CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218637Orig1s000

OTHER REVIEW(S)

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:	November 26, 2024
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 218637
Product Name, Dosage Form, and Strength:	Raldesy (trazodone hydrochloride) oral solution, 10 mg/mL
Applicant Name:	Kamat Pharmatech LLC
FDA Received Date:	November 25, 2024
TTT ID #:	2023-5960-3
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

Kamat Pharmatech LLC submitted revised carton labeling received on November 25, 2024 for Raldesy in response to email communication sent on November 22, 2024 advising the sponsor to change the (b) (4) listed under Contents to conventional names of the printed materials. The sponsor changed (b) (4) to list out the printed material as "Prescribing Information, Medication Guide and Instructions for Use". The Division of Psychiatry (DP) requested that we review the revised carton labeling for Raldesy (Appendix A) to determine if they are acceptable from a medication error perspective.

2 CONCLUSION

Kamat Pharmatech LLC implemented all of our recommendations and we have no additional recommendations at this time.

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/s/

YEVGENIYA M KOGAN
11/26/2024 09:38:15 AM

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:	November 25, 2024
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 218637
Product Name, Dosage Form, and Strength:	Raldesy[a] (trazodone hydrochloride), oral solution, 100 mg/10 mL
Device Constituent:	Bottle with adapter and dosing syringe
Applicant Name:	Kamat Pharmatech LLC (Kamat)
FDA Received Date:	November 13, 2024
TTT ID #:	2023-5961-1
DMEPA 1 Safety Evaluator:	Avinash Konkani, PhD, MS, BE
DMEPA 1 Team Leader:	Matthew Barlow, RN, BSN

[a] The proposed proprietary name, Raldesy, was found conditionally acceptable by DMEPA 1 on September 23, 2024 (PNR# 2024-1044725879).

1 PURPOSE OF MEMORANDUM

Kamat Pharmatech LLC submitted the revised instructions for use (IFU) on November 13, 2024, for Raldesy (trazodone hydrochloride) 100 mg/10 mL oral solution. The Division of Psychiatry (DP) requested that we review the revised IFU for Raldesy (trazodone hydrochloride) 100 mg/10 mL oral solution (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous use-related risk analysis (URRA) and comparative analyses review.[b]

2 CONCLUSION

We find that Kamat's revised IFU, incorporating the recommendation to *"remove the proposed* (b) (4) *from the proposed IFU* (b) (4) (b) (4) acceptable, and we have no additional recommendations at this time.

[b] Konkani, A. Use-Related Risk Analysis and Comparative Analyses Review for Raldesy (trazodone hydrochloride) (NDA 218637). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 AUG 06. TTT ID: 2023-5961.

APPENDIX A. REVISED IFU RECEIVED ON NOVEMBER 13, 2024

Instructions for use (IFU) received on November 13, 2024, available via EDR:
\\CDSESUB1\EVSPROD\nda218637\0024\m1\us\raldesy-brand-labeling-text-ifu-clean.docx
(word version)
\\CDSESUB1\EVSPROD\nda218637\0024\m1\us\raldesy-brand-labeling-text-ifu-clean.pdf
(pdf version)

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/s/

AVINASH KONKANI
11/25/2024 03:57:11 PM

MATTHEW J BARLOW
11/25/2024 04:04:42 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:	November 15, 2024
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 218637
Product Name, Dosage Form, and Strength:	Raldesy (trazodone hydrochloride) oral solution, 10 mg/mL
Applicant Name:	Kamat Pharmatech LLC
FDA Received Date:	November 13, 2024
TTT ID #:	2023-5960-2
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

Kamat Pharmatech LLC submitted revised container labels and carton labeling received on November 13, 2024 for Raldesy. The Division of Psychiatry (DP) requested that we review the revised container labels and carton labeling for Raldesy (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

Kamat Pharmatech LLC implemented all of our recommendations and we have no additional recommendations at this time.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[a] Kogan, Y. Label and Labeling Review for Raldesy (NDA 218637). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 Nov 5. TTT ID: 2023-5960-1.

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/s/

YEVGENIYA M KOGAN
11/15/2024 11:59:15 AM

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:	November 7, 2024
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 218637
Product Name, Dosage Form, and Strength:	Raldesy (trazodone hydrochloride) oral solution, 10 mg/mL
Applicant Name:	Kamat Pharmatech LLC
FDA Received Date:	November 5, 2024
TTT ID #:	2023-5960-1
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 PURPOSE OF MEMORANDUM

Kamat Pharmatech LLC submitted revised container labels and carton labeling received on November 5, 2024 for Raldesy. The Division of Psychiatry (DP) requested that we review the revised container labels and carton labeling for Raldesy (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 container labels and carton labeling are unacceptable from a medication error perspective and can be improved for clarity. We provide one general label recommendation for Kamat Pharmatech LLC in Section 3.

3 RECOMMENDATIONS FOR KAMAT PHARMATECH LLC

A. General Comments (Container Label(s) and Carton Labeling)

1. We note that the container label submitted on November 5, 2024 contains a placeholder for the product expiration date; however the format of the expiration date is MMM YYYY is not in accordance with the USP General Chapter <7>. When all-numeric dates are used, they must be formatted using the year, the month, and, if applicable, the day, separated by hyphens or forward slashes in one of the following formats: YYYY- MM-DD or YYYY-MM. When alphanumeric dates are used, months must be displayed using at least three letters in one of the following formats: YYYY-MMM-DD or YYYY-MMM. Ensure the expiration date format you choose is consistent across all labeling.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[a] Holmes, L. Label and Labeling Review for Raldesy (NDA 218637). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 Oct 29. TTT ID: 2023-5960.

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YEVGENIYA M KOGAN
11/07/2024 09:04:58 AM

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

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

Memorandum

Date: November 4, 2024

To: Sarah Seung, PharmD, MS, Regulatory Project Manager, Division of Regulatory Operations for Neuroscience – Psychiatry Group

Shamir Kalaria, PharmD, PhD, Clinical Reviewer, Division of Psychiatry (DP)

Kimberly Updegraff, Associate Director for Labeling, DP

From: Emily Foltz, PharmD, RPh, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Taylor Burnett Mmagu, PharmD, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for RALDESY™ (trazodone hydrochloride) oral solution

NDA: 218637

Background:
In response to DP's consult request dated February 15, 2024, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide, Instructions for Use (IFU), and carton and container labeling for the original NDA submission for Raldesy.

PI/Medication Guide/IFU:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on October 21, 2024, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed Medication Guide and IFU, and comments were sent under separate cover on October 31, 2024.

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 July 4, 2024, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Emily Foltz at 301-796-2939 or Emily.Foltz@fda.hhs.gov.

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/s/

EMILY M FOLTZ
11/04/2024 02:41:40 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	October 31, 2024
To:	Sarah Seung, PharmD, MS Regulatory Project Manager **Division of Psychiatry (DP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Laurie Buonaccorsi, PharmD Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Maria Nguyen, MSHS, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Emily Foltz, PharmD, RPh Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	RALDESY (trazodone hydrochloride)
Dosage Form and Route:	oral solution
Application Type/Number:	NDA 218637
Applicant:	Kamat Pharmatech, LLC.

1 INTRODUCTION

On January 29, 2024, Kamat Pharmatech, LLC. resubmitted for the Agency's review an original New Drug Application (NDA) 218637 for RALDESY (trazodone hydrochloride) oral solution. The NDA is a resubmission in response to a refuse to file on September 20, 2023, due to the lack of agreed Pediatric Study Plan (PSP). The PSP has been agreed upon under Preinvestigational New Drug (PIND) Application 143176 and has been included in the resubmission. The Applicant is relying on NDA 018207 DESYREL (trazodone hydrochloride) as the listed drug with trazodone hydrochloride 100mg as the reference standard.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Psychiatry (DP) on February 15, 2024, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for RALDESY (trazodone hydrochloride) oral solution.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on August 6, 2024.

2 MATERIAL REVIEWED

- Draft RALDESY (trazodone hydrochloride) MG and IFU received on January 29, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 22, 2024.
- Draft RALDESY (trazodone hydrochloride) Prescribing Information (PI) received on January 29, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 22, 2024.
- Approved DESYREL (trazodone hydrochloride) comparator labeling dated July 18, 2018.
- Approved TRINTELLIX (vortioxetine) comparator labeling dated August 23, 2023.
- Approved LEXAPRO (escitalopram) comparator labeling dated April 19, 2024.
- Approved FETZIMA (levomilnacipran) comparator labeling dated April 19, 2024.
- Approved PAXIL (paroxetine) comparator labeling dated August 18, 2023.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. In our review of the IFU, the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG and IFU document using the Arial font, size 10.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the PI
- rearranged information due to conversion of the PI to Physicians Labeling Rule (PLR) format
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the IFU meets the criteria as specified in both the FDA Guidance for Useful Written Consumer Medication Information (published July 2006) and Instructions for Use-Patient Labeling for Human Prescription Drug and Biological Products (published July 2022)
- ensured that the MG and IFU are consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/

MARIA T NGUYEN
10/31/2024 12:28:31 AM
DMPP-OPDP review of trazadone hydrochloride (RALDESY) NDA 218637 MG and IFU

EMILY M FOLTZ
10/31/2024 08:06:37 AM

LASHAWN M GRIFFITHS
10/31/2024 08:25:52 AM

LABELS 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, 2024
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 218637
Product Name, Dosage Form, and Strength:	Raldesy (trazodone hydrochloride) oral solution, 10 mg/mL
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant Name:	Kamat Pharmatech LLC
FDA Received Date:	July 5, 2024
TTT ID #:	2023-5960
DMEPA 1 Safety Evaluator:	Loretta Holmes, BSN, PharmD
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

1 INTRODUCTION

As part of the approval process for Raldesy (trazodone hydrochloride) oral solution, the Division of Psychiatry (DP) requested that we review the proposed Raldesy Prescribing Information (PI), Medication Guide (MG), Instructions for Use (IFU), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

Raldesy (trazodone hydrochloride) is a proposed 505(b)(2) drug product and the Listed Drug (LD) is Desyrel (trazodone hydrochloride), NDA 018207.

2 MATERIALS REVIEWED

This section lists the materials considered for our review of NDA 218637.

Table 1. Materials Considered for this Label and Labeling Review	
Materials Reviewed	Appendix Section
Relevant Product Information	A
Labels and Labeling	B

3 CONCLUSION

We evaluated the proposed Raldesy Prescribing Information (PI)[a] with a focus on Section 2 *Dosage and Administration*, Section 3 *Dosage Forms and Strengths*, Section 16 *How Supplied/Storage and Handling*, and Section 17 *Patient Counseling Information* as well as the Medication Guide (MG) and determined they are acceptable from a medication error perspective.

We evaluated the Instructions for Use (IFU) and noted there are multiple areas that need improvement (e.g., identification of supplies, aligning the steps and illustrations with the inclusion of figure letters, etc.) We defer to the Patient Labeling Team for a review of the IFU and will collaborate with the PLT as needed.

We evaluated the container labels and carton labeling and noted they may be improved to promote the 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 Kamat Pharmatech LLC in Section 4.

4 RECOMMENDATIONS FOR KAMAT PHARMATECH LLC

Table 2. Identified Issues and Recommendations for Kamat Pharmatech LLC (entire table to be conveyed to Applicant)

[a] We reviewed the proposed PI received on July 5, 2024 and the PI (working document) revised by the Division of Psychiatry as of October 24, 2024.

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels and Carton Labeling			
1.	The trademark symbol "TM" is too prominent.	The prominence of the trademark symbol distracts from the readability of the proprietary name.	Decrease the size of the trademark symbol.
2.	Your established name is not presented in tall man lettering.	Your established name is subject to confusion with the similar established name, traMADol. See FDA's list of established drug names recommended to use tall man lettering available at: https://www.fda.gov/drugs/medication-errors-related-cder-regulated-drug-products/fda-name-differentiation-project. Failure to highlight the differences between similar drug names may lead to wrong drug errors due to confusion between the name pair.	We recommend revising the presentation of the established name to be presented as, traZODone. For more information on tall man lettering, see *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).*
3.	The strength presentation in the Prescribing Information (PI) has been revised to 10 mg/mL.	As currently presented, the strength, (b) (4) is not consistent with the strength presentation in the PI.	For consistency with the PI, revise the statement of strength to: 10 mg/mL.
4.	The net quantity statement is too prominent and is in close proximity to the product strength.	The prominence of the net quantity statement distracts from other critical information on the Principal Display Panel (PDP).	Unbold the net quantity statement. Additionally, relocate the net quantity statement away from the product strength, such as to the bottom of the principal display panel. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).
5.	The terminology within the statement of dosage	The terminology used on the containers and cartons	We recommend revising the statement of dosage to read,

	(i.e., [redacted] and [redacted]) is inconsistent with the terminology in the PI.	should be consistent with the terminology in the PI.	"Recommended Dosage: See Prescribing Information."
6.	The statement "For Oral Use Only" is not present on the container labels and carton labeling.	To minimize the risk of wrong route of administration errors, the route of administration statement should be on the container labels and carton labeling.	We recommend adding the statement, "For Oral Use Only" to the principal display panel.
7.	The placeholder for the lot number is missing.	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 21 CFR 201.10(i)(1).
8.	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>. The USP Chapter <7>Labeling requires the expiration date to appear on the immediate container and all other packaging. When all-numeric dates are used, they must be formatted using the year, the month, and, if applicable, the day, separated by hyphens or forward slashes in one of the following formats: YYYY-MM-DD or YYYY-MM. When alphanumeric dates are used, months must be displayed using at least three letters in one of the following formats: YYYY-MMM-DD or YYYY-MMM. We recommend you ensure that there are no other numbers located in close proximity to the expiration date. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the expiration date format you intend to use.

9.	The storage statement is not consistent with the storage statement in the PI.	Inconsistency with the statement in the PI may lead to confusion.	Revise the storage statement to ensure it is consistent with the PI.
10.	Instructions on when to discard the unused product after first opening are not on the container labels or carton labeling.	Absence of this information may pose the risk of administration of degraded drug product.	We recommend adding a space for the end-user to document the date that the bottle is opened. Add the following statement and use a bold font: Discard any unused Raldesy remaining in the bottle 20 days after first opening the bottle. Date bottle is first opened: __/__/__.
Carton Labeling			
1.	A list of the carton contents is missing.	The carton contents information should be provided.	Provide a list of the items contained in the carton.
2.	All of the type on the carton labeling for the 300 mL amber glass bottle appears to be in bold type.	This is not consistent with the other carton labeling submitted.	Revise, as appropriate, for consistency with the other carton labeling.

APPENDICES: METHODS AND RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 3 presents relevant product information for Raldesy received on July 5, 2024 from Kamat Pharmatech LLC, and the Listed Drug (LD).

Table 3. Relevant Product Information for Raldesy and the Listed Drug (LD).		
Product Name	Raldesy	Desyrel[b] (NDA 018207), discontinued
Initial Approval Date	N/A	12/24/1981
Active Ingredient	trazodone hydrochloride	trazodone hydrochloride
Indication	Treatment of major depressive disorder (MDD) in adults	Treatment of major depressive disorder (MDD) in adults
Dosage Form	oral solution	tablets
Strengths	10 mg/mL	50 mg, 100 mg, 150 mg, and 300 mg
Route of Administration	Oral	Oral
Dose and Frequency	An initial dose of 150 mg/day in divided doses is suggested. The dosage should be initiated at a low-dose and increased gradually, noting the clinical response and any evidence of intolerance. Occurrence of drowsiness may require the administration of a major portion of the daily dose at bedtime or a reduction of dosage. The dose may be increased by 50 mg/day every 3 to 4 days. The maximum dose for outpatients usually should not exceed 400 mg/day in divided doses. Inpatients (i.e., more severely depressed patients) may be given up to but not in excess of 600 mg/day in divided doses.	An initial dose of 150 mg/day in divided doses is suggested. The dosage should be initiated at a low-dose and increased gradually, noting the clinical response and any evidence of intolerance. Occurrence of drowsiness may require the administration of a major portion of the daily dose at bedtime or a reduction of dosage. The dose may be increased by 50 mg/day every 3 to 4 days. The maximum dose for outpatients usually should not exceed 400 mg/day in divided doses. Inpatients (i.e., more severely depressed patients) may be given up to but not in excess of 600 mg/day in divided doses. Once an adequate response has been achieved, dosage may be

[b] Desyrel [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. Oct 2018. [cited 2024 Oct 23]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/018207s033lbl.pdf.

Table 3. Relevant Product Information for Raldesy and the Listed Drug (LD).		
Product Name	Raldesy	Desyrel[b] (NDA 018207), discontinued
	Once an adequate response has been achieved, dosage may be gradually reduced, with subsequent adjustment depending on therapeutic response.	gradually reduced, with subsequent adjustment depending on therapeutic response.
How Supplied	Raldesy (Trazodone Hydrochloride) Oral Solution contains (b) (4) of Trazodone hydrochloride. It is a clear, colorless solution and is supplied in bottles of: 150 mL, Amber Glass Bottle - NDC (b) (4) 150 mL, White, Opaque, HDPE Bottle - NDC (b) (4) 300 mL, Amber Glass Bottle - NDC (b) (4) 300 mL, White, Opaque, HDPE Bottle - NDC (b) (4) 150 mL amber glass bottle NDC (b) (4) with child-resistant cap along with a 10 mL calibrated oral dosing syringe. 150 mL white, opaque, HDPE bottle NDC (b) (4) with child-resistant cap along with a 10 mL calibrated oral dosing syringe. 300 mL amber glass bottle NDC (b) (4) with child-resistant cap along with a 10 mL calibrated oral dosing syringe. 300 mL white, opaque, HDPE bottle NDC (b) (4) with child-resistant cap along with a 10 mL calibrated oral dosing syringe. The bottle and the dosing syringe are placed in a carton.	• 50 mg: White, round, scored, film-coated tablet; bisected with “50” and “P 005” debossed on one side and plain on the other side. Bottles of 100 NDC 58463-005-01 • 100 mg: White, round, scored, film-coated tablet; bisected with “100” and “P 006” debossed on one side and plain on the other side. Bottles of 100 NDC 58463-006-01 • 150 mg: White, rectangular, scored tablet; trisected on both sides, debossed with “P” and “007” on one side and “50”, “50”, “50” on the other side, with a bisect on each edge. Bottles of 100 NDC 58463-007-01 • 300 mg: White, rectangular, scored tablet; trisected on one side debossed with “100”, “100”, “100” and bisected on the other side debossed with “P” and “008”. Bottles of 100 NDC 58463-008-01

Table 3. Relevant Product Information for Raldesy and the Listed Drug (LD).		
Product Name	Raldesy	Desyrel[b] (NDA 018207), discontinued
Storage	Store at 20°C to 25°C (68°F to 77°F). Excursions permitted between 15ºC and 30ºC (59°F to 86ºF) [see USP Controlled Room Temperature].	Store at 20°C to 25°C (68°F to 77°F). Excursions permitted between 15°C and 30°C (59°F to 86°F) [see USP Controlled Room Temperature].
Container Closure	Child-resistant cap	

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,[c] along with postmarket medication error data, we reviewed the following Raldesy labels and labeling submitted by Kamat Pharmatech LLC. received on July 5, 2024.

- Container Labels
- Carton Labeling
- Instructions For Use
- Prescribing Information (no image)
- Medication Guide (no image)

B.2 Container Labels and Carton Labeling Images (not to scale)

Container Labels:

(b) (4)

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

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/s/

LORETTA HOLMES
10/29/2024 04:07:58 PM

YEVGENIYA M KOGAN
10/29/2024 05:00:44 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Division of Pediatrics and Maternal Health Review

Date: October 15, 2024 **Date consulted:** June 27, 2024

From: Kerry R. Shaab, MD, Medical Officer, Maternal Health
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Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
Division of Pediatrics and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatrics and Maternal Health

To: Division of Psychiatry (DP)

Drug: RALDESY (Trazodone hydrochloride oral solution 100 mg/10 mL)

NDA: 218637

Applicant: Kamat Pharmatech LLC

Subject: Pregnancy and Lactation Labeling

Indication: For the treatment of major depressive disorder (MDD) in adults.

Materials Reviewed:

- DPMH consult request, dated 6/27/2024. DARRTS Reference ID: 5404635.
- Applicant's background package and proposed labeling for NDA 218637, Sequence Number (SN) 0006, 1/29/2024.
- Applicant's response to DPMH Information Request (IR), dated 7/11/2024, SN 0016, submitted 8/2/2024.
- Applicant's response to DPMH IR, dated 9/3/2024, SN 0018, submitted 9/13/2024.

- Applicant's response to DPMH IR, dated 9/24/2024, SN 0019, submitted 10/1/2024.
- DPMH Pregnancy and Lactation Labeling Review for the Referenced Listed Drug, Desyrel (trazodone hydrochloride) NDA 018207 by Catherine Roca, MD, dated 5/24/2018. DARRTS Reference ID: 4268512.
- Desyrel labeling, approved 10/18/2018.

Consult Question: "Please review the FPI for PLLR conversion and provide any additional labeling recommendations regarding the FPI and MG to ensure the safe use of trazodone in patients of childbearing potential."

I. INTRODUCTION AND BACKGROUND

On January 29, 2024, the Applicant, Kamat Pharmatech LLC, submitted a 505(b)(2) New drug Application for Raldesy (trazodone hydrochloride oral solution) for the treatment of Major Depressive Disorder (MDD) in adults. The Division of Psychiatry consulted the Division of Pediatrics and Maternal Health (DPMH) on June 27, 2024, to assist with the Pregnancy and Lactation subsections of labeling. The listed drug for the application is Desyrel, for which DPMH completed a Pregnancy and Lactation Labeling Consult review for the conversion of the Desyrel labeling to PLLR format on May 24, 2018. Thus, this review will focus from the time of our previous consult to the present.

Relevant Regulatory History

- DESRYL (trazodone) was approved for use in the U.S. on December 24, 1981, for the treatment of major depressive disorder.
- Desyrel was discontinued in the U.S. Per Federal register determination, Desyrel was not discontinued or withdrawn for safety or effectiveness reasons.[1]
- Trazodone Hydrochloride Tablet, USP 100 mg (A071196), approved on March 25, 1987, is listed as the Reference Standard Drug in the Orange Book.

Drug Characteristics

Drug Class	Serotonin-antagonist and reuptake inhibitor[2]
Mechanism of Action	Mechanism of antidepressant action is not fully understood, but it is thought to be related to its enhancement of serotonergic activity in the CNS. Trazodone is both a selective serotonin reuptake inhibitor (SSRI) and a 5HT2 receptor antagonist and the net result of this action on serotonergic transmission and its role in trazodone's antidepressant effect is unknown.[3]
Dosage form	Oral solution 100 mg/10 mL

[1] Approved Drug Products with Therapeutic Equivalence Evaluations (The Orange Book). Food and Drug Administration.
[2] Shin JJ, Saadabadi A. Trazodone. [Updated 2024 Feb 29]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470560/
[3] Desyrel labeling, approved 10/18/2018.

Dosage administration	Starting dose: 150 mg in divided doses daily. May be increased by 50 mg per day every 3 to 4 days. Maximum dose: 400 mg per day in divided doses.[3]
Molecular weight	408.33[3]
Half-life	Approximately 17 hours[4]
% protein bound	89% - 95%[3]
Bioavailability of oral solution	Unknown[4]

Current State of the Desyrel (trazodone) Labeling[3]

Labeling is in the PLR and PLLR format.
There is no boxed warning of embryofetal toxicity.
There is no contraindication for pregnancy or lactation.
Highlights of Prescribing Information - Warnings and Precautions: Serious adverse reactions include suicidal thoughts and behavior in children, serotonin syndrome, cardiac arrythmias, orthostatic hypotension and syncope, increased risk of bleeding, priapism, activation of mania or hypomania, potential for cognitive and motor impairment, angle-closure glaucoma, and hyponatremia.
Subsection 8.1 Pregnancy • There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants during pregnancy. Contact information for the National Pregnancy Registry for Antidepressants is provided. • The Risk Summary states, "Published prospective cohort studies, case series, and case reports over several decades with DESYREL use in pregnant women have not identified any drug-associated risks of major birth defects, miscarriage, or adverse maternal or fetal outcomes."[3] • Animal data indicate no teratogenic effects observed at dose levels 11 and 22 times, in rats and rabbits respectively, the maximum recommended human dose (MRHD). Increased fetal resorption and other adverse effects on the fetus in rats at 7.3 to 11 times the MRHD and increase in congenital anomalies in rabbits at 7.3 to 22 times the MRHD were observed. "No further details on these studies are available."[3]
Subsection 8.2 Lactation labeling states data from published literature report the transfer of trazodone into human milk and limited postmarketing data have not identified an association of adverse effects on the breastfed child. There are no data on the effect on milk production.
Subsection 8.3 is omitted.
Section 13 Nonclinical Toxicology: Impairment of Fertility states "trazodone has no effect in rats at doses up to 7.3 times the MRHD in adults on a mg/m^2 basis."[3]
Section 17 includes counseling information on advising patients to notify healthcare providers if they become or intend to become pregnant and on the existence of the pregnancy exposure registry.
There are no pregnancy testing/contraception recommendations.
There are no listed drug interactions with hormonal contraceptives.

[4] Electronic correspondence with Clinical Pharmacology team, dated 9/23/2024.

II. REVIEW

PREGNANCY

Major Depressive Disorder (MDD) and Pregnancy

- Within the general U.S. population, the prevalence of depressive syndromes is approximately two times greater in women than men.[5,6]
- Women diagnosed with MDD who discontinue their antidepressant medication before or during pregnancy are at a greater risk of relapse than those who continue their medication.[7]
- Two risk factors for postnatal depressive syndromes that have the largest effect and are most consistently associated with postpartum depression are a prior history of depression and depression during pregnancy.[8]
- A meta-analysis published in JAMA Psychiatry in 2016 that included data from 25,663 women found significantly increased risk of both preterm birth (OR=1.56, 95%CI, 1.25-1.94) and low birth weight (OR=1.96, 05% CI, 1.24-3.11)[9] in women with untreated depression during pregnancy.
- The American College of Obstetricians and Gynecologists (ACOG) strongly recommends against withholding or discontinuing medications for mental health conditions due to pregnancy or lactation status alone.[10]

Nonclinical Experience

The Applicant did not conduct any nonclinical developmental toxicity studies and is relying on information from the listed drug, Desyrel. The Desyrel labeling states "no teratogenic effects were observed when trazodone was given to pregnant rats and rabbits during the period of organogenesis at oral doses up to 450 mg/kg/day. This dose is 11 and 22 times, in rats and rabbits, respectively, the maximum recommended human dose (MRHD) of 400 mg/day in adults on mg/m^2 basis. Increased fetal resorption and other adverse effects on the fetus in rats at 7.3 to 11 times the MRHD and increase in congenital anomalies in rabbits at 7.3 to 22 times the MRHD on a mg/m2 basis were observed. No further studies are available."[3]

[5] Krishnan, R. Unipolar depression in adults: Epidemiology. In:UpToDate, Connor RF (Ed), Wolter Kluwer. (Accessed on 9/17/2024)

[6] Kuehner, C. Why is depression more common among women than among men? The Lancet Psychiatry, 2017. 4(2):146-158. doi.org/10.1016/S2215-0366(16)30263-2.

[7] Cohen L, et al. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. JAMA. 2006. 295(5):499-507.

[8] Viguera, A. Postpartum unipolar major depression: Epidemiology, clinical features, assessment, and diagnosis. In:UpToDate, Connor RF (Ed), Wolter Kluwer. (Accessed on 9/17/2024)

[9] Jarde A, et al. Neonatal outcomes in women with untreated antenatal depression compared with women without depression: A systematic review and meta-analysis. JAMA Psych. 2016;73(8):826-837.

[10] ACOG Committee on Clinical Practice Guidelines–Obstetrics: Treatment and management of mental health conditions during pregnancy and postpartum: ACOG Clinical Practice Guideline No. 5. Obstet Gynecol 2023; 141(6):1262-1288.

Review of Safety Database

Study 097-21 was a three treatment, three period, cross over, oral comparative bioavailability study with a washout period of at least 7 days between study periods. The Applicant reported one subject (no. (b) (6) with a positive pregnancy test during the clinical development program (Study 097-21). "Post study safety evaluation", including a urine pregnancy test for female subjects, was done at the "end of the study"[11]. The Analysis Data Reviewer's Guide indicates subject no. (b) (6) withdrew due to "increased Beta-HCG".[12] In response to an information request, the Applicant clarified that, due to a history of previously undergoing a "family planning operation", this subject had a repeat beta-HCG test which was negative. Still, the subject was withdrawn from "Period-III".[13] The Applicant concluded that this case is not related to pregnancy. No further data were provided.

The Applicant included a tabular listing of adverse events reported in the FDA Adverse Event Reporting System (FAERS) for which oral trazodone was a primary or secondary suspect from "the year 2022 to the latest available data year 2023."[14] This included the following: "poor feeding infant" (7, 0.16% frequency), "fetal exposure during pregnancy" (7, 0.16% frequency), "drug withdrawal syndrome neonatal" (7, 0.16% frequency), and "exposure via breast milk" (7, 0.16% frequency).[15] The Applicant provided 7 case narratives from FAERS for these reported adverse events. All 7 of the case narratives were very similar, if not identical. The case reports were Canadian, reported between March 1, 2023 to March 22, 2023, with one outlier dated October 22, 2022. In summary, the narratives describe a 2-day old infant born to a mother who received an unknown amount of Trazodone on an unknown date. The mother also received "co-suspects Buprenorphine, Suboxone, Vitamins NOS, Wellbutrin XL and Zofran for the indication of drug dependence, nausea, vomiting and product used for unknown indication." On "unknown" dates, the infant was exposed to Trazodone during pregnancy and during breast feeding. The narratives state the infant developed "withdrawal syndrome" and, again on "unknown date", the infant was hospitalized and was a "poor feeding infant". According to all 7 narratives, the action taken with suspect Trazodone was "unknown", the outcome of the reported events was "unknown" and "no further follow-up is expected" in each case.[16]

> *Reviewer comment:*
> *Based on the information provided by the Applicant for subject no (b) (6) the first urine pregnancy test was obtained at the "end of the study", thus, this subject's pregnancy status at the start of the study is unclear. Additionally, there are no details regarding the interval between the first and second urine pregnancy tests performed prior to the subject withdrawing from Period-III of the study. As a result, it remains unclear if the first beta-HCG was a false positive as the Applicant inferred in the response to the additional information request and if, in fact, this case is not related to pregnancy.*

[11] NDA 218637, Module 2.5.5.1, Clinical Overview, p. 15.
[12] NDA 218637, Analysis Data Reviewer's Guide, Protocol Number 097-21, p. 4.
[13] NDA 218637, SN 0018, Annexure-I: Applicant's response to DPMH IR, dated 9/3/2024, SN 0018, submitted 9/13/2024, p. 3.
[14] NDA 218637, Module 2.5.5.4, Clinical Overview, p. 19.
[15] NDA 218637, Module 2.7.4-9, Summary of Clinical Safety Appendix, p. 25 and 26.
[16] NDA 218637, SN 0019. Annexure-II: Applicant's response to DPMH IR, dated 9/24/2024, submitted 10/1/2024.

After reviewing the 7 case narratives for the FAERS reported adverse events, this reviewer suspects that the narratives describe the same infant, not 7 unique infants. The description of the infant's adverse events is identical in all 7 narratives. The differences between the narratives are subtle. Six of the 7 identify the infant as a "2-day old baby boy" and 1 narrative reports an infant of "unknown age and unknown [redacted] . Six of the 7 narratives list the maternal medication "co-suspects" as Buprenorphine, Suboxone, Wellbutrin XL and Zofran with 2 of the 6 also listing Vitamins. One narrative only reports Buprenorphine and Vitamins as "co-suspects". One narrative was reported by a "health professional" while the others were reported by a "consumer". Despite the outlying date, the details from the October 22, 2022 narrative are the same as the other narratives. In addition to the similarities in content, the narratives also have similar missing data. There are no details regarding the doses, frequency, route of administration, or timing of any of the mother's medications and there are no details on the timeframe of the infant's exposures to the listed maternal medications in relation to the occurrence of the reported adverse events. As such, it is unclear if the reported adverse events are due to trazodone-exposure and, therefore, these narratives are not sufficient to identify safety signals related to the use of trazodone in pregnancy or lactation.

Review of Literature

Applicant's Review:

The Applicant conducted a literature search of PubMed for "trazodone OR Desyrel" AND (infertility OR reproduction OR fertility OR impotence OR impotent OR impotency OR sterile OR steriliz*)" or "trazadone OR Desyrel AND (Pregnancy OR pregnant OR lactation OR nursing OR mother* OR breast feed*)" with the interval limit as January 1, 2018 to September 4, 2024.

The Applicant provided one article by Dao, et al. (2023)[17] which pertains to pregnancy outcomes in women exposed to trazodone. The Applicant summarized the study findings. Dao, et al., 2023, is further discussed below under DPMH review of the literature.

DPMH review:

DPMH conducted a search of published human studies from January 1, 2016 to present in PubMed and Embase, using the search terms "trazodone" and "pregnancy", "pregnancy outcomes", "birth defects", "congenital malformations", "miscarriage", "spontaneous abortion", and "stillbirth".

In addition, DPMH conducted a search for trazodone in Micromedex[18], Reprotox[19], TERIS[20], and Shepard's[21].

[17] Dao K, et al. Reproductive safety of trazodone after maternal exposure in early pregnancy: a comparative ENTIS cohort study. J Clin Psychopharmacology 2023;43(1):12-19. doi: 10.1097/jcp.0000000000001630.
[18] Truven Health Analytics information, http://www.micromedexsolutions.com Accessed 8/21/2024.
[19] Reprotox Website: www.Reprotox.org. Accessed 8/20/2024.
[20] TERIS database, Truven Health Analytics, Micromedex Solutions. Accessed 8/20/2024.
[21] Shepard's database. Truven Health Analytics. Micromedex Solutions. Accessed 8/20/2024.

Micromedex[18] reports that it is unknown if trazodone or its metabolites cross the placenta.

Reprotox[19] states "Based on experimental animal studies and limited experience in human pregnancies, trazodone therapy is not expected to increase congenital anomalies."

Dao, et al., (2023) report the pregnancy outcomes in a multicenter exposure cohort study conducted by the European Network of Teratology Information Specialists comparing trazodone-exposed pregnancies to SSRI-exposed pregnancies. The trazodone exposure cohort included pregnant women exposed to trazodone during the first trimester of pregnancy who themselves, or whose practitioner, contacted one of the 7 participating Teratology Information Services (TIS). For each pregnancy outcome with trazodone exposure, 4 patients were selected for the SSRI reference group. The reference group was defined as pregnancies exposed during the first trimester of pregnancy to sertraline, citalopram, or escitalopram, randomly selected within the same TIS prospective cohort and in the same contact timeframe (+/- 3 years). The median daily trazodone dose was 100 mg with an interquartile range of 50-150 mg. Of the 78% of women in the trazodone group for which the indication for the antidepressant was reported, 52.9% had depression. Of the 82% of women in the SSRI group with a reported indication for the antidepressant, 50.4% had depression. In this study, the frequency of major congenital anomalies was not increased among the infants of 169 women treated with trazodone in the first trimester compared to infants of 730 women treated with a selective serotonin reuptake inhibitor. Additionally, no significant differences were observed in the rates of spontaneous abortion, stillbirth, and small for gestational age among 214 women treated with trazodone in pregnancy compared to the SSRI control group of pregnant women.[17]

> *Reviewer Comment:*
> *Trazodone has been marketed since 1981 and no teratogenic signals have been reported to date. The limited published literature has not identified an increased risk for major congenital malformations, spontaneous abortion, or other adverse maternal or fetal effects.[22] The pregnancy outcomes described by Dao et al., (2023) support the previously published data and the observed postmarketing experience. However, there were limitations to the study. As mentioned, the median daily trazodone dose was 100 mg with an IQR of 50-150 mg. The standard therapeutic dosing range for the indication of MDD is 150 mg to 400 mg per day. Thus, the majority of women were on lower trazodone doses compared with the doses typically used to manage depression. Also, only 11% of women in the trazodone group were on monotherapy, while 55% reported concomitant use of "another antidepressant or psychostimulant." In fact, with respect to the one reported congenital anomaly in the trazodone-exposed cohort, the woman was on both trazodone and citalopram. The authors did not address why this outcome was attributed to trazodone alone. Although this study found the pregnancy outcomes after trazodone exposure were like that of the reference group exposed to SSRIs, including a cohort of women with untreated depression would have controlled for the underlying disease and served to investigate trazodone's reproductive safety further.*

[22] DPMH Pregnancy and Lactation Labeling Review for the Referenced Listed Drug, Desyrel (trazodone hydrochloride) NDA 018207 by Catherine Roca, MD, dated 5/24/2018. DARRTS Reference ID: 4268512.

LACTATION

Nonclinical Experience

Trazodone is present in rat milk.[22]

Review of Safety Database

The Applicant did not provide any cases of exposure during lactation from their safety database.[23]

As mentioned above in the Pregnancy Review of Safety Database section, the tabular listing of adverse events reported in FAERS for which oral trazodone was a primary or secondary suspect from "the year 2022 to 2023" included "exposure via breast milk" (7, 0.16% frequency).[15] The Applicant provided the case narratives for this reported adverse event and these were addressed above in the Pregnancy Review of Safety Database section.

Review of Literature

Applicant's Review:

The Applicant conducted a literature search of PubMed for "trazodone OR Desyrel" AND (infertility OR reproduction OR fertility OR impotence OR impotent OR impotency OR sterile OR steriliz*)" or "trazadone OR Desyrel AND (Pregnancy OR pregnant OR lactation OR nursing OR mother* OR breast feed*)" with the interval limit as January 1, 2018 to September 4, 2024.

The Applicant provided one article by Saito, et al. (2021)[24] which is a case report describing trazodone levels in maternal blood, cord blood, breast milk, and neonatal serum in a woman taking trazodone during pregnancy and lactation. The Applicant summarized the case report findings. Saito, et al., 2021, is further discussed below under DPMH review of the literature.

DPMH Review:

DPMH conducted a search of published human studies from January 1, 2016 to present in PubMed and Embase, using the search terms "trazodone" and "lactating", "lactation", "nursing", "breast fed", "neonates", and "infants".

In addition, DPMH conducted a search for trazodone in Micromedex[18], Reprotox[19], Hale's *Medications and Mothers' Milk*[25], the Drugs and Lactation Database (LactMed)[26], and Briggs *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*[27].

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[23] NDA 218637, SN 0018, Annexure-I: Applicant's Response to DPMH IR, dated 9/3/2024, SN 0018, submitted 9/13/2024.

[24] Saito J, Ishii M, Mito A, Yakuwa N, Kawasaki H, Tachibana Y, Suzuki T, Yamatani A, Sago H, Murashima A. Trazodone Levels in Maternal Serum, Cord Blood, Breast Milk, and Neonatal Serum. Breastfeed Med. 2021 Nov;16(11):922-925. doi: 10.1089/bfm.2021.0191. Epub 2021 Aug 3. PMID: 34348038.

[25] Hale, Thomas W. Hale's Medications and Mother's Milk 2021: A Manual of Lactational Pharmacology. 19th ed. New York: Springer Publishing Company, 2020. www.halesmeds.com. Accessed 7/31/2024.

[26] Drugs and Lactation Database (LactMed). Accessed 8/21/2024.

[27] Briggs, Gerald G., Craig V. Towers, and Alicia B. Forinash. Briggs Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk. 12th edition. Philadelphia, PA: Lippincott Williams & Wilkins, 2021.

LactMed states “levels in milk are low and would not be expected to cause any adverse effects, especially if infant > 2 months or when doses of 100 mg or less used at bedtime for sleep.” Additionally, “a safety scoring system finds trazodone use to be “possible to use cautiously” during breast feeding.”[26,28]

The publication by Saito et al., (2021) is referenced in Hale’s and LactMed. DPMH reviewed this case report of a 44-year-old mother who delivered a 38-week gestational age infant while consuming Trazodone 50 mg/day during pregnancy and breast feeding. Concentrations of both trazodone and mCPP, its active metabolite, in cord blood 7.4 hours after dosing were comparable with maternal serum levels. Breast milk samples were collected 4 times on days 5 and 6 postpartum. Concentrations in breast milk collected 7.2 hours after maternal dosing were 50.2 ng/mL for Trazodone and 3.2 ng/mL for mCPP. Additional breast milk concentrations for Trazodone and mCPP were 21.2 and 1.3 ng/mL at 18.9 hours after dose, 18.2 ng/mL and 0.9 ng/mL at 20.4 hours after dose and 8 and < 0.2 ng/mL at 29 hours after dose. Trazodone and mCPP were detected in infant serum 14.2 hours after maternal administration. mCPP was below the detection limit at 83.0 hours after maternal dosing. Trazodone decreased to 1.3 ng/mL 5 days after maternal dosing. The author’s calculated daily infant dose of trazodone through breast milk based on the largest trazodone concentration in breast milk (50.2 ng/mL) and the average breast milk intake (150 mL/kg/day) was 0.008 mg/kg•day and the infant dose through breast milk was 0.8% of the maternal daily dose. The exposed infant developed normally, with no drug-related adverse effects at 1, 3 and 6 months of age.[24]

> *Reviewer comment:*
> *This case report supports data from previous published literature reporting the transfer of trazodone into human milk. This reviewer calculated the weight-adjusted relative infant dose using the infant’s birth weight of 2.918 kg and the mother’s reported weight of 63 kg. The weight-adjusted relative infant dose would be 0.945%, similar to the author’s calculation. However, 50 mg/day, the maternal dose of trazodone, is less than the standard therapeutic dosing range for the indication of MDD which is 150 mg to 400 mg per day, potentially resulting in lower infant exposure, and thus, potentially reducing the likelihood of adverse events in the breastfed infant. As such, this case report may not fully support any conclusions about the safety of trazodone use during lactation.*
> *Per the Clinical Pharmacology team, published literature case reports, like Saito et al., lack information, such as the specific formulation used, bioanalytical method validation, and subject level data, resulting in “uncertain data quality”. In addition, since the data is only from one subject, “making any quantitative statements based on the article would be difficult.”[4] Thus, this case report is insufficient to inform the Raldesy lactation labeling.*

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Trazodone has no effects on fertility in rats at doses up to 6 times the MRHD on mg/m^2 basis.[22]

[28] Uguz, F. A new safety scoring system for use of psychotropic drugs during lactation. Am J Ther. 2021;28: e118-e126.

Review of Safety Database
The Applicant did not provide any cases reporting effects on male or female fertility from their safety database.[23]

Review of Literature
Applicant's Review:
The Applicant conducted a literature search of PubMed for "trazodone OR Desyrel" AND (infertility OR reproduction OR fertility OR impotence OR impotent OR impotency OR sterile OR steriliz*)" or "trazadone OR Desyrel AND (Pregnancy OR pregnant OR lactation OR nursing OR mother* OR breast feed*)" with the interval limit as January 1, 2018 to September 4, 2024.
The Applicant reported no clinical literature related to males and females of reproductive potential.

DPMH Review:
DPMH conducted a search of published human studies from January 1, 2016 to present in PubMed and Embase, using the search terms "trazodone" and "fertility", "infertility", "decreased sperm count", "contraceptive", "oral contraceptives", and "reproduction".

In addition, DPMH conducted a search for trazodone in Micromedex[18], Reprotox[19] , and TERIS[20]. No publications or additional information on the effects of trazodone on fertility or interactions with hormonal contraceptives were found in the literature search.

III. DISCUSSION AND CONCLUSIONS

Pregnancy
Available data over several decades from published sources and postmarketing experience have not demonstrated a drug-associated risk of major congenital malformations, miscarriage, or other adverse maternal or infant outcomes with trazodone use during pregnancy. The limited data identified by this review supports this. There are no new safety data identified that serve to inform changing the labeling from that of the listed drug. Of note, however, the contact information for the National Pregnancy Registry for Antidepressants has changed and the proposed labeling for Raldesy reflects this.

With decades of trazodone hydrochloride tablet use, new postmarketing safety issues have not been identified. As such, DPMH does not recommend a postmarketing pregnancy safety study at this time. Continued monitoring for new safety signals with routine drug pharmacovigilance and literature reviews is reasonable.

Lactation
Trazodone is present in breast milk. Since the 2018 DPMH review, the available data are limited by a single case report which is insufficient to inform changing the labeling from that of the listed drug.

While there are limited data about trazodone use in lactation, no known adverse events have been reported. As such, DPMH does not recommend a postmarketing pregnancy safety study at this

time. Continued monitoring for new safety signals with routine drug pharmacovigilance and literature reviews is reasonable.

Females and Males of Reproductive Potential

Subsection 8.3 was omitted from the Desyrel labeling as it was deemed not necessary. No new data were located regarding the effects of trazodone on fertility or hormonal contraception. In addition, there is no evidence of fetal harm that would require pregnancy testing or contraceptive use during treatment with trazodone. Therefore, DPMH recommends that subsection 8.3 remain omitted from the Raldesy labeling.

LABELING RECOMMENDATIONS

No new safety concerns were identified during this review, so DPMH does not recommend any content changes in subsections 8.1, 8.2, or section 17 of labeling for Raldesy from the content in the Desyrel labeling. However, DPMH proposes using the wording below which includes minor editorial updates aligning the language in the Raldesy labeling with the labeling of more recently approved antidepressants. DPMH discussed our labeling recommendations with the Division of Psychiatry on 10/10/2024. DPMH recommendations are below and reflect the discussions with the Division. DPMH refers to the final NDA action for final labeling.

DPMH PROPOSED PREGNANCY AND LACTATION LABELING

(b) (4)

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

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/s/

KERRY R SHAAB
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10/17/2024 02:57:05 PM

USE-RELATED RISK ANALYSIS AND COMPARATIVE ANALYSES 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)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	August 06, 2024
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 218637
Product Type:	Combination Product (Drug-Device)
Product Name, Dosage Form and Strength:	Trazodone Hydrochloride, dosage form, strength
Device Constituent:	Bottle with adapter and dosing syringe
Rx or OTC:	Rx
Applicant/Sponsor Name:	Kamat Pharmatech LLC (Kamat)
Submission Date:	January 29, 2024; March 25, 2024
OSE TTT #:	2023-5961
DMEPA 1 Safety Evaluator:	Avinash Konkani, PhD, MS, BE
DMEPA 1 Team Leader (Acting):	Matthew Barlow, RN, BSN
DMEPA 1 Associate Director for Human Factors:	Ariane O. Conrad, PharmD, BCACP, CDCES, FISMP

1 REASON FOR REVIEW

This review evaluates the use-related risk analysis (URRA) and threshold analyses (hereafter, called comparative analyses) submitted under NDA 218637 for Trazodone Hydrochloride oral solution to determine whether Kamat needs to submit a human factors (HF) validation study to support their marketing application.

1.1 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review.

Table 1. Materials Considered for this Review	
Material Reviewed	Section/ Appendix
Product Information	Section 1.2
Background Information Previous HF Reviews (DMEPA)	Section 1.3
Use Related Risk Analysis and Comparative Analyses	Appendix A
Information Requests Issued During the Review	Appendix B
Product Sample, Labels and Labeling and Packaging	Appendix C

1.2 PRODUCT DESCRIPTION

Table 2. Relevant Product Information for Proposed Product and Comparator Product		
Product Name	Trazodone Hydrochloride	Trileptal[1] (oxcarbazepine)
Application Number	NDA 218637	NDA 021285
Initial Approval Date	N/A	May 25, 2001
Active Ingredient	established/proper name	Oxcarbazepine
Indication	Major depressive disorder (MDD) in adults.	Adult patients: Monotherapy or adjunctive therapy in the treatment of partial-onset seizures

[1] Trileptal [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2024 March 26. [cited 2019 Jan 04]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021285s036lbl.pdf

Table 2. Relevant Product Information for Proposed Product and Comparator Product		
		<u>Pediatric patients</u>: • Monotherapy in the treatment of partial-onset seizures in children 4 to 16 years • Adjunctive therapy in the treatment of partial-onset seizures in children 2 to 16 years
Route of Administration	Oral	
Dosage Form	Oral solution	• Film-coated tablets • Oral suspension
Strength	100 mg/10 mL (10 mg/mL)	• Film-coated tablets: 150 mg, 300 mg, and 600 mg • Oral suspension: 300 mg/5 mL (60 mg/mL)
Dose and Frequency	• Starting dose: 150 mg in divided doses daily. May be increased by 50 mg per day every three to four days. • Maximum dose: 400 mg per day in divided doses. • Trazodone Hydrochloride Oral Solution should be taken shortly after a meal or light snack. • When discontinued, gradual dose reduction is recommended.	<u>Adults patients:</u> Initiate with a dose of 600 mg per day, given twice-a-day. • Adjunctive Therapy: Maximum increment of 600 mg/day at approximately weekly intervals. The recommended daily dose is 1200 mg/day • Conversion to Monotherapy: withdrawal concomitant over 3 to 6 weeks; reach maximum dose of Trileptal in 2 to 4 weeks with increments of 600 mg/day at weekly intervals to a recommended daily dose of 2400 mg/day • Initiation of Monotherapy: Increments of 300 mg/day every third day to a dose of 1200 mg/day

Table 2. Relevant Product Information for Proposed Product and Comparator Product		
		• Initiate at one-half the usual starting dose and increase slowly in patients with a creatinine clearance <30 mL/min <u>Pediatric patients:</u> Initiation with 8 to 10 mg/kg/day, given twice-a-day. For patients aged 2 to <4 years and under 20 kg, a starting dose of 16 to 20 mg/kg/day may be considered. Recommended daily dose is dependent upon patient weight. • Adjunctive Patients (Aged 2–16 Years): For patients aged 4 to 16 years, target maintenance dose should be achieved over 2 weeks. For patients aged 2 to <4 years, maximum maintenance dose should be achieved over 2 to 4 weeks and should not exceed 60 mg/kg/day. • Conversion to Monotherapy for Patients (Aged 4–16 Years) Maximum increment of 10 mg/kg/day at weekly intervals, concomitant antiepileptic drugs can be completely withdrawn over 3 to 6 weeks. • Initiation of Monotherapy for Patients (Aged 4–16 Years) Increments of 5 mg/kg/day every third day
How Supplied	Trazodone Hydrochloride Oral Solution is an aqueous solution of Trazodone Hydrochloride for oral administration by means of a dosing syringe.	<u>Tablets:</u> • 150 mg Film-Coated Tablets: pale grey-green, ovaloid, slightly biconvex, scored on both sides. Imprinted with

Table 2. Relevant Product Information for Proposed Product and Comparator Product		
	The syringe is a 10 mL syringe with adapter and has markings at every 0.25 mL for dose titration. The product is supplied in two (2) configurations: <u>Configuration 1:</u> • <u>Amber glass bottle</u> containing medication with child resistant (CR) cap. o 300 mL glass bottle o 150 mL glass bottle • An adapter and a 10 mL dosing syringe. • A carton enclosing all above components and pack insert. <u>Configuration 2:</u> • <u>White, opaque, High-density polyethylene (HDPE) bottle</u> containing medication with CR cap. o 300 mL HDPE bottle o 150 mL HDPE bottle • An adapter and a 10 mL dosing syringe. • A carton enclosing all above components and pack insert.	T/D on one side and C/G on the other side. o Bottle of 100, Unit Dose (blister pack) o Box of 100 (strips of 10) • 300 mg Film-Coated Tablets: yellow, ovaloid, slightly biconvex, scored on both sides. Imprinted with TE/TE on one side and CG/CG on the other side. o Bottle of 100, Unit Dose (blister pack) o Box of 100 (strips of 10) • 600 mg Film-Coated Tablets: light pink, ovaloid, slightly biconvex, scored on both sides. Imprinted with TF/TF on one side and CG/CG on the other side. o Bottle of 100, Unit Dose (blister pack) o Box of 100 (strips of 10) <u>Suspension:</u> • 300 mg/5 mL (60 mg/mL) Oral Suspension: off-white to slightly brown or slightly red suspension. • Available in amber glass bottles containing 250 mL of oral suspension. • Supplied with a 10 mL dosing syringe and press-in bottle adapter.
Storage	Store at 20°C to 25°C (68°F to 77°F). Excursions permitted between 15ºC and 30ºC (59°F to 86ºF) *[see USP Controlled Room Temperature]*.	• Store Trileptal oral suspension in the original container. • Shake well before using.

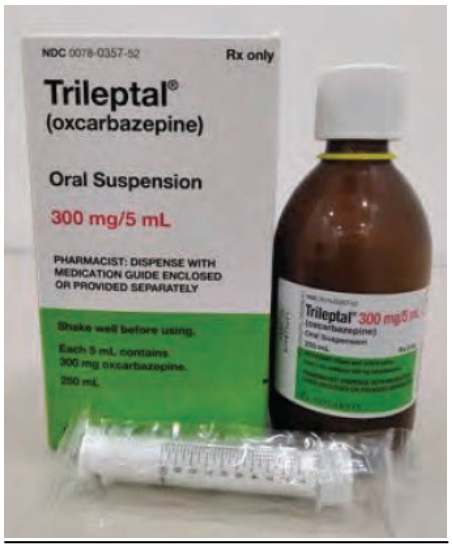
Table 2. Relevant Product Information for Proposed Product and Comparator Product		
		• Use within 7 weeks of first opening the bottle. • Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].
Container Closure/Device Constituent	<u>Configuration 1:</u> Amber glass bottle (b) (4) <u>Configuration 2:</u> White, opaque, High-density polyethylene (HDPE) bottle (b) (4)	<u>Amber glass bottle</u> 
Intended users	Adult patients, lay caregivers, Healthcare Professionals (HCPs)	

Table 2. Relevant Product Information for Proposed Product and Comparator Product	
Intended use environments	Non-clinical (i.e., Home), Clinical (i.e., Hospital or HCP Office)

1.3 RELEVANT REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

On March 26,2024, we searched for previous DMEPA reviews and FDA/Kamat interactions relevant to this current review using the terms, "*Trazodone Hydrochloride*" and "NDA 218637". See details below.

- On May 08, 2023, Kamat submitted a Pre-NDA meeting request under NDA 218637 to obtain the Agency's feedback on the content and presentation of the proposed New Drug Application (NDA) submission for trazodone hydrochloride oral solution.
    - In the written response dated July 10, 2023, we stated that " *in light of your proposed timeline for submitting your NDA, we request that you submit only the URRA portion of the threshold analysis document to the NDA for our review.*"[2]
- On July 25, 2023, Kamat submitted NDA 218637, which included a use-related risk analysis (URRA), comparative analyses and justification for not submitting HF validation study results. We did not review this submission, because on September 20, 2023, the Agency issued a Refuse to File (RTF) letter due to failure to address the requirements under the Pediatric Research Equity Act (PREA) and stated that "*You have not provided an agreed initial pediatric study plan (iPSP) with your new drug application for trazadone hydrochloride oral solution for the treatment of major depressive disorder (MDD)*."[3]
- On January 29, 2024, we received the Kamat's resubmission of their marketing application under NDA 218637, including a URRA, comparative analyses, and justification for not submitting HF validation study results, which are the subject of this review.

2 OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide our evaluation of the URRA and comparative analyses.

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[2] Shim, J. Final written response for Trazodone Hydrochloride Oral solution. Silver Spring (MD): FDA, CDER, OND; 2023 JUL 10, NDA 218637. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806ddb2b

[3] Shim,J. Refuse to File letter for Trazodone Hydrochloride Oral solution. Silver Spring (MD): FDA, CDER, OND; 2023 SEP 20, NDA 218637. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806f612a

2.1 USE-RELATED RISK ANALYSIS

Kamat submitted a URRA for their proposed product Trazodone Hydrochloride oral solution.

We reviewed the URRA for the proposed product, and based on the information we have at this time, the tasks evaluated appear to be comprehensive and appropriate based on what Kamat proposes for the design and intended use of this product. We did not identify any additional use-related issues that were not analyzed, and we determined the risks are mitigated by the proposed labels and labeling.

2.2 COMPARATIVE ANALYSES

Consideration	Same	Different	Discussion of Differences
Indication	☐	☒	Trileptal FDA-Approved Indications: Adult patients: Monotherapy or adjunctive therapy in the treatment of partial-onset seizures Pediatric patients: • Monotherapy in the treatment of partial-onset seizures in children 4 to 16 years • Adjunctive therapy in the treatment of partial-onset seizures in children 2 to 16 years Trazodone Hydrochloride Proposed indication: Major depressive disorder (MDD) in adults.
Intended user population	☐	☒	Trileptal Intended Users: Adult and pediatric patients with partial-onset seizures and/or their caregivers Trazodone Intended Users: Adult patients with Major Depressive Disorder and/or their caregivers. We find these differences in the user populations do not introduce any new or unique risks that would impact use of the proposed product.

Use environment	☒	☐	
Dosing	☐	☒	Dosing is different based on the medication and the indication (see table 2 above). Since both products are administered using a co-packaged 10 mL oral syringe and bottle adapter, we find the differences in dosing do not introduce any new or unique risks that would impact use of the proposed product.
Route of administration	☒	☐	
Strength	☐	☒	Strength is different based on the medication (see table 2 above).

2.2.1 PHYSICAL COMPARISON

Consideration	Yes	No	N/A	Discussion of Other Design Differences
Are there other design differences identified?	☐	☒		
Are the identified other design differences likely to negatively impact users' ability to complete the critical tasks needed to use this product safely and effectively?	☐	☐	☒	

2.2.2 COMPARATIVE TASK ANALYSES

Consideration	Yes	No	N/A	Discussion of Other Task Differences
New, differing, or unique tasks identified?	☒	☐		Sponsor Identified: None DMEPA Identified: • If the prescribed dose is more than 10 mL, then the patient needs to refill the syringe to complete the full dose; however, to complete this task, the proposed product's IFU has instructions to refill the syringe to make up the

				full dose (b) (4) (b) (4) (b) (4) Conversely, the comparator product has instructions to refill the syringe if necessary to prepare a full dose that is more than 10 mL (b) (4) In their justification, Kamat stated that, (b) (4) (b) (4) The proposed (b) (4) in the IFU may lead to confusion because (b) (4) (b) (4) (b) (4) Furthermore, the (b) (4) (b) (4) is not included in the IFU for the comparator product, Trileptal, Oxcarbazepine Oral Suspension. Therefore, it is not clear how users will (b) (4) As such, we recommend removing the (b) (4) (b) (4) (b) (4) from the proposed IFU so that the proposed IFU matches the comparator product's IFU.
Are the identified tasks unlikely to negatively impact users' ability to	☒	☐	☐	

complete the critical tasks needed to use this product safely and effectively?				

2.2.3 LABELING COMPARISON

Kamat's labeling comparison considered the Instruction for Use (IFU) .

Consideration	Yes	No	N/A	Discussion of Other Labeling Differences
Labeling differences identified?	☒	☐		Sponsor Identified: None DMEPA Identified: The proposed IFU includes (b) (4) which is a concern from a medication error perspective. Therefore, we recommend removing references to (b) (4) (b) (4) from the proposed IFU (see discussion in section 2.2.2 above).
Are the identified differences unlikely to negatively impact users' ability to complete the critical tasks needed to use this product safely and effectively?	☒	☐	☐	

We note that the DMEPA 1 primary and nomenclature review team evaluated product specific label and labeling under a separate cover.

3 CONCLUSION

Our review of the URRA and comparative analyses did not identify any new, differing, or unique risks for the proposed product as compared to currently approved Trileptal (oxcarbazepine) oral suspension. As such, we agree with Kamat's justification for not submitting human factors (HF) validation study results as part of their marketing application. Thus, we have no HF recommendations for this marketing application

However, we note that the proposed IFU includes [redacted] We are concerned that the proposed [redacted] which may lead to confusion and increase the risk for medication dosing errors. Additionally, we note the Trileptal (oxcarbazepine) oral suspension IFU does not include this information. We provide recommendations below in section 3.1 for Kamat regarding their proposed [redacted]

3.1 RECOMMENDATIONS FOR KAMAT PHARMATECH LLC

Based on our review of your use-related risk analysis (URRA), comparative analyses, and justification for not submitting human factors (HF) validation study results for Agency review, we have determined that HF validation study results do not need to be submitted as part of your marketing application. However, we note that the proposed IFU includes [redacted] We note that the proposed [redacted] which may lead to confusion and increase the risk for medication dosing errors. Additionally, we note the Trileptal (oxcarbazepine) oral suspension IFU does not include a similar [redacted] Therefore, to minimize confusion, we recommend that you remove the proposed [redacted] from the proposed IFU ([redacted]).

Further, because the proposed product is a combination product as provided in 21 CFR Part 4, the combination product must comply with the Quality System regulation, 21 CFR Part 820. §820.30 Design Controls includes requirements relevant to human factors testing. For additional information see FDA guidance Current Good Manufacturing Practice Requirements for Combination Products.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. URRA, COMPARATIVE ANALYSES AND HF-RELATED SUPPORTING DOCUMENTS

The use-related risk analysis and comparative analyses for Trazodone Hydrochloride submitted on January 29, 2024 can be accessible in EDR via:
\\CDSESUB1\EVSPROD\nda218637\0006\m5\53-clin-stud-rep\535-rep-effic-safety-stud\major-depressive-disorder-mdd\5354-other-stud-rep\threshold-report\threshold-analysis-report.pdf

APPENDIX B. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On March 21, 2024, we issued an information request (IR) to obtain revised use-related risk analysis and revised comparative analyses for the proposed Trazodone Hydrochloride oral solution. Kamat submitted their response on March 25, 2024, that is accessible in EDR via:
\\CDSESUB1\EVSPROD\nda218637\0009\m5\53-clin-stud-rep\535-rep-effic-safety-stud\major-depressive-disorder-mdd\5354-other-stud-rep\threshold-report\threshhold-analysis-report.pdf

APPENDIX C. PRODUCT SAMPLE, LABELS AND LABELING

C.1 Product Sample

The product samples were submitted for our review, and we did not identify any recommendations for improvement at this time.

C.2 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[4] along with postmarket medication error experiences with similar products, we reviewed the following Trazodone Hydrochloride labeling submitted by Kamat Pharmatech LLC on January 29, 2024.

- Carton Labeling
- Container Label
- Instructions for Use (image not shown) available in the EDR via:
  \\CDSESUB1\EVSPROD\nda218637\0006\m1\us\kamat-labeling-text-word.docx

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

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/s/

AVINASH KONKANI
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ARIANE O CONRAD
08/06/2024 05:05:46 PM

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: 4/29/2024

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

FROM: Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct on-site inspections**

RE: NDA 218637

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

Rationale

Ecron AcuNova, Chennai: The Office of Regulatory Affairs (ORA) The Office of Regulatory Affairs (ORA) conducted an inspection for the site in November 2022. The inspection was conducted under the following submissions: NON-RESPONSIVE

The following items were discussed with the site:

- The site SOP on informed consent was deficient, Specifically, the SOP lacked the following points:
  - a statement informing that subjects could have one-on-one conversations with the study doctor to discuss informed consent forms (ICFs).
  - Required time stamps for when the ICF is signed.
  - A statement that the informed consent process is conducted in a group setting.
- The site SOP on adverse events specified an unreasonably long period (21 days) to follow up on AEs.

After review of the inspection findings and the response from the site, OSIS concluded that data from the reviewed study was reliable.

(b) (4) OSIS conducted a Remote Regulatory Assessment (RRA) for the site in (b) (4) The RRA was conducted under the following submissions: NON-RESPONSIVE NON-RESPONSIVE

The following objectionable condition was observed:

(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 – (b) (4)

Sites

Facility Type	Facility Name	Facility Address
Clinical	Ecron AcuNova, Ltd.	No. 56, Ragas Building, Dr. Radhakrishnan Road, Opposite CSI Kalyani Hospital, Jagadambal Colony, Rotary Nagar, Mylapore, Chennai, Tamil Nadu, India
Analytical		(b) (4)

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/s/

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