CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

220358Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: February 18, 2026

To: Sandy Chang, Regulatory Project Manager, Division of Psychiatry (DP)

Paul Bossie, Clinical Reviewer, DP

From: Rachael Oyewole, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Taylor Burnett Mmagu, Team Leader, OPDP

Subject: OPDP Labeling Comments for BYSANTI™ (milsaperidone) tablets, for oral use (Bysanti)

NDA: 220358

Background:
In response to DP's consult request dated April 4, 2025, OPDP has reviewed the proposed Prescribing Information (PI) and carton and container labeling for the original NDA submission for Bysanti.

PI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on February 17, 2026, and we do not have any comments at this time.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on January 16, 2026, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Rachael Oyewole at 301-796-0586 or Rachael.Oyewole@fda.hhs.gov.

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/s/

RACHAEL O OYEWOLE
02/18/2026 04:27:02 PM

MEMORANDUM
REVIEW OF REVISED LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	February 11, 2026
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 220358
Product Name, Dosage Form, and Strength:	Bysanti (milsaperidone) tablets, 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg
Applicant Name:	Vanda Pharmaceuticals Inc.
FDA Received Date:	February 10, 2026
TTT ID #:	2025-13360-3
DMEPA 1 Safety Evaluator:	Amy J. Bao, PharmD, MPH
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

Vanda Pharmaceuticals Inc. submitted revised titration pack labeling received on February 10, 2026 for Bysanti. The Division of Psychiatry (DP) requested that we review the revised titration pack labeling for Bysanti (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

Vanda Pharmaceuticals Inc. implemented all of our recommendations and we have no additional recommendations at this time.

[a] Bao, A. Review of Revised Label and Labeling for Bysanti (NDA 220358). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2026 Feb 04. TTT ID: 2025-13360-2.

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/s/

AMY J BAO
02/11/2026 10:59:53 AM

YEVGENIYA M KOGAN
02/11/2026 01:42:26 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	February 4, 2026
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 220358
Product Name, Dosage Form, and Strength:	Bysanti (milsaperidone) tablets, 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg
Applicant Name:	Vanda Pharmaceuticals Inc.
FDA Received Date:	January 16, 2026
TTT ID #:	2025-11360-2
DMEPA 1 Safety Evaluator:	Amy J. Bao, PharmD, MPH
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

Vanda Pharmaceuticals Inc. submitted revised container labels and carton labeling received on January 16, 2026 for Bysanti. The Division of Psychiatry (DP) requested that we review the revised container labels and carton labeling for Bysanti (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The titration pack labeling is unacceptable from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for Vanda Pharmaceuticals Inc. in Section 3.

[a] Bao, A. Review of Revised Label and Labeling for Bysanti (NDA 220358). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2026, Jan 02. TTT ID: 2025-11360-1.

3 RECOMMENDATIONS FOR VANDA PHARMACEUTICALS INC.

A. General Comments (Commercial and Professional Sample Titration Pack Labeling)

1. We note the location and presentation of the statement of dosage ("Recommended Dosage: See Prescribing Information") continues to compete in prominence with other critical information on the Principal Display Panel. We recommend unbolding the statement. Additionally, consider relocating the statement away from the proprietary name, established name, and titration pack name.

2. We acknowledge that you have updated the opening instructions, however we note the word "PEEL" in step 2 is not readily apparent as part of the instructions due to its positioning and surrounding black tab. We recommend revising the opening instructions so the step 2 instructions can be read more clearly. Consider moving "PEEL" to appear in-line with the second row of text so it is more clearly distinguished as part of the text instructions (see example shown below), or other methods.

B. Commercial Titration Pack Labeling

1. We note Titration Pack C is missing (b) (4) under the Day 3 dosage instructions. Revise the instructions to read "Take one 6 mg tablet in the morning (AM), and one 6 mg tablet in the evening (PM).".

C. Professional Sample Titration Pack Labeling

1. We note in Titration Pack B, there appears to be extra spacing between the dosage instructions and the "Day 2" and "Day 4" headers, which does not align with the formatting of the other titration days. We recommend centering the text consistently for clarity and ease of reading.

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/s/

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MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	January 2, 2026
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 220358
Product Name, Dosage Form, and Strength:	Bysanti (milsaperidone) tablets, 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg
Applicant Name:	Vanda Pharmaceuticals Inc.
FDA Received Date:	November 14, 2025
TTT ID #:	2025-13360-1
DMEPA 1 Safety Evaluator:	Amy J. Bao, PharmD, MPH
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

Vanda Pharmaceuticals Inc. submitted revised container labels and carton labeling received on November 14, 2025 for Bysanti. The Division of Psychiatry (DP) requested that we review the revised container labels and carton labeling for Bysanti (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a] Of note, Vanda did not submit a revised container label or carton labeling for the (b) (4) as it is no longer requested for market authorization.

2 CONCLUSION

The commercial container labels and titration pack labeling, and professional sample container labels, carton labeling, and titration pack labeling are unacceptable from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for Vanda Pharmaceuticals Inc. in Section 3.

[a] Bao, A. Label and Labeling Review for Bysanti (NDA 220358). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2025 Oct 29. TTT ID: 2025-13360.

3 RECOMMENDATIONS FOR VANDA PHARMACEUTICALS INC.

A. Commercial Container Labels

1. Revise “Washington D,.C.” to read “Washington, D.C.”.
2. We note the storage conditions may appear more clearly on two lines of text instead of three lines. Additionally, revise the storage conditions to delete the extraneous spaces between the degree symbols and Celsius (C) and Fahrenheit (F) symbols, i.e.:

   Store at 20°C to 25°C (68°F to 77°F), with excursions
   permitted between 15°C to 30°C (59°F to 86°F).

B. Professional Sample Container Labels

1. Revise the storage conditions to delete the extraneous spaces between the degree symbols and Celsius (C) and Fahrenheit (F) symbols.

C. Professional Sample Carton Labeling

1. Revise the storage conditions to delete the extraneous spaces between the degree symbols and Celsius (C) and Fahrenheit (F) symbols.
2. We note there are two stray period marks (marked within red squares in the image below) in the storage and handling information. Delete the stray period marks so the storage and handling information is legible.

D. General Comments (Commercial and Professional Sample Titration Pack Labeling)

1. The titration pack name (e.g., Titration Pack A) continues to lack prominence. We recommend further increasing the size of the titration pack name if possible.
2. We note the statement of dosage, and storage and handling information compete in prominence with other critical information on the Principal Display Panel. We recommend unbolding the statement of dosage, and storage and handling information. Additionally, consider relocating the statement of dosage away from the titration pack name and into the colored block of the Principal Display Panel. Furthermore, if space allows, we recommend relocating the storage and handling information to the back panel (where “HOW TO BEGIN THERAPY WITH Bysanti” appears), in order to avoid cluttering of information on the Principal Display Panel.
3. On the back panel of the titration packs, we recommend revising the statement (b) (4) to read “as directed by your healthcare provider”, as (b) (4) is a narrow term which does not encompass all potential prescribers.

4. We note the instructions for removal of the tablets may be improved for clarity. For example, consider:

   1. Push through the perforated tab above or below the tablet cavity
   2. Turn card over and peel tab to expose foil
   3. Push out the tablet through the foil

   We recommend using the word "tablet" instead of (b) (4) for consistency in language throughout labeling.

   Additionally, we recommend you consider adding images associated with each step to assist users with comprehending the removal instructions.

5. To further assist in clarity of the tablet removal instructions, we recommend adding the text "PUSH" on top of the tabs above or below each tablet cavity.

6. We recommend revising the "EVENING" row to have "Evening" appear above the tablet cavity and the strength appear below the tablet cavity, in the same layout as the "MORNING" row, in order to assist with visual differentiation between the morning and evening doses.

7. We acknowledge that you have included a plus sign (+) and "take together" to signal that two tablets should be taken together. For additional visual clarity, consider also adding a circle around the tablet cavities (see example shown in red, below).

   

8. We note the (b) (4) letter string in "DOSAGE INSTRUCTIONS:" on the back panel of Titration Pack A appears slightly different visually and is not recognized as text by a PDF reader. Please ensure this text will be printed as intended.

9. We note inconsistencies in the size of the tablet cavity size for the 1 mg tablet in Titration Packs B and C (i.e., depicted as a larger size on Day 2 compared to Day 1). Please verify the correct dimensions for all tablet cavities and make corrections as needed.

10. We note Titration Pack B does not list the correct contents of the pack. Revise the list of contents to read:

    Six 1 mg tablets
    Two 2 mg tablets

Two 6 mg tablets
Two 8 mg tablets

11. We note Titration Pack B has the "HOW TO BEGIN THERAPY WITH Bysanti™" statement bolded, while Packs A and C do not. We recommend aligning the formatting between all packs for consistency.

12. We note Titration Pack B has (b) (4) while all other instances where two tablets must be taken together have "Morning/Evening" written above/below each individual tablet cavity. We find either presentation acceptable, but recommend you standardize the presentation between all titration packs that require two tablets being taken together.

E. Commercial Titration Pack Labeling

1. As currently presented, the linear barcode and 2D data matrix barcode are located in close proximity to each other. The drug barcode is often used as an additional verification during the medication use process. The presence of barcodes in close proximity to one another could lead to scan errors. We recommend rearranging the barcodes (and their associated human-readable information) so that they not appear directly next to one another.

F. Professional Sample Titration Pack Labeling

1. We recommend unbolding the "PROFESSIONAL SAMPLE – NOT FOR SALE" statement so it does not compete in prominence with other critical information on the Principal Display Panel. Additionally, consider relocating the statement away from the titration pack name and into the colored block of the Principal Display Panel.

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/s/

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YEVGENIYA M KOGAN
01/02/2026 04:49:16 PM

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: December 2, 2025

To: Tiffany Farchione, MD, Director, Division of Psychiatry

Through: Dominic Chiapperino, PhD, Director, Controlled Substance Staff (CSS)

From: Joshua M. Lloyd, MD, Medical Officer Team Leader, CSS

Subject: **NDA 220358** for Bysanti (milsaperidone) tablets
Proposed Indication: Treatment of schizophrenia in adults and acute treatment of manic or mixed episodes associated with bipolar I disorder in adults
Dosage Form and Strengths: Immediate-release oral tablets; 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg
Applicant: Vanda Pharmaceuticals, Inc.
PDUFA Goal Date: February 21, 2026

Submission: Original New Drug Application (NDA) Submission, Supporting Document 1, received February 21, 2025, and relevant subsequent amendments

I. Background

This memorandum is in response to a consult request dated October 27, 2025, from the Division of Psychiatry (DP) pertaining to NDA 220358 for review of the Applicant's proposed labeling in Sections 9 and 10, along with the proposed edits to these sections from the labeling team.

Vanda Pharmaceuticals, Inc. (the "Applicant" or "Vanda") submitted a New Drug Application (NDA) for milsaperidone under the 505(b)(1) regulatory pathway cross referencing their approved NDA for iloperidone (NDA 22192; approved 5/6/2009). Milsaperidone is a major active metabolite of iloperidone, which is approved in adults for treatment of schizophrenia and acute manic or mixed episodes associated with bipolar I disorder. Both milsaperidone and iloperidone are atypical antipsychotic agents that have moderate to strong affinity for adrenergic α1, α2B, and α2C; dopamine D1, D2, D3, and D4; histamine H1; and serotonin 5-HT1B, 5-HT2A, and 5-HT2C receptors. Atypical antipsychotics are thought to mediate their therapeutic

effects through a combination of dopamine type 2 (D2) and serotonin type 2a (5-HT2a) receptor antagonism. Milsaperidone is believed to contribute to the efficacy of iloperidone, and there is rapid interconversion between the two compounds in vivo in humans.

The NDA currently under review for milsaperidone does not contain any efficacy studies and is based on bioavailability studies that demonstrate "milsaperidone and iloperidone have equivalent exposure and that milsaperidone has met bioequivalence criteria with respect to iloperidone at both 1) single oral doses… and 2) under steady-state conditions at the highest approved therapeutic dose of iloperidone (12mg BID)."

The approved labeling for iloperidone contains the following information in Section 9:

II. Conclusions

- Milsaperidone is an atypical antipsychotic proposed for the treatment of schizophrenia in adults and the acute treatment of manic or mixed episodes associated with bipolar I disorder in adults.
- Milsaperidone is a major active metabolite of the approved atypical antipsychotic medication iloperidone, and there is rapid interconversion between these substances in

vivo in humans. The NDA for milsaperidone is based on demonstrating bioequivalence to iloperidone.

- Milsaperidone, like other atypical antipsychotic agents, exhibits complex receptor pharmacology but is thought to primarily mediate its therapeutic effects through antagonism at the D2 (dopamine) and 5HT2a (serotonin) receptors.
- Milsaperidone and iloperidone, like other atypical antipsychotic agents, are not controlled under the Controlled Substances Act. Furthermore, there are no specific abuse-related data for milsaperidone to convey to prescribers. Therefore, Section 9 of the Prescribing Information is not relevant for the proposed product and, ideally, would be deleted from the listed drug's label as well.
    - Misuse, as defined in the draft guidance for industry, *Drug Abuse and Dependence Section of Labeling for Human Prescription Drug and Biological Products — Content and Format Guidance for Industry* (July 2019), is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a health care provider or for whom it was not prescribed. Misuse is a distinct concept from abuse described in Section 9 of labeling to inform prescribers of that risk; it does not, by default, get paired with the term abuse in labeling.
    - Assuming arguendo that Section 9 were to be included in the approved labeling, CSS would not recommend (b) (4) as there are currently no systematic nonclinical or clinical studies to determine the extent to which a drug may be misused, as there are for abuse potential.
- The Division also requested that CSS provide input on the labeling team's proposed revisions to Section 10 Overdosage. However, Section 10 of the labeling pertains to the signs and symptoms of overdose, as well as the clinical management of an overdose and related information, whether the overdose is related to abuse or not. Although CSS reviews information related to overdose cases to inform the abuse potential of a substance, as these cases may be related to abuse; Section 10 of the labeling does not typically contain abuse-related information. Therefore, we defer to the Division on the acceptability of the Applicant's proposed labeling and the labeling team's proposed edits for Section 10.

III. Recommendations

- CSS recommends omitting Section 9 in the proposed labeling if the product were to be approved.

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/s/

JOSHUA M LLOYD
12/02/2025 11:18:03 AM

DOMINIC CHIAPPERINO
12/03/2025 03:41:45 PM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	October 29, 2025
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 220358
Product Name, Dosage Form, and Strength:	Bysanti (milsaperidone) tablets, 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Vanda Pharmaceuticals Inc.
FDA Received Date:	February 21, 2025 and June 18, 2025
TTT ID #:	2025-13360
DMEPA 1 Safety Evaluator:	Amy J. Bao, PharmD, MPH
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 INTRODUCTION

As part of the approval process for Bysanti (milsaperidone) tablets, the Division of Psychiatry (DP) requested that we review the proposed Bysanti Prescribing Information (PI); commercial container labels and titration pack labeling; and professional sample container labels, carton labeling, and titration pack labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS CONSIDERED

This section lists the materials considered for our review.

Table 1. Materials Considered for this Review	
Materials Considered	Appendix Section
Relevant Product Information	A
Labels and Labeling	B
Information Request (IR)	C

3 CONCLUSION

The proposed Bysanti Prescribing Information (PI); commercial container labels and titration pack labeling; and professional sample container labels, carton labeling, and titration pack labeling may be improved to promote safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Psychiatry (DP) in Section 4 and for Vanda Pharmaceuticals Inc. in Section 5.

4 RECOMMENDATIONS FOR THE DIVISION OF PSYCHIATRY (DP)

A. Prescribing Information

1. Section 2 Dosage and Administration

    a. As currently presented in Table 1, the titration schedule table does not make it clear that the target dose (6 mg to 12 mg twice daily) may be reached before Day 7 (12 mg twice daily). We recommend adding a statement to clarify that titration on Days 5, 6, and 7 is only continued as needed.

    b. Consider revising the title of Table 2 so that it is also applicable to administration with strong CYP2D6/CYP3A4 inhibitors, as those dosage modifications are the same as the dosage modifications for CYP2D6 poor metabolizers.

    c. We recommend changing the dosage modification instructions in Sections 2.2 and 2.4 from (b) (4) to "Follow the titration schedule outlined in Table 2 for dosage modifications".

2. Section 16 How Supplied/Storage and Handling

    a. We are concerned that it is unclear which indications correspond to which titration packs (A, B, or C). We recommend adding a separate package configuration table for the titration packs and clarifying the indications that each pack is associated with.

    b. The storage information is missing the "C" and "F" units for Celsius or Fahrenheit after the first temperature numerical value. We recommend revising from "15° to 30 °C (59° to 86°F)" to "15°C to 30°C (59°F to 86°F)"

5 RECOMMENDATIONS FOR VANDA PHARMACEUTICALS INC.

A. General Comments (All Commercial and Professional Sample Labels and Labeling)

1. The established name (active ingredient and dosage form) is not at least half the size of the proprietary name. We refer you to 21 CFR 201.10(g)(2) which states that the established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Revise the established name to be in accordance with 21 CFR 201.10(g)(2).

2. The strength lacks adequate spacing between the number and the unit of measure. Lack of adequate spacing may impact readability and might result in wrong strength errors. We recommend placing adequate space between the numerical dose and unit of measure (e.g., "1 mg" instead of "1mg") to improve readability.

3. For the commercial container labels, professional sample container labels, and professional sample carton labeling, the terminology within the statement of dosage (i.e., [redacted] (b) (4) and [redacted] (b) (4)) is inconsistent with the terminology in the Prescribing Information. To ensure consistency with the terminology in the Prescribing Information, we recommend revising the statement of dosage to read, "Recommended Dosage: see Prescribing Information.".

4. For the commercial container labels, professional sample titration pack labeling, and professional sample carton labeling, the placeholder for the expiration date is missing. The label of an official drug product shall bear an expiration date per USP General Chapter <7>. Add the placeholder for the expiration date in accordance with USP General Chapter <7>.

5. For the commercial container labels, professional sample container labels, professional sample titration pack labeling, and professional sample carton labeling, the format for the expiration date is not defined. We are unable to assess the proposed expiration date format from a medication safety perspective. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend identifying the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical

characters are used to represent the month. FDA recommends that a hyphen or forward slash to separate the portions of the expiration date. See *Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021)*.

6. For the commercial container labels, professional sample titration pack labeling, and professional sample carton labeling, the placeholder for the lot number is missing. The lot number statement is required on the immediate container AND carton labeling when there is sufficient space per 21 CFR 201.10(i)(1). Add the placeholder for the lot number in accordance with 21 CFR 201.10(i)(1).
7. The storage instructions can be revised for clarity. We recommend revising the storage instructions to include the Celsius (C) and Fahrenheit (F) symbols following each numeric degree measurement of temperature ranges, and to replace the dash symbol with its intended meaning. For example, we recommend revising "15°-30°C (59°-86°F)" to read "15°C to 30°C (59°F to 86°F)".

B. General Comments (Commercial and Professional Sample Container Labels)

1. The "Rx only" statement competes in prominence with other critical information (e.g., established name, strength, net quantity) on the principal display panel. We recommend unbolding and decreasing the font size of the "Rx only" statement so it does not compete in size or prominence with critical information on the principal display panel. See *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)*.
2. The net quantity appears prominently on the PDP. Product selection or dosing errors can occur if the net quantity statement is mistaken for the product strength, leading to incorrect dosing. We recommend reducing the prominence of the net quantity (e.g., decreasing the size and unbolding the font).

C. Commercial Container Labels

1. The 10 mg strength is not clearly differentiated due to the overlap with the (b) (4) . Lack of adequate differentiation may contribute to wrong strength errors. Color differentiation is most effective when the color used has no association with a particular feature and there is no pattern in the application of the color scheme. We recommend revising the color scheme of the 10 mg strength such that it does not overlap with the (b) (4)
2. The product identifier is missing. In June 2021, FDA finalized the Guidance for Industry on product identifiers required under the Drug Supply Chain Security Act (DSCSA). The Act requires manufacturers and re-packagers to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce. The product identifier includes the NDC, serial number, lot number, and expiration date in

both a human-readable form and machine-readable (2D data matrix barcode) format. Add the product identifier placeholder to the container label. See *Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).*

3. On the PDP the NDC is bolded. Overuse of bold font may diminish its effect on prominence of more important information. We recommend unbolding the NDC.

D. Professional Sample Container Labels

1. For clarity and readability, we recommend updating the statement by decreasing the spacing within the statement:

   "PROFESSIONAL SAMPLE NOT FOR SALE"

   to read

   "PROFESSIONAL SAMPLE – NOT FOR SALE"

2. We recommend ensuring the proprietary name, established name, and strength appear in the same field of view without requiring the user to turn the bottle to read critical information. Consider relocating the strength to appear directly beneath the established name.

E. General Comments (Commercial and Professional Sample Titration Pack Labeling)

1. There is inadequate differentiation between Titration Packs A, B, and C. Lack of adequate differentiation may contribute to titration pack selection medication errors. We recommend using different colors for each individual titration pack; additionally consider utilizing boxing, or some other means to ensure adequate differentiation between the different titration pack configurations. See *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)*.

2. The titration pack name (e.g., Titration Pack A) lacks prominence. Increasing the prominence of the titration pack name will improve readability. We recommend increasing the size of the titration pack name.

3. We recommend updating the statement [redacted] (b) (4) to read "This titration pack contains:" for clarity.

4. For increased clarity, we recommend removing the dash marks that appear between the numerical strength and units (e.g., update "1-mg" to read "1 mg").

5. As currently presented, the usual dosage statement located on the PDP is confusing. The intended meaning of the displayed usual dosage information (e.g., [redacted] (b) (4) is unclear. [redacted] (b) (4) We recommend deleting [redacted] (b) (4) from the

PDP, and instead, adding the statement of dosage "Recommended Dosage: See Prescribing Information" to the titration packs consistent with 21 CFR 201.55.

6. The titration packs have a (b) (4) area on the inside. The purpose for having this area on the trade titration packs is unclear and may be omitted by providers causing confusing. Please provide your rationale for this area. If it is not needed, please delete the statement (b) (4)

7. There are no instructions that state how the tablets should be removed from the titration pack. The lack of instructions may lead the user to attempt to push the tablet through the packaging and to result in tablet breakage when removing them from the titration pack. Provide brief instructions on how to remove the tablets from the titration pack on the back panel.

8. We are concerned that the "MORNING" and "EVENING" row headers (b) (4) are not clearly distinguished as row headers. We recommend separating the "MORNING" and "EVENING" row headers into a column distinct from the "DAY 1" column. Additionally, consider the use of two distinct colors for the "MORNING" and "EVENING" headers for enhanced visual distinction.

9. On certain days, the user must combine more than one tablet strength (i.e., 2 tablets) to achieve the specified dose. As currently presented, the user may inadvertently take the tablets that are positioned vertically rather than horizontally. Consider using a symbol or graphic that would signify which of the two tablets should be taken together (e.g., double ended arrow (↔), plus sign (+), encircling the two strengths together, etc.,) and a clarifying statement (i.e., "take together"), or other means to "link" the two tablets that should be taken together.

F. Commercial Titration Pack Labeling

1. We note Titration Pack C contains unsupported characters in the distributor information on the back panel. Update the labeling to replace the unsupported characters with legible characters.

(b) (4)

G. Professional Sample Titration Pack Labeling

1. We note Titration Packs B and C contain an unsupported character on the Principal Display Panel, where the "tt" in "permitted" should appear. Update the labeling to replace the unsupported characters with legible characters.

(b) (4)

H. Professional Sample Carton Labeling

1. We note for the 1 mg and 8 mg strengths, the letter “y” in “Bysanti” appears misaligned on the first and third panels, respectively. Adjust the letter spacing so that the proprietary name is legible.

APPENDICES: MATERIALS CONSIDERED FOR THIS REVIEW

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Bysanti received on June 18, 2025 from Vanda Pharmaceuticals Inc.

Table 2. Relevant Product Information for Bysanti	
Initial Approval Date	N/A
Active Ingredient	milsaperidone
Indication	• Treatment of schizophrenia in adults. • Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults.
Dosage Form	tablets
Strength	1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg
Route of Administration	Oral
Dose and Frequency	(b) (4)

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Bysanti</th></tr>
<tr><td>How Supplied</td><td>

1 mg tablets: yellow, oval shaped, debossed with "1" on one side and “ ” logo on other side
2 mg tablets: pink oblong oval shaped, debossed with "2" on one side and “ ” logo on other side
4 mg tablets: blue oval shaped, debossed with "4" on one side and “ ” logo on other side
6 mg tablets: orange oblong oval shaped, debossed with "6" on one side and “ ” logo on other side
8 mg tablets: white, oval shaped, debossed with "8" on one side and “ ” logo on other side
10 mg tablets: white, oblong oval shaped, debossed with "10" on one side and “ ” logo on other side
12 mg tablets: purple, octagon shaped, debossed with "12" on one side and “ ” logo on other side

<table>
<tr><th>Package Configuration</th><th>Tablet Strength (mg)</th><th>NDC Code</th></tr>
<tr><td>Bottles of 60</td><td>1 mg</td><td>43068-701-02</td></tr>
<tr><td>Bottles of 60</td><td>2 mg</td><td>43068-702-02</td></tr>
<tr><td>Bottles of 60</td><td>4 mg</td><td>43068-704-02</td></tr>
<tr><td>Bottles of 60</td><td>6 mg</td><td>43068-706-02</td></tr>
<tr><td>Bottles of 60</td><td>8 mg</td><td>43068-708-02</td></tr>
<tr><td>Bottles of 60</td><td>10 mg</td><td>43068-710-02</td></tr>
<tr><td>Bottles of 60</td><td>12 mg</td><td>43068-712-02</td></tr>
</table>
(b) (4)
</td></tr>
<tr><td>Storage</td><td>Store at controlled room temperature, (b) (4) excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from exposure to light and moisture.</td></tr>
<tr><td>Container Closure</td><td>HDPE bottles and titration packs</td></tr>
</table>

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Bysanti labels and labeling submitted by Vanda Pharmaceuticals Inc.

- Prescribing Information received on June 18, 2025, available from \\CDSESUB1\evsprod\NDA220358\0007\m1\us\114-label\1141-draft-label\proposed.docx
- Container labels received on February 21, 2025
- Titration pack labeling received on February 21, 2025
- Professional sample container labels, carton labeling, and titration pack labeling received on June 18, 2025

B.2 Container Labels and Carton Labeling Images

Container Labels:

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

14 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

APPENDIX C. INFORMATION REQUEST (IR)

FDA Information Request sent on May 01, 2025 (in Filing Communication):

We note that carton labeling for the commercial 60-count bottle presentations was not included in your submission, while the professional sample 14-count bottles were submitted with a container label as well as carton labeling. Additionally, we note that only commercial container labels were provided for the 4 mg, 10 mg, and 12 mg strengths, while both commercial and professional sample labeling was provided for the 1 mg, (b) (4) 6 mg, and 8 mg strengths. Please confirm that all container labels and carton labeling were submitted as intended, and if needed, submit any missing labeling for our review.

Applicant Response received on June 18, 2025, available from:
\\CDSESUB1\evsprod\NDA220358\0007\m1\us\12-cov-let\cover.pdf

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/

AMY J BAO
10/29/2025 10:42:49 AM

YEVGENIYA M KOGAN
10/29/2025 12:53:23 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatrics and Maternal Health Review

Date: 10/17/2025 **Date consulted:** 7/10/2025

From: Katherine Kratz, MD, Medical Officer, Maternal Health Team (MHT)
Division of Pediatrics and Maternal Health (DPMH)

Through: CDR Miriam Dinatale, DO, Team Leader, MHT, DPMH

Lynne P. Yao, MD, OND, Division Director, DPMH

To: Division of Psychiatry (DP)

Drug: BYSANTI (milsaperidone)

NDA: 220358

Applicant: Vanda Pharmaceuticals, Inc.

Subject:

- Pregnancy and Lactation Labeling
- Recommendations for post-marketing studies related to pregnancy and lactation

Proposed Indications:

- Treatment of schizophrenia in adults
- Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults

Materials Reviewed:

- DPMH consult request dated 7/10/2025. DARRTS Reference ID: 5622529
- Applicant's submitted background package and proposed labeling for NDA 220358, Sequence Number (SN) 0001, dated 2/21/25.

- DPMH review of Risperdal (risperdone) NDAs 20272, 20588, 21444, 21346, 21999, 22264, 207946 by Catherine Roca, MD, dated 4/17/2018. DARRTS Reference ID: 4248840
- DPMH review of Fanapt (iloperidone) NDA 022192 by Miriam Dinatale, DO, dated 5/3/2016. DARRTS Reference ID: 3925448
- Information Request for NDA 220358, dated 7/28/2025, DARRTS Reference ID: 5632850
- Applicant's response to IR for NDA 220358, SN 0011, dated 8/25/2025

Consult Request: "DP would like DPMH to weigh in and provide input on 1) whether to recommend a [postmarketing requirement] PMR for a clinical lactation study, and if so 2) guidance on the type of studies needed." Additionally, DP is requesting DPMH input on labeling for subsections 8.1 and 8.2.

I. INTRODUCTION AND BACKGROUND

On February 1, 2025, the Applicant, Vanda Pharmaceuticals, Inc., submitted a 505(b)(1) New Drug Application (NDA) for New Molecular Entity (NME) Bysanti (milsaperidone) for the treatment of schizophrenia and acute manic or mixed episodes associated with bipolar I disorder in adults. Milsaperidone is the active metabolite of Fanapt (iloperidone) and was approved by FDA in 2009 for the treatment of schizophrenia in adults. Fanapt was subsequently approved in 2024 for acute treatment of manic or mixed episodes associated with bipolar I disorder (BD) in adults. Fanapt is marketed by the Applicant. The Applicant is relying on nonclinical and clinical efficacy and safety data from the iloperidone development program. Nonclinical and clinical reproductive toxicity data submitted under iloperidone will not be included in this review; the reader is referred to the iloperidone review completed by DPMH for nonclinical reproductive toxicity data.[1] (b) (4) The new data in this submission pertain to bioequivalence and bioavailability studies comparing milsaperidone to iloperidone. DP consulted the DPMH on July 10, 2025, to provide input on a PMR for a clinical lactation study and on proposed labeling for subsections 8.1 and 8.2.

Relevant Regulatory History

- FDA has approved other atypical antipsychotic drug products indicated to treat both schizophrenia and acute manic or mixed episodes associated with bipolar I disorder in adults with therapeutic activity that is not clearly known but could be mediated through the dopamine Type 2 (D_2) and serotonin Type 2A (5-HT_{2A}) receptor antagonism as is the case for milsaperidone. Examples of D_2/5-HT_{2A} antagonists approved by FDA to treat both schizophrenia and BD over the last three decades include risperidone, olanzapine, quetiapine, ziprasidone, paliperidone, asenapine, lurasidone, and iloperidone.
    - The labeling for D_2/5-HT_{2A} antagonists states the following under the Highlights of Prescribing Information, Use in Specific Populations:

[1] DPMH review of Fanapt (iloperidone) NDA 022192 by Miriam Dinatale, DO, dated 5/3/2016. DARRTS Reference ID: 3925448

        - "Pregnancy: May cause extrapyramidal and or/withdrawal symptoms in neonates with third trimester exposure (8.1)."
    - The labeling for some D_2/5-HT_{2A} antagonists (risperidone, olanzapine, quetiapine, ziprasidone, and paliperidone) states the following under 8.1, Pregnancy, Clinical Considerations, Disease-associated maternal and/or embryo/fetal risk:
        - There is risk to the mother from untreated schizophrenia or bipolar I disorder, including increased risk of relapse, hospitalization, and suicide. Schizophrenia and bipolar I disorder are associated with increased adverse perinatal outcomes, including preterm birth. It is not known if this is a direct result of the illness or other comorbid factors.
- 2016: Fanapt labeling was converted to the Pregnancy and Lactation Labeling Rule (PLLR) format. DPMH was consulted for the PLLR labeling conversion. With the PLLR labeling conversion, a Pregnancy Exposure Registry section was added under subsection 8.1 that refers prescribers to the National Pregnancy Registry for Atypical Antipsychotics that is overseen by the MGH Center for Women's Mental Health. Of note, Vanda has declined to sponsor the Registry.[2] Vanda requested data related to iloperidone from the National Pregnancy Registry for Atypical Antipsychotics, but the Registry stated that it "does not provide reports of adverse events to manufacturers who are not sponsors." In terms of lactation, the Fanapt labeling includes a warning against breastfeeding in the Highlights of Prescribing Information because it was found to be present in rat milk and there is a potential for adverse reactions in breastfed infants.

II. REVIEW

PREGNANCY

Schizophrenia and Pregnancy

DPMH has previously reviewed schizophrenia and pregnancy.[3,4] Additional information presented here is from a published review by Dazzan.[5] Schizophrenia is present in 1% of the general population and is diagnosed in women between the ages of 25 and 35 years. Symptoms of schizophrenia include hallucinations or delusions, disorganized or poverty of speech, flat affect, and cognitive impairments in attention, memory, and executive functioning.
Pregnant women with schizophrenia have higher rates of gestational diabetes compared to pregnant women in the general population. They also have an increased risk of adverse pregnancy outcomes, including preterm birth, placental abnormalities, and antepartum hemorrhage. Infants born to women with schizophrenia have adverse outcomes such as being small for gestational age (SGA) and having low APGAR scores of less than 8 at one and five minutes. Medical treatment of schizophrenia during pregnancy involves typical antipsychotics, especially haloperidol, perphenazine, and chlorpromazine,[6] and atypical antipsychotics,

[2] https://womensmentalhealth.org/research/pregnancyregistry/
[3] DPMH review of Fanapt (iloperidone) NDA 022192 by, Miriam Dinatale, DO, dated 5/3/2016. DARRTS Reference ID: 3925448
[4] DPMH review of Risperdal (risperdone) NDAs 20272, 20588, 21444, 21346, 21999, 22264, 207946 by Catherine Roca, MD, dated 4/17/2018. DARRTS Reference ID: 4248840
[5] Dazzan P. Schizophrenia during pregnancy. Curr Opin Psychiatry. 2021 May 1;34(3):238-244. doi: 10.1097/YCO.0000000000000706. PMID: 33656465.
[6] ACOG Practice Bulletin No. 92: Use of Psychiatric Medications During Pregnancy and Lactation. Obstetrics & Gynecology 111(4):p 1001-1020, April 2008. | DOI: 10.1097/AOG.0b013e31816fd910

especially olanzapine, quetiapine, clozapine, aripiprazole, and risperidone.[7] Non-pharmacologic treatment includes psychotherapy, cognitive-behavioral therapy, and family therapy.[8]

Bipolar I Disorder (BD) and Pregnancy

DPMH has previously reviewed BD and pregnancy.[9] Additional information presented here is from a publication by Mohamed et al.[10] BD is characterized by alternating manic and depressive episodes, occurring over several days or weeks. The prevalence of BD is approximately 1% in the general population in the U.S.[11] BD tends to occur between 18-30 years of age, with the average age of onset of 21 years. BD in pregnancy is associated with an increased risk of gestational hypertension, preterm birth, SGA and microcephaly. Pharmacologic management of BD involves mood stabilizers, such as lithium, valproate, lamotrigine, carbamazepine/oxcarbazepine and topiramate, and/or antipsychotics, including olanzapine, quetiapine, aripiprazole, risperidone, paliperidone, amisulpiride, asenapine, ziprasidone and haloperidol.[12] The first-line medical treatment of BD in pregnant women is lamotrigine.[13] For pregnant patients who do not respond to lamotrigine or cannot tolerate it, then quetiapine is used.[14] For pregnant patients who are refractory to lamotrigine and quetiapine, then fluoxetine plus olanzepine or lamotrigine plus lithium may be used.[15] Lithium is teratogenic, causing cardiac anomalies, especially Ebstein's anomaly.[16] Non-pharmacologic treatments include electroconvulsive therapy, psychotherapy and psychoeducation.[17]

Nonclinical Data

No nonclinical data were submitted by the Applicant pertaining to milsaperidone. The labeling for iloperidone states that iloperidone was not teratogenic in rats or rabbits when administered during organogenesis as doses up to 26 and 20 times the maximum recommended human dose (MRHD) of 24 mg/day on a mg/m^2 basis, respectively.

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[7] Rojnic Kuzman M, Nordentoft M, Raballo A, Mohr P, Fiorillo A, Dom G, Mihajlovic G, Jendricko T, Chumakov E, Barjaktarov S, Carpiniello B, Patarák M, Martin L, Dudek D, Samochowiec J, Taube M, Courtet P, Babic D, Racetovic G, Catthoor K, Arango C, Maruta N, Basar K, Vahip S, Szekeres G, Lien L, Popova A, Zhelev R, Jääskeläinen E, Delic M, Chkonia E, Chichai J, Telles-Correia D, Cosman DCM, Beezhold J, Falkai P. Schizophrenia treatment preferences of psychiatrists versus guidelines: A European perspective. Eur Psychiatry. 2025 Aug 1;68(1):e107. doi: 10.1192/j.eurpsy.2025.10072. PMID: 40745910.

[8] See ref 7.

[9] DPMH review of Risperdal (risperdone) NDAs 20272, 20588, 21444, 21346, 21999, 22264, 207946 by Catherine Roca, MD, dated 4/17/2018. DARRTS Reference ID: 4248840

[10] Mohamed MA, Elhelbawy A, Khalid M, AbdAllatif LA, Lialy HE. Effects of bipolar disorder on maternal and fetal health during pregnancy: a systematic review. BMC Pregnancy Childbirth. 2023 Aug 28;23(1):617. doi: 10.1186/s12884-023-05924-8. PMID: 37641006; PMCID: PMC10464164.

[11] Rowland TA, Marwaha S. Epidemiology and risk factors for bipolar disorder. Ther Adv Psychopharmacol. 2018 Apr 26;8(9):251-269. doi: 10.1177/2045125318769235. PMID: 30181867; PMCID: PMC6116765.

[12] Shah, N, Grover, S, Prasad, R. Clinical Practice Guidelines for Management of Bipolar Disorder. Indian Journal of Psychiatry 59 (Suppl 1):p S51-S66, January 2017. | DOI: 10.4103/0019-5545.196974

[13] Hendrick V. Bipolar Disorder in pregnant women: Treatment of Major Depression. UpToDate. Topic 82788 Version 21.0

[14] See ref 13.

[15] See ref 13.

[16] USPI, Eskalith (lithium carbonate).

[17] See ref 13.

Pharmacovigilance (PV) Data

The Applicant reported that as of July 31, 2025, there have been nine cases of pregnancy with iloperidone exposure have been reported to the PV database with the following outcomes:

- Healthy full-term infant: 1 (unknown dose and timing of exposure)
- Termination of pregnancy: 1
- Ectopic pregnancy: 1
- Lost to follow-up: 2
- Unknown: 4

Reviewer comment: *Only nine pregnancies have been reported to be exposed to iloperidone after 15 years marketed iloperidone. Due to the small number of pregnancies and the large number of these pregnancies that were lost to follow-up or had unknown outcomes, it is not possible to draw conclusions about the safety of iloperidone use during pregnancy.*

Review of Literature

Applicant's review:

The Applicant provided a review and summary of all available published literature regarding iloperidone use in pregnant women from January 31, 2015 through August 19, 2025. The reader is referred to the Applicant's submission for the search terms used. The Applicant provided the publications in the table in Appendix A and concluded that "the data specific to iloperidone/milsaperidone are insufficient to define a drug-associated risk."

DPMH review:

DPMH conducted a search of published human studies related to iloperidone and pregnancy in PubMed, using the search terms "D_2 and 5-HT_2 antagonist" or "iloperidone" and "pregnancy," "pregnancy outcomes," "birth defects," "malformations," "stillbirth," or "spontaneous abortion." No relevant publications were found.

Reviewer comment:

DPMH reviewed the publications provided by the Applicant and noted that there was one case report of a 25-year-old pregnant woman treated with iloperidone 12 mg daily until at least 18 weeks of pregnancy who had a normal fetal ultrasound at 22 weeks of gestation. No additional information was provided about the pregnancy outcome beyond 22 weeks of gestation. The three other publications identified by the Applicant did not provide data specific to iloperidone.

DPMH agrees with the Applicant that the data specific to iloperidone are insufficient to define a drug-associated risk of use during pregnancy.

LACTATION

Nonclinical Data

No nonclinical data were submitted by the Applicant pertaining to milsaperidone. The iloperidone labeling states that iloperidone is present in rat milk.

PV Data

No cases of breastfed infants exposed to iloperidone have been reported to the Applicant's PV database.

Review of Literature

Applicant's review:

The Applicant provided a review and summary of all available published literature regarding iloperidone use in lactating women from January 31, 2015 through August 19, 2025. The reader is referred to the Applicant's submission for the search terms used. The Applicant did not identify any published data specific to iloperidone and breastfeeding.

DPMH review:

DPMH conducted a search for published human studies from to present in PubMed and Embase, using the search terms: "D_2 and 5-HT_2 antagonist" or "iloperidone" and "lactation" and "breastfeeding." No relevant publications were found.

> ***Reviewer comment:***
> *There are no nonclinical or clinical data to inform lactation labeling for milsaperidone. Although there are no available data, milsaperidone is likely to be present in breast milk for the following reasons: 1) the parent drug, iloperidone is known to be present in rat milk and milsaperidone and iloperidone rapidly interconvert in vivo; when a drug is present in animal milk, it is likely to be present in human milk; 2) milsaperidone has a molecular weight of 428.50 Daltons[18] and drugs with a MW < 800 Daltons may be excreted into milk.[19] It is also possible that milsaperidone will accumulate in breast milk due to its half-life of 26 hours in extensive metabolizers and 37 hours in poor metabolizers.[20] Drugs with an elimination half-life longer than 24 hours have the potential to accumulate in milk.[21] Finally, if milsaperidone is present in human milk, then it is likely to be absorbed by breastfed infants because it has a high oral bioavailability, comparable to that of iloperidone for which the oral bioavailability is 96%.[22] Iloperidone labeling includes a warning against breastfeeding due to the potential for adverse events in breastfed infants. Given the potential for absorption of milsaperidone by infants exposed through breast milk and adverse events associated with milsaperidone, including QT prolongation, neuroleptic malignant syndrome, tardive dyskinesia, metabolic changes, orthostatic hypotension, seizures, cytopenias, priapism, and cognitive and motor impairment,[23] DPMH recommends that labeling includes language advising*

[18] NDA 220358, SN 0001, Annotated Labeling, under review by DP.
[19] Nice FJ, Luo AC. Medications and breast-feeding: Current concepts. J Am Pharm Assoc (2003). 2012 Jan-Feb;52(1):86-94. doi: 10.1331/JAPhA.2012.10139. PMID: 22257621.
[20] See ref 18.
[21] See ref 19.
[22] See ref 18.
[23] See ref 18.

women not to breastfeed during treatment with milsaperidone and for 5-6 half-lives after the last dose. The clinical pharmacology (CP) team recommended that 5-6 half-lives be specified for normal metabolizers and poor metabolizers as follows: 6 days after the last dose for CYP2D6 normal metabolizers and 8 days after the last dose for CYP2D6 poor metabolizers.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Data

No nonclinical data were submitted by the Applicant pertaining to milsaperidone. The iloperidone labeling states that iloperidone was not mutagenic and did not cause decreased fertility in male and female rats at 1.6 times the MRHD of 24 mg/day on a mg/m^2 basis

PV Data

The Applicant reported that as of July 31, 2025, the following fertility-related events have been reported to their PV database:

- Sperm concentration decreased: 6
- Amenorrhea: 3
- Breast pain: 1
- Retrograde ejaculation: 1

Reviewer comment:

The current labeling for iloperidone reports decreased fertility, amenorrhea, breast pain and sexual dysfunction (including ejaculation failure, erectile dysfunction, retrograde ejaculation, and ejaculation delayed); therefore, the reports to the PV database are known adverse events that appear current labeling. Although there is likely under-reporting to the PV database, the number of events related to fertility is small and not suggestive of a new safety signal.

Review of Literature

Applicant's review:

The Applicant provided a review and summary of all available published literature regarding iloperidone use in females and males of reproductive potential from January 31, 2015 through August 19, 2025. The reader is referred to the Applicant's submission for the search terms used. The Applicant did not identify any published human studies directly assessing the impact of iloperidone, milsaperidone, or their metabolites on fertility. The Applicant identified a case report[24] describing hyperprolactinemia and galactorrhea associated with iloperidone treatment in a female patient. Hyperprolactinemia and galactorrhea are known to occur with iloperidone and appear in the current iloperidone labeling. The Applicant also identified one publication[25] that

[24] Dutta A, Barua S, Dan A, Chakraborty K, Mandal M. Iloperidone-induced Galactorrhea in a Middle-aged Female. Indian J Psychol Med. 2012 Oct;34(4):396-8. doi: 10.4103/0253-7176.108233. PMID: 23723555; PMCID: PMC3662144.

[25] Rodriguez-Cabezas LA, Kong BY, Agarwal G. Priapism associated with iloperidone: a case report. Gen Hosp Psychiatry. 2014 Jul-Aug;36(4):451.e5-6. doi: 10.1016/j.genhosppsych.2014.03.011. Epub 2014 Mar 22. PMID: 24726763.

reported priapism associated with iloperidone and another[26] that reported ejaculatory dysfunction. Both priapism and ejaculatory failure appear in the current iloperidone labeling.
DPMH review:
DPMH conducted a literature search for studies in humans using PubMed and Embase, using the search terms "D_2 and 5-HT_2 antagonist" or "iloperidone" and "fertility," "contraception," "oral contraceptives," and "infertility." No information was retrieved.

> ***Reviewer comment:***
> *There are no new data to inform the labeling of females and males of reproductive potential since the time that iloperidone was approved. The iloperidone labeling does not include subsection 8.3, and DPMH does not recommend including subsection 8.3 after this review as there are no new data to convey.*

III. DISCUSSION AND CONCLUSIONS

Pregnancy

No new nonclinical data related to pregnancy were submitted to this NDA. The nonclinical data that are available pertain to iloperidone. Clinical data are limited to iloperidone exposure only; no clinical data pertaining to milsaperidone are available. There were ten iloperidone-exposed pregnancies (nine from PV and one in the published literature). Among the iloperidone-exposed pregnancies, no major birth defects or adverse pregnancy, maternal or fetal outcomes were identified; however, the data are limited by a large amount of missing information about pregnancy outcomes (six cases without information) and a small number of cases. DPMH recommends a statement in labeling about iloperidone cases being insufficient to inform safe use during pregnancy. DPMH also recommends including the nonclinical information about iloperidone along with the general benefit-risk statement about birth defects and miscarriage under the Risk Summary.

In the Highlights of Prescribing Information and subsection 8.1 under Clinical Considerations *Fetal/Neonatal Adverse Reactions*, DPMH recommends including information about extrapyramidal and withdrawal symptoms that may occur in neonates after exposure to milsaperidone during the third trimester. This information appears in the labeling for other atypical antipsychotic medications, including the parent drug iloperidone.

DPMH also recommends a section under Clinical Considerations titled *Disease-associated maternal and/or embryo/fetal risk* to explain the risk of adverse perinatal outcomes associated with schizophrenia and BD, such as preterm birth. Although a *Disease-associated maternal and/or embryo/fetal risk* section does not appear in iloperidone labeling, this information appears in the labeling for other atypical antipsychotic medications, including risperidone, olanzapine, quetiapine, ziprasidone, and paliperidone.

As this review did not uncover a new safety signal related to iloperidone or milsaperidone, DPMH does not recommend issuing a post-marketing requirement (PMR) for a pregnancy safety

[26] Cheng Y, Chen Y, Zhao X, Mou F, Wang W, Qian R, Huang J, Li H, Xu Q, Yu S. The atypical antipsychotics and sexual dysfunction: a pharmacovigilance-pharmacodynamic study. Front Pharmacol. 2024 Jul 9;15:1423075. doi: 10.3389/fphar.2024.1423075. PMID: 39045047; PMCID: PMC11263075.

study. Iloperidone is part of the National Pregnancy Registry for Atypical Antipsychotics, so this information should be conveyed in subsection 8.1 under Pregnancy Exposure Registry.

Lactation

There are no new nonclinical or clinical data related to lactation to inform lactation labeling for milsaperidone. Iloperidone labeling advises not to breastfeed during treatment due to the potential for serious adverse reactions. Due to the potential for serious adverse reactions in infants exposed to milsaperidone via breast millk, such as QT prolongation, neuroleptic malignant syndrome, tardive dyskinesia, metabolic changes, seizures, cytopenias, priapism, and cognitive and motor impairment, DPMH recommends advising in labeling that women not breastfeed during treatment with milsaperidone and for 5-6 half-lives after the last dose (i.e., 6 days after the last dose for CYP2D6 normal metabolizers and 8 days after the last dose for CYP2D6 poor metabolizers).

In terms of PMRs for lactation, DPMH recommends issuing a PMR for a milk-only clinical lactation study because schizophrenia and biopolar I disorder are common in females of reproductive potential and the parent drug, iloperidone, is known to be present in rat milk.[27] A milk-only study would quantify the amount of drug in milk and provide an assessment of the potential risk to breastfed infants. The information from a clinical lactation study has the potential to change labeling of subsection 8.2.

Females and Males of Reproductive Potential

There are no new nonclinical or clinical data related to fertility. Iloperidone is not known to be genotoxic or to have drug-drug interactions with hormonal contraceptives. For these reasons, DPMH recommends omitting subsection 8.3, as there are no data to convey to prescribers.

LABELING RECOMMENDATIONS

DPMH recommendations are below and reflect the discussions with DP on 10/7/2025. DPMH defers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

(b) (4)

2 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

APPENDIX A – APPLICANT-GENERATED TABLE OF PUBLICATIONS RELATED TO PREGNANCY

Author, Year	Study Design	N Exposed	N Unexposed	Endpoints	Outcomes	Point Estimates	P-values	Confidence Intervals
Shenoy et al., 2015	Case report (pregnancy)	1 (iloperidone-exposed)	NR	Maternal and neonatal outcomes; symptom control	No drug-related adverse pregnancy or neonatal outcomes reported.	NA	NA	NA
Viguera et al., 2021	Prospective pregnancy registry (SGAs)	889 exposed	1017	Major congenital malformations	Malformations: 2.5% (16/640) exposed vs 1.99% (14/704) controls.	OR 1.48	NR	95% CI 0.63–3.52
Freeman et al., 2018	Cohort study (pregnancy; SGA-treated vs control)	NR	NR	Pre-pregnancy BMI; gestational weight gain	Higher baseline BMI/obesity in SGA-treated; gestational weight gain similar to controls.	NR	NR	NR
Coughlin et al., 2015	Systematic review (13 studies; ~6,289 antipsychotic-exposed pregnancies)	6289	Variable controls	Major congenital malformations; perinatal outcomes	Slight increase in risk of malformations (pooled OR ≈ 2.1). No significant difference typical vs atypical APs. No association with miscarriage or stillbirth.	OR=2.1	NR	NR

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/s/

KATHERINE G KRATZ
10/17/2025 09:40:40 AM

MIRIAM C DINATALE
10/17/2025 10:15:49 AM

LYNNE P YAO
10/20/2025 10:30:07 AM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 9/25/2025

TO: Division of Psychiatry (DP)
Office of Neuroscience (ON)

FROM: Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 220358

The Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not needed for the site listed below. The rationale for this decision is noted below.

Rationale

The Office of Inspections and Investigations (OII) conducted an inspection of the site in March 2025. The inspection was conducted under the following submission: NDA 210745.

The following item was discussed with the site:

- The raw data logs for centrifuge times did not indicate what centrifuge was used for processing biological samples for the study.

After review of the discussion item, OSIS concluded that the findings did not impact data reliability or human subject protection.

Site

Facility Type	Facility Name	Facility Address
Clinical	QPS Bio-Kinetic Clinical Applications, LLC.	1816/1820 West Mount Vernon Street, Springfield, MO

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/s/

JAMES J LUMALCURI
09/25/2025 09:22:58 AM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 5/15/2025

TO: Division of Psychiatry (DP)
Office of Neuroscience (ON)

FROM: Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 220358

The Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not needed for the site listed below. The rationale for this decision is noted below.

Rationale

OSIS conducted an inspection for the analytical site in (b) (4). The inspection was conducted under the following submission: NON-RESPONSIVE.

The following objectionable condition was observed:

- The site did not follow their SOP on reinjection of analytical runs during method validation (b) (4)

After review of the objectionable conditions and the written response from the site, OSIS concluded that data from the reviewed studies were reliable. (Final OSIS Review - March 2025).

Site

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	

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/s/

FOLAREMI ADEYEMO
05/15/2025 10:10:58 AM