CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217645Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABELS 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)

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

Date of This Review:	May 24, 2024
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 217645
Product Name, Dosage Form, and Strength:	Onyda XR[a] (clonidine hydrochloride) extended-release oral suspension, 0.1 mg/mL
Applicant Name:	Tris Pharma, Inc. (Tris)
FDA Received Date:	May 24, 2024
TTT ID #:	2023-5708-1
DMEPA 1 Safety Evaluator:	Loretta Holmes, BSN, PharmD
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

[a] Holmes, L. Proprietary Name Review for Onyda XR (NDA 217645). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 Oct 20. PNR ID No. 2023-1044725252.

1 PURPOSE OF MEMORANDUM

This memorandum is an addendum to our previous labels and labeling review.[b] Since our previous labels and labeling review, (b) (4) it has been determined that the product should be dispensed in the original bottle. Additionally, the instructions for use have changed such that the patient, (b) (4) as previously proposed, is now responsible for inserting the bottle adapter. Therefore, the recommendations in our previous review were revised before being communicated to Tris (see Appendix A).

Tris Pharma, Inc. submitted revised container labels and carton labeling, received on May 24, 2024 via email, for Onyda XR. The Division of Psychiatry (DP) requested that we review the revised container labels and carton labeling for Onyda XR (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to the revised recommendations that we provided and follow up recommendations communicated to Tris (see Appendix A).

2 CONCLUSION

Tris Pharma, Inc. implemented all of our recommendations and we have no additional recommendations at this time.

[b] Holmes, L. Labels and Labeling Review for Onyda XR (NDA 217645). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 May 15. TTT ID: 2023-5708.

APPENDIX A. RECOMMENDATIONS COMMUNICATED TO TRIS PHARMA INC.

Recommendations communicated on May 21, 2024

Table 2. Identified Issues and Recommendations for Tris Pharma, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
All Container Labels and Carton Labeling			
1.	The trademark symbol (™) is too prominent.	The prominence of the trademark symbol interferes with the readability of the proprietary name.	Decrease the size of the trademark symbol.
2.	The established name 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).
3.	The "Rx Only" and net quantity statements are too prominent. The NDC number is also too prominent.	The prominence of the "Rx Only" and net quantity statements as well as the NDC number distract from other critical information such as the proprietary name, established name, and strength.	Unbold the "Rx Only" and net quantity statements as well as the NDC number. On the professional sample container labels, decrease their size as well.

Table 2. Identified Issues and Recommendations for Tris Pharma, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
4.	The terminology within the statement of dosage (i.e., (b) (4)) is inconsistent with the terminology in the Prescribing Information (PI).	There should be consistency with the terminology in the PI.	Revise the statement of dosage statement to read, "Recommended Dosage: See Prescribing Information."
5.	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.	Add the statement, "For Oral Use Only" to the principal display panel (PDP).
6.	The storage statement reads as follows: "Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]." We note that some of the numerical units are not followed by their corresponding temperature unit.	For clarity, each numerical unit should be followed by its corresponding temperature unit.	Revise the storage statement to read: "Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]."
7.	The statement "Protect from light" is not on the container labels or carton labeling.	For consistency with the Prescribing Information the statement should be added to the storage statement.	Add the following statement to the storage statement: "Protect from light."
8.	Instructions on when to discard the unused product after first opening the bottle are not on the container labels or carton labeling.	Absence of this information may pose the risk of administration of degraded drug product.	Based on the review of your submitted data, 60 days will be the use by date for your product. Add the following statement (or similar verbiage) to the container labels and carton labeling: "Discard unused

Table 2. Identified Issues and Recommendations for Tris Pharma, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			Onyda XR 60 days after first opening the bottle. Date bottle first opened: __/__/__."
9.	The statement (b) (4) is not aligned with the statement regarding shaking in the PI.	Inconsistencies with the PI may lead to confusion.	Revise the statement to read: "Shake gently (to avoid foaming) for at least 10 seconds before each use."
10.	The statement (b) (4) is on the container labels and carton labeling.	(b) (4) Therefore, the statement is no longer necessary.	Delete the statement (b) (4) .
Professional Sample Container Label			
1.	The "Rx Only" statement and net quantity statement are in too close proximity to the statement of strength.	In their current location, the "Rx Only" and net quantity statements distract from the readability of the statement of strength.	Consider relocating the "Rx Only" and net quantity statements to locations away from the statement of strength.
2.	The manufacturer logo is too prominent.	The prominence of the manufacturer logo distracts from other critical information such as the proprietary name, established name, and strength.	Decrease the size of the manufacturer logo and consider moving to a side panel.
Trade and Professional Sample Container Labels and Professional Sample Carton Labeling			
1.	As currently presented, 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

Table 2. Identified Issues and Recommendations for Tris Pharma, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			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).*
Trade Carton Labeling			
1.	The lot number and expiration date are not clearly identified.	The lot number and expiration date should be clearly identified for ease of location on the carton.	Clearly identify the lot number and expiration date by specifying “Lot” and “Exp” respectively or using similar terminology.
2.	The statement “Store and dispense in the original bottle” is not on the carton labeling.	This information should be on the carton labeling.	Add the statement “Store and dispense in the original bottle” to the carton labeling.

Table 2. Identified Issues and Recommendations for Tris Pharma, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
3.	(b) (4) The instructions for use will be revised to instruct the patient on this task.	The (b) (4) information is no longer necessary.	Delete the (b) (4) heading and the associated information below it.
Trade and Professional Sample Carton Labeling			
1.	The carton contents information lacks prominence.	For improved readability, the carton contents should be more prominent.	Increase the size of the heading "This carton contains" as well as the carton contents information.
2.	The "This carton contains" information does not list the actual drug product or the Instructions for Use.	The "This carton contains" information is incomplete.	Under "This carton contains" add the statement "One (1) bottle of Onyda XR XX mL" as first on the list. Also, add (b) (4) to the list. Furthermore, on the trade carton labeling, change "dispenser" to "dispensers".
3.	As currently presented, the carton labeling does not indicate that the product is not substitutable with other clonidine products on a milligram-per-milligram basis.	Inadvertent substitution can lead to medication errors such as, but not limited to, wrong drug errors leading to no treatment effect, overdose or underdose leading to adverse events or lack of efficacy.	We recommend adding the statement to the principal display panel (PDP): "Do not substitute for other clonidine products on a milligram-per-milligram basis.

Recommendations communicated on May 23, 2024

All Container Labels and Carton Labeling

To improve visibility, place the following statements in bold font: “Discard unused Onyda XR 60 days after first opening the bottle. Date bottle first opened: __/__/__.” Additionally, for the professional sample container label, increase the length of the horizontal lines in order to increase the amount of space for writing in the date.

All Carton Labeling

Under “This carton contains,” change [redacted] (b) (4) to “Instructions for Use”.

Trade Carton Labeling

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. We recommend that you review the guidance to determine if the product identifier requirements apply to your product’s labeling. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021). If you determine that the product identifier requirements apply to your product’s labeling, we request you add a place holder to the carton labeling.

7 mL Carton

Please correct typo on this carton label, i.e., place “mg” next “0.1” (see highlight) below:

Each mL of the extended-release
suspension contains 0.1
mg of clonidine hydrochloride
equivalent to 0.09 mg of
clonidine base.

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/

LORETTA HOLMES
05/24/2024 03:19:50 PM

YEVGENIYA M KOGAN
05/24/2024 03:40:30 PM

USE-RELATED RISK ANALYSIS 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:	May 17, 2024
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 217645
Product Type:	Single Ingredient Product
Product Name, Dosage Form and Strength:	Onyda XR[1] (clonidine hydrochloride) extended-release oral suspension, 0.1 mg/mL
Device Constituent:	Oral dosing dispenser and bottle adapter
Rx or OTC:	Rx
Applicant/Sponsor Name:	Tris Pharma, Inc. (Tris Pharma)
Submission Date:	July 24, 2023; December 6, 2023, January 17, 2024
OSE TTT #:	2023-5710
DMEPA 1 Safety Evaluator:	Avani Bhalodia, PharmD, BCPS
DMEPA 1 Team Leader:	Murewa Oguntimein, PhD, MHS, CPH, MCHES
DMEPA 1 Associate Director for Human Factors:	Ariane O. Conrad, PharmD, BCACP, CDCES

[1] The proposed proprietary name, Onyda XR, was found conditionally acceptable on October 21, 2023.

1. REASON FOR REVIEW

The review evaluates the human factors (HF) assessment and use-related risk analysis (URRA) submitted under NDA 217645 for Onyda XR (clonidine hydrochloride) extended-release oral suspension to determine whether Tris Pharma needs to submit HF validation results of as part of this marketing application. Of note, Tris Pharma initially submitted a HF assessment for review, which was designed to evaluate "*the ease of self-dosing after receiving each dose of test product…as part of the multiple-dose study*".[2] Subsequently, they were advised to submit a URRA for review.

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 1.1
Background Information Previous HF Reviews (DMEPA)	Section 1.2
Use Related Risk Analysis and HF-Related Supporting Documents	Appendix A
Information Requests Issued During the Review	Appendix B
Labels and Labeling	Appendix C

N/A=not applicable for this review

1.1 PRODUCT DESCRIPTION

Table 2. Relevant Product Information	
Initial Approval Date	N/A
Active Ingredient (Drug or Biologic)	clonidine hydrochloride
Indication	indicated for the treatment of attention-deficit/hyperactivity disorder (ADHD) as monotherapy and as adjunctive therapy to stimulant medications
Route of Administration	oral
Dosage Form	oral suspension
Strength	0.1 mg/mL
Dose and Frequency	The dose of Onyda XR, administered either as monotherapy or as adjunctive therapy to a psychostimulant, should be individualized according to the

[2] Human Factor Assessment: NDA 217645 for Onyda XR (clonidine hydrochloride). Monmouth Junction (NJ): Tris Pharma, Inc.; 2023 JUL 24. Available from: \\CDSESUB1\EVSPROD\nda217645\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\adhd\5354-other-stud-rep\comp-task-analyses\comparativetaskanalyses.pdf.

	therapeutic needs and response of the patient. Dosing should be initiated with 1 mL (0.1 mg) dose at bedtime. The daily dose should be adjusted in increments of 0.1 mg/day (1 mL/day) at weekly intervals until the desired response is achieved.
How Supplied	7 mL oral suspension bottle packaged with one oral dosing dispenser and a press-in bottle adapter in a carton. 120 mL oral suspension bottle packaged with two oral dosing dispensers and two press-in bottle adapters in a carton.
Storage	Store at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F)
Container Closure/Device Constituent	Bottle packaged with oral dosing dispenser and press-in bottle adapter
Intended Users	Patients and Caregivers
Intended Use Environment	Home environment

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

On January 3, 2024, we searched for previous DMEPA reviews and FDA/Tris Pharma interactions relevant to this current review using the terms, NDA 217645, IND 128004, and clonidine hydrochloride. Our search did not identify any previous reviews or FDA/Tris Pharma interactions.

- On July 24, 2023, Tris Pharma submitted a new drug application (NDA) for clonidine hydrochloride extended-release oral suspension, 0.1 mg/mL under NDA 217645. This submission included a HF assessment study which is the subject of this review.
- On November 10, 2023, we issued an information request (IR), asking Tris Pharma to submit a comprehensive URRA.
- On December 6, 2023, Tris Pharma submitted the URRA, which is also the subject of this review.

2. OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The section below provides our evaluation of the use-related risk analysis (URRA). Of note, Tris Pharma submitted a human factors (HF) assessment study and our review of that data determined that there were multiple methodology flaws that limit our ability to interpret the study data and determine that user interface supports the safe and effective use of the proposed product. Therefore, we determined that a comprehensive URRA would be needed to inform our determination regarding HF data needs and issued an information request to request that Tris Pharma submit a URRA for review.

2.1 USE-RELATED RISK ANALYSIS (URRA)

Tris Pharma submitted a URRA for their proposed product Onyda XR on December 6, 2023, for our review.

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 Tris Pharma 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.

3. CONCLUSION

Our review of the URRA determined that the tasks evaluated appear to be comprehensive and appropriate based on Tris Pharma's design and intended use for Onyda XR. As such, we conclude that Tris Pharma does not need to submit the results of an HF validation study as part of this marketing application. We have no recommendations for this marketing application.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. USE-RELATED RISK ANALYSIS AND HF-RELATED SUPPORTING DOCUMENTS

The human factors assessment can be accessible in EDR via:
\\CDSESUB1\EVSPROD\nda217645\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\adhd\5354-other-stud-rep\comp-task-analyses\comparativetaskanalyses.pdf

The use-related risk analysis can be accessible in EDR via:
\\CDSESUB1\EVSPROD\nda217645\0006\m5\53-clin-stud-rep\535-rep-effic-safety-stud\adhd\5354-other-stud-rep\comp-task-analyses\use-related-risk-analysis.pdf

APPENDIX B. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On November 10, 2023, we issued an information request (IR) to request comprehensive use-related risk analysis (URRA).
The Applicant provided an acceptable response on December 6, 2023, that can be accessible in EDR via: \\CDSESUB1\EVSPROD\nda217645\0006\m5\53-clin-stud-rep\535-rep-effic-safety-stud\adhd\5354-other-stud-rep\comp-task-analyses\use-related-risk-analysis.pdf

On January 13, 2024, we issued an IR to

- request a revised URRA with detailed descriptions of the clinical impact of potential use errors and comprehensively evaluating all tasks in the IFU.
- request a final intend to market IFU.

The Applicant provided an acceptable response on January 17, 2024, that can be accessible in EDR via:
\\CDSESUB1\EVSPROD\nda217645\0007\m5\53-clin-stud-rep\535-rep-effic-safety-stud\adhd\5354-other-stud-rep\comp-task-analyses\use-related-risk-analysis.pdf and
\\CDSESUB1\EVSPROD\nda217645\0007\m1\us\onyda-xr-draft-labeling-text.pdf

APPENDIX C. LABELS AND LABELING

C.1 LIST OF LABELING REVIEWED

Using the principles of human factors and Failure Mode and Effects Analysis,[3] along with postmarket medication error experiences with similar products, we reviewed the following Onyda XR labeling submitted by Tris Pharma, Inc. on 7/24/2023 and 1/17/2024.

Carton labeling	Images shown below

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

Container labels	Images shown below
Instructions for Use (Image not shown)	\\CDSESUB1\EVSPROD\nda217645\0007\m1\us\onyda-xr-draft-labeling-text.pdf

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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/

AVANI BHALODIA
05/17/2024 10:37:55 AM

OLUWAMUREWA OGUNTIMEIN
05/17/2024 10:57:21 AM

ARIANE O CONRAD
05/17/2024 11:54:05 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:	May 15, 2024
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 217645
Product Name, Dosage Form, and Strength:	Onyda XR (clonidine hydrochloride) extended-release oral suspension, 0.1 mg/mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Tris Pharma, Inc.
FDA Received Date:	July 24, 2023 and February 15, 2024
TTT ID #:	2023-5708
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 Onyda XR (clonidine hydrochloride) extended-release oral suspension, the Division of Psychiatry (DP) requested that we review the proposed Onyda XR Prescribing Information (PI), Patient Package Insert (PPI), Instructions for Use (IFU), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

Onyda XR (clonidine hydrochloride) is a proposed 505(b)(2) drug product and the Listed Drug (LD) is Kapvay (clonidine hydrochloride), NDA 022331.

2 MATERIALS REVIEWED

This section lists the materials considered for our review of NDA 217645.

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

3 CONCLUSION

We evaluated the proposed Onyda XR Patient Package Insert (PPI) and determined that it is acceptable from a medication error perspective.

However, the proposed Onyda XR Prescribing Information (PI)[a], Instructions for Use (IFU), container labels, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. Our evaluation of the PI focused 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. We note that Sections 2 and 16 can be improved for clarity. We collaborated with the Division of Psychiatry's review team to improve the clarity of the information in these sections from a medication error perspective. Our evaluation of the Instructions for Use also noted there are areas that may be improved for clarity. We deferred to the Patient Labeling Team (PLT) for a review of the IFU, however, we collaborated them to improve the clarity of the information from a medication error perspective.

Our evaluation of the container labels and carton labeling 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 Tris Pharma, Inc. in Section 4.

[a] We reviewed the PI received on July 24, 2023 and revised by the Division of Psychiatry as of May 15, 2024.

4 RECOMMENDATIONS FOR TRIS PHARMA, INC.

Table 2. Identified Issues and Recommendations for Tris Pharma, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
All Container Labels and Carton Labeling			
1.	The trademark symbol (™) is too prominent.	The prominence of the trademark symbol interferes with the readability of the proprietary name.	Decrease the size of the trademark symbol.
2.	The established name 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).
3.	The "Rx Only" and net quantity statements are too prominent. The NDC number is also too prominent.	The prominence of the "Rx Only" and net quantity statements as well as the NDC number distract from other critical information such as the proprietary name, established name, and strength.	Unbold the "Rx Only" and net quantity statements as well as the NDC number. On the professional sample container labels, decrease their size as well.

Table 2. Identified Issues and Recommendations for Tris Pharma, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
4.	The terminology within the statement of dosage (i.e., (b) (4)) is inconsistent with the terminology in the Prescribing Information (PI).	There should be consistency with the terminology in the PI.	Revise the statement of dosage statement to read, "Recommended Dosage: See Prescribing Information."
5.	The statement "For Oral Use" is not present on the container label and/or carton labeling.	To minimize the risk of wrong route of administration errors, the route of administration statement should be on the container label and/or carton labeling.	Add the statement, "For Oral Use Only" to the principal display panel (PDP).
6.	The storage statement reads as follows: "Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]." We note that some of the numerical units are not followed by their corresponding temperature unit.	For clarity, each numerical unit should be followed by its corresponding temperature unit.	Revise the storage statement to read: "Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]."
7.	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.	Based on the review of your submitted data, 60 days will be the use by date for your product (b) (4)

Table 2. Identified Issues and Recommendations for Tris Pharma, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			(b) (4) (b) (4) The following statement (or similar verbiage) should be added to the container labels and carton labeling: "Discard unused Onyda XR 60 days after opening bottle. Date bottle opened: __/__/__."
8.	The statement (b) (4) is not aligned with the statement regarding shaking in the PI.	Inconsistencies with the PI may lead to confusion.	Revise the statement to read: "Shake gently (to avoid foaming) for at least 10 seconds before each use."
Professional Sample Container Label			
1.	The "Rx Only" statement and net quantity statement are in too close proximity to the statement of strength.	In their current location, the "Rx Only" and net quantity statements distract from the readability of the statement of strength.	Consider relocating the "Rx Only" and net quantity statements to locations away from the statement of strength.
2.	The manufacturer logo is too prominent.	The prominence of the manufacturer logo distracts from other critical information such as the proprietary name, established name, and strength.	Decrease the size of the manufacturer logo and consider moving to a side panel.
Trade and Professional Sample Container Labels and Professional Sample Carton Labeling			
1.	As currently presented, 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

Table 2. Identified Issues and Recommendations for Tris Pharma, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			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).*
2.	The "This carton contains" information does not list the actual drug product.	The "This carton contains" information is incomplete.	Under "This carton contains" add the statement "One (1) bottle of Onyda XR XX mL" as first on the list. Additionally, on the trade carton labeling, change "dispenser" to "dispensers".

Table 2. Identified Issues and Recommendations for Tris Pharma, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Trade Carton Labeling			
1.	The lot number and expiration date are not clearly identified.	The lot number and expiration date should be clearly identified for ease of location on the carton.	Clearly identify the lot number and expiration date by specifying “Lot” and “Exp” respectively or using similar terminology.
Trade and Professional Sample Carton Labeling			
1.	The carton contents information lacks prominence.	For improved readability, the carton contents should be more prominent.	Increase the size of the heading “This carton contains” as well as the carton contents information.
2.	As currently presented, the carton labeling does not indicate that the product is not substitutable with other clonidine products on a milligram-per-milligram basis.	Inadvertent substitution can lead to medication errors such as, but not limited to, wrong drug errors leading to no treatment effect, overdose or underdose leading to adverse events or lack of efficacy.	We recommend adding the statement to the principal display panel (PDP): “Do not substitute for other clonidine products on a milligram-per-milligram basis.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 3 presents relevant product information for Onyda XR received on February 15, 2024 from Tris Pharma, Inc., and the Listed Drug (LD).

Table 3. Relevant Product Information for Onyda XR and the Listed Drug (LD).		
Product Name	Onyda XR	Kapvay[b]
Initial Approval Date	N/A	09/29/2009
Active Ingredient	clonidine hydrochloride	clonidine hydrochloride
Indication	Treatment of attention-deficit/hyperactivity disorder (ADHD) as monotherapy and as adjunctive therapy to stimulant medications	Treatment of attention deficit hyperactivity disorder (ADHD) as monotherapy and as adjunctive therapy to stimulant medications
Dosage Form	extended-release oral suspension	extended-release tablets
Strength	0.1 mg/mL	0.1 mg
Route of Administration	Oral	Oral
Dose and Frequency	(b) (4)	The dose of Kapvay, administered either as monotherapy or as adjunctive therapy to a psychostimulant, should be individualized according to the therapeutic needs and response of the patient. Dosing should be initiated with one 0.1 mg tablet at bedtime, and the daily dosage should be adjusted in increments of 0.1 mg/day at weekly intervals until the desired response is achieved. Doses should be taken twice a day, with either an equal or higher split dosage being given at bedtime (see Table 1). Table 1. Kapvay Dosing Guidance

[b] Kapvay [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. February 2020. [cited 2024 Apr 02]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022331s021lbl.pdf.

Table 3. Relevant Product Information for Onyda XR and the Listed Drug (LD).		
Product Name	Onyda XR	Kapvay[b]
	(b) (4)	<table><tr><th>Total Daily Dose</th><th>Morning Dose</th><th>Bedtime Dose</th></tr><tr><td>0.1 mg/day</td><td></td><td>0.1 mg</td></tr><tr><td>0.2 mg/day</td><td>0.1 mg</td><td>0.1 mg</td></tr><tr><td>0.3 mg/day</td><td>0.1 mg</td><td>0.2 mg</td></tr><tr><td>0.4 mg/day</td><td>0.2 mg</td><td>0.2 mg</td></tr></table>
How Supplied	(b) (4)	NDC 59212-658-60 – 0.1 mg tablets supplied in a carton containing one bottle of 60 tablets
Storage	Store at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. (b) (4)	Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature]. Dispense in a tight container.
Container Closure	Child-resistant closure	This information was not provided in the Prescribing Information.

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 Onyda XR labels and labeling submitted by Tris Pharma, Inc.

Labels and Labeling	Date Received	Available From
Prescribing Information	February 15, 2024	\\Cdsesub1\evsprod\NDA217645\0009\m1\us
Patient Package Insert		
Instructions for Use		
Trade Container Label	July 24, 2023	\\CDSESUB1\EVSPROD\nda217645\0001\m1\us\draft-container-carton-labels-onyda.pdf
Trade Carton Labeling		
Professional Sample Container Label		
Professional Sample Carton Labeling		

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

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

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/s/

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YEVGENIYA M KOGAN
05/16/2024 12:37:54 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:	May 6, 2024
To:	Iram Baig, 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)**
From:	Laurie Buonaccorsi, PharmD 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: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	ONYDA XR (clonidine hydrochloride)
Dosage Form and Route:	extended-release oral suspension
Application Type/Number:	NDA 217645
Applicant:	Tris Pharma, Inc.

1 INTRODUCTION

On July 24, 2023, Tris Pharma, Inc. submitted for the Agency's review an original New Drug Application (NDA) 217645 for ONYDA XR (clonidine hydrochloride) extended-release oral suspension. The Applicant proposes an indication for the treatment of attention deficit hyperactivity disorder (ADHD) as either monotherapy or as adjunctive therapy to stimulant medications. This 505(b)(2) application references KAPVAY (clonidine hydrocholoride) extended-release tablets (NDA 022331).

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 August 9, 2023 and August 3, 2023, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for ONYDA XR (clonidine hydrochloride) extended-release oral suspension.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU is forthcoming.

2 MATERIAL REVIEWED

- Draft ONYDA XR (clonidine hydrochloride) extended-release oral suspension PPI received on February 15, 2024, and received by DMPP and OPDP on April 25, 2024.
- Draft ONYDA XR (clonidine hydrochloride) extended-release oral suspension IFU received on January 17, 2024, and received by DMPP and OPDP on April 25, 2024.
- Draft ONYDA XR (clonidine hydrochloride) extended-release oral suspension Prescribing Information (PI) received on July 24, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 25, 2024.
- Approved KAPVAY (clonidine hydrochloride) comparator labeling dated February 6, 2020.

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%. A reading ease score of 60% corresponds to an 8th grade reading level. 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 PPI and IFU using Arial font.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the PI
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that they are free of promotional language
- ensured that the PPI and IFU meet 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 PPI and IFU are consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI 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 PPI and IFU is 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 PPI and IFU.

Please let us know if you have any questions.

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/s/

LAURIE J BUONACCORSI
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SUSANNAH O'DONNELL
05/06/2024 09:04:00 AM
Signing for Emily Foltz

LASHAWN M GRIFFITHS
05/06/2024 09:14:26 AM

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

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

Memorandum

Date: May 1, 2024

To: Iram Baig, MS, Regulatory Project Manager, Division of Regulatory Operations for Neuroscience

Roberta Glass, MD, Division of Psychiatry (DP)

Kimberley Updegraff, Associate Director for Labeling, DP

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

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for ONYDA™ XR (clonidine hydrochloride) extended-release oral suspension (Onyda XR)

NDA: 217645

Background:
In response to DP's consult request dated August 3, 2023, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), Instructions for Use (IFU), and carton and container labeling for the original NDA submission for Onyda XR.

PI, PPI, and IFU:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on April 24, 2024, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the proposed PPI and IFU, and comments will be sent under separate cover.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling accessed from SharePoint on April 30, 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
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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: 11/27/2023

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 217645

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

Pharma Medica, Toronto: The Office of Regulatory Affairs (ORA) conducted an inspection of the site in December 2022. The inspection was conducted under the following submission: Non-responsive.

The following items were discussed with the site:

- Lack of a standardized time period for conducting adverse event follow up.
- Confusion about eligibility criteria for subjects with blood loss or donation ≥500 mL within 56 days prior to study drug administration. Specifically, one subject was identified as being ineligible for the study due to a record noting blood loss of >500 mL, but the calculation was later determined to be incorrect.

After review of the inspection findings, OSIS determined that data from the reviewed study were reliable with the exception of data for 1 subject. OSIS recommended that the review division consider the eligibility of the subject due to OSIS's inability to verify the subject's eligibility.

(b) (4) OSIS conducted a Remote Regulatory Assessment (RRA) for the site in (b) (4). The RRA was conducted under the following submission: Non-responsive.

The following objectionable condition was observed:

(b) (4)

After review of the objectionable condition and the site's response, OSIS concluded that the data were reliable. (Final OSIS Review – (b) (4)).

Sites

Facility Type	Facility Name	Facility Address
Clinical	Pharma Medica Research, Inc.	4770 Sheppard Avenue East, Toronto, Ontario, Canada
Analytical	(b) (4)	

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/s/

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