotics, including Bysanti, may cause somnolence, postural hypotension, motor and sensory instability, which may lead to falls and, consequently, fractures or other injuries.
- Like other antipsychotics, Bysanti may cause seizures. The risk antipsychotic drug-associated is greatest is in patients with a history of seizures or with conditions that lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in older patients.
  - Use Bysanti cautiously in patients with a history of seizures or with other conditions that lower seizure threshold.
- In clinical trial and postmarketing experience, leukopenia and neutropenia have been reported temporally related to antipsychotic drug treatment. Agranulocytosis has also been reported with antipsychotic drug use.
  - Patients with a preexisting low white blood cell (WBC) or absolute neutrophil count (ANC) or a history of drug induced leukopenia or neutropenia should have frequently monitoring of their complete blood count during the first few months of Bysanti therapy and should discontinue Bysanti at the first sign of a decline in WBC in the absence of other causative factors.
- As with other drugs that antagonize dopamine D2 receptors, Bysanti elevates prolactin levels.
- Atypical antipsychotics may disrupt the body's ability to reduce core body temperature. Strenuous exercise, exposure to extreme heat, dehydration, and anticholinergic medications may contribute to an elevation in core body temperature.
  - Use Bysanti with caution in patients who may experience these conditions.
- Esophageal dysmotility and aspiration have been associated with antipsychotic drug use.
- Drugs with alpha-adrenergic blocking effects, including Bysanti, have been reported to induce priapism. Severe priapism may require surgical intervention.
- Bysanti may cause somnolence and has the potential to impair judgement, thinking or motor skills.
  - Patients should be cautioned about driving a motor vehicle or operating hazardous machinery, until they are reasonably certain that therapy with Bysanti does not adversely affect them.
- Intraoperative floppy iris syndrome has been observed during cataract surgery in some patients on or previously treated with alpha-1 adrenergic blockers.
  - The initiation of Bysanti in patients for whom cataract or glaucoma surgery is scheduled is not recommended. There does not appear to be a benefit of stopping alpha1 blocker therapy prior to cataract surgery.

- **Common adverse drug reactions**:
  - Listed % incidence for adverse drug reactions= reported % incidence for drug (iloperidone 10-16mg/day) minus reported % incidence from placebo in schizophrenia trials in adult patients. Please note that an incidence of 0% means the incidence was the same as or less than placebo
    - The most frequently reported adverse events included dizziness (3%), somnolence (4%), tachycardia (2%), dry mouth (7%), nausea (0%), weight increased (0%), nasal congestion (3%), diarrhea (1%), fatigue (1%), orthostatic hypotension (2%), extrapyramidal disorder (1%), nasopharyngitis (1%), arthralgia (1%), tremor (1%), upper respiratory tract infection (1%), abdominal discomfort (0%), hypotension (0%), musculoskeletal stiffness (0%), ejaculation failure (<2%), dyspnea (<2%), rash (1%), lethargy (2%), and vision blurred (`1%).
  - Listed % incidence for adverse drug reactions= reported % incidence for drug (iloperidone 24mg/day) minus reported % incidence from placebo in bipolar mania trial in adult patients. Please note that an incidence of 0% means the incidence was the same as or less than placebo
    - The most frequently reported adverse events included tachycardia (18%), dizziness (11%), dry mouth (7%), hepatic enzyme increased (7%), somnolence (5%), hypotension (3%), nasal congestion (5%), weight increased (5%),

headache (1%), nausea (1%), sexual dysfunction (<4%), akathisia (4%), fatigue (2%), and urinary urgency and polyuria (3%).

- **Drug interactions:**
  - Milsaperidone and iloperidone are CYP2D6 substrates.
    - Reduce the dosage of Bysanti when administered with a strong CYP2D6 inhibitor.
    - When the strong CYP2D6 inhibitor is stopped in Bysanti-treated patients, gradually increase the Bysanti dosage to the pre-inhibitor dosage.
  - Milsaperidone and iloperidone are CYP3A4 substrates.
    - Reduce the dosage of Bysanti when administered with a strong CYP3A4 inhibitor.
    - When the strong CYP3A4 inhibitor is stopped in Bysanti-treated patients, gradually increase the Bysanti dosage to the pre-inhibitor dosage.
  - Concomitant administration with a strong CYP2D6 inhibitor and a strong CYP3A4 inhibitor resulted in an increase in steady-state exposure of milsaperidone and iloperidone, which may increase the risk of Bysanti-associated adverse reactions.
    - Reduce the dosage of Bysanti if administered concomitantly with both a strong CYP2D6 inhibitor and a strong CYP3A4 inhibitor.
  - Iloperidone causes QTc interval prolongation.
    - Avoid concomitant use of Bysanti with other drugs that prolong the QTc interval.
  - Concomitant use of Bysanti with drugs that lower blood pressure could potentially cause symptomatic hypotension.
    - Avoid concomitant administration of Bysanti with alpha-adrenergic blocking agents and consider lowering the dosage of other drugs that lower blood pressure.

- **Special populations:**
    - Neonates exposed to antipsychotic drugs, including Bysanti, during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery.
      - There are no available data with use during pregnancy and available data from pharmacovigilance reports with iloperidone (iloperidone and milsaperidone rapidly interconvert in vivo) use during pregnancy are not sufficient to inform a drug-associated risk for major birth defects and miscarriage.
      - There are risks to the mother associated with untreated schizophrenia or bipolar I disorder.
      - There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Bysanti during pregnancy. For more information contact the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or visit online.
  - The safety and efficacy of use in the pediatric population have not been established.

Conclusion

- Schizophrenia is a persistent psychiatric condition described by a combination of positive symptoms (for instance hallucinations, delusions, and disorganized speech) as well as negative symptoms (for instance social withdrawal, flattened affect, and no motivation), and associated with general impairment in cognitive function (*Kovacevich et al 2025*).
- Bipolar Disorder (BP) is a mood disorder described as having recurrent episodes of unusually and continually elevated, expansive, or irritable mood, and fluctuating or interweaving episodes of major depression (*Zimmerman et al 2025*).
- Bysanti is an atypical antipsychotic indicated for:
  - Treatment of schizophrenia in adults.
  - Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults.

- It has a box warning regarding increased mortality in elderly patients with dementia-related psychosis.
- In a QTc study, the use of iloperidone (iloperidone and milsaperidone rapidly interconvert in vivo) was associated with QTc interval prolongation, especially with concomitant use of a CYP2D6 inhibitor or a CYP3A4 inhibitor.
  - The concomitant use of Bysanti should be avoided with other drugs that prolong the QTc interval.
  - Bysanti should be discontinued in patients who are found to have persistent QTc measurements >500 msec.
- The efficacy of Bysanti in the treatment of schizophrenia in adults has been established from adequate and well-controlled studies of iloperidone tablets (referred to as iloperidone [iloperidone and milsaperidone rapidly interconvert in vivo]) in adults with schizophrenia.
- The efficacy of Bysanti in the acute treatment of manic or mixed episodes associated with bipolar I disorder has been established from an adequate and well-controlled study of iloperidone tablets (referred to as iloperidone [iloperidone and milsaperidone rapidly interconvert in vivo]) in adults with manic or mixed episodes associated with bipolar I disorder.
- Guidelines do not currently include Bysanti as guidelines were published prior to its FDA approval. Other atypical antipsychotics that may be comparators to Bysanti include Fanapt (iloperidone), Latuda (lurasidone), Zyprexa (olanzapine), Risperdal (risperidone), Seroquel (quetiapine), and Vraylar (cariprazine), among others.

- There is no evidence to suggest that Bysanti is safer or more effective than other currently preferred, more cost-effective medications. It is therefore recommended that Bysanti remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

- **PDL Placement:**
  - ☐ Preferred
  - ☒ Non-Preferred Step 3

References

- Bysanti. Package insert. Vanda Pharmaceuticals Inc.; February 2026.
- Keepers GA, Fochtmann LJ, Anzia JM, et al. The American Psychiatric Association Practice Guideline for the treatment of patients with schizophrenia. *Am J Psychiatry*. 2020; 177:9.
- Kovacevich A, Rae-Grant A, Jolanda van Zuuren E. Schizophrenia. Dynamed Website. Updated December 19, 2025. Accessed June 16, 2026. https://www.dynamed.com.
- VA/DoD Clinical Practice Guideline. (2023). Management of Bipolar Disorder Work Group. Washington, DC: U.S. Government Printing Office. May 2023. Accessed June 16, 2026. https://www.healthquality.va.gov/HEALTHQUALITY/guidelines/MH/bd/VA-DOD-CPG-BD-Full-CPGFinal508.pdf.
- VA/DoD Clinical Practice Guideline. (2023). Management of first-episode psychosis and schizophrenia Work Group. Washington, DC: U.S. Government Printing Office. April 2023. Accessed June 16, 2026. https://www.healthquality.va.gov/HEALTHQUALITY/guidelines/MH/scz/VA-DOD-CPG-Schizophrenia-CPG_Finalv231924.pdf.
- Zimmerman M, Preda A, Rae-Grant A, et al. Bipolar disorder in adults. Dynamed Website. Updated December 19, 2025. Accessed June 16, 2026. www.dynamed.com.

Publication Date: June 2026.