CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216655Orig1s000

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:	July 22, 2024
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 216655
Product Name, Dosage Form, and Strengths:	Opipza[a] (aripiprazole) oral film, 2 mg, 5 mg, and 10 mg
Applicant Name:	Xiamen LP Pharmaceutical Co., Ltd. (Xiamen)
FDA Received Date:	July 22, 2024
TTT ID #:	2022-1053-1
DMEPA 1 Safety Evaluator:	Loretta Holmes, BSN, PharmD
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

[a] The proposed name, Opipza, was found conditionally acceptable in the following review: Holmes, L. Proprietary Name Review for Opipza (NDA 216655). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 Jun 24. PNR ID No. 2024-1044725705.

1 PURPOSE OF MEMORANDUM

Xiamen LP Pharmaceutical Co., Ltd. (Xiamen) submitted revised container labels and carton labeling received via email on July 22, 2024 for Opipza. The Division of Psychiatry (DP) requested that we review the revised container labels and carton labeling for Opipza (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 labels and labeling review[b] and follow up recommendations communicated to Xiamen via email.

2 CONCLUSION

Xiamen implemented all of our recommendations and we have no additional recommendations at this time.

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[b] Holmes, L. Labels and Labeling Review for Aripiprazole (NDA 216655). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 Jun 24. TTT ID: 2022-1053-1.

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
07/22/2024 05:49:35 PM

YEVGENIYA M KOGAN
07/23/2024 08:45:22 AM

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

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

Memorandum

Date: June 25, 2024

To: Shin-Ye Chang, Regulatory Project Manager, DP

Roberta Glass, DP

Kim Updegraff, Associate Director for Labeling, DP

From: Lindsay McCann, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, Team Leader, OPDP

Subject: OPDP Labeling Comments for TRADENAME (aripiprazole) oral film

NDA/BLA: 216655

Background: In response to DP's consult request dated November 21, 2023, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide (MG), Instructions for Use (IFU) and carton and container labeling for the original 216655 submission for TRADENAME (aripiprazole) oral film.

PI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on June 13, 2024, and our comments are provided below.

Medication Guide/IFU
A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed MG and IFU, and comments were sent under separate cover on June 20, 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 April 19, 2024 and our comments are provided below.
Thank you for your consult. If you have any questions, please contact Lindsay McCann at 301-796-3719 or Lindsay.McCann@fda.hhs.gov.

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/s/

LINDSAY M MCCANN
06/25/2024 11:12:00 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)

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

Date of This Review:	June 24, 2024
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 216655
Product Name, Dosage Form, and Strength:	Aripiprazole oral film, 2 mg, 5 mg, and 10 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Xiamen LP Pharmaceutical Co., Ltd. (Xiamen)
FDA Received Date:	April 19, 2024
TTT ID #:	2022-1053
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 Aripiprazole oral film, the Division of Psychiatry (DP) requested that we review the proposed Aripiprazole 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 DELETE IF NOT APPLICABLE

Aripiprazole oral film is a proposed 505(b)(2) drug product and the Listed Drug (LD) is Abilify (aripiprazole) tablets, NDA 021436.

1.2 REGULATORY HISTORY DELETE IF NOT APPLICABLE

Xiamen LP Pharmaceutical Co., Ltd. (Xiamen) previously submitted NDA 216655 on August 24, 2022. On October 21, 2022, the Division refused to file the application due to Chemistry, Manufacturing, and Controls (CMC) and clinical issues.[a]

Subsequently, Xiamen resubmitted the NDA on September 19, 2023 in response to the refusal to file letter.[b]

2 MATERIALS REVIEWED

This section lists the materials considered for our review of NDA 216655.

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 Aripiprazole oral film Medication Guide (MG) and determined that it is acceptable from a medication error perspective.

However, the proposed Aripiprazole Prescribing Information (PI)[c], 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.

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[a] Chang, S on behalf of Tiffany Farchione. Refusal to File for NDA 216655. Silver Spring (MD): FDA, CDER, OND, Division of Psychiatry (DP) (US); 2022 OCT 21.

[b] Cover Letter for Resubmission after RTF (NDA 216655 Aripiprazole Oral Soluble Film). Xiamen (China): Xiamen LP Pharmaceutical Co., Ltd.; 2023 SEP 19. Available from: \\CDSESUB1\EVSPROD\nda216655\0004\m1\us\coverletter.pdf.

[c] We reviewed the proposed PI received on December 15, 2023 and revised by the Division of Psychiatry as of June 14, 2024.

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 are collaborating 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 defer to the Patient Labeling Team (PLT) for a review of the IFU.

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 Xiamen LP Pharmaceutical Co., Ltd. in Section 4.

4 RECOMMENDATIONS FOR XIAMEN LP PHARMACEUTICAL CO., LTD.

Table 2. Identified Issues and Recommendations for Xiamen LP Pharmaceutical Co., Ltd. (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels and Carton Labeling			
1.	The dosage form statement on the container labels and carton labeling is presented as (b) (4) (b) (4)	It has been determined that the dosage form is "oral film".	Revise the dosage form to "oral film".
2.	The statement "Do not cut or chew the oral film" is not present.	The oral film should not be cut or chewed.	Add the statement "Do not cut or chew the oral film" to the principal display panel (PDP).
3.	The use instructions on the container label are not consistent with the "How To Use" instructions on the carton labeling.	To avoid confusion, the instructions should be consistent.	Replace the instructions on the container label with the "How To Use" instructions that are on the carton labeling and use the same "How To Use" heading (also, see Carton Labeling recommendation #5).
4.	The "Manufactured By" text is too prominent.	The heading distracts from other important information on the panel.	Unbold the "Manufactured By" text.

Table 2. Identified Issues and Recommendations for Xiamen LP Pharmaceutical Co., Ltd. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels			
1.	The net quantity statement "1 Film" does not completely describe the dosage form.	The dosage form is "oral film".	Revise the net quantity statement to read "1 Oral Film"
2.	The net quantity statement has a colored banner as a background which makes the net quantity statement too prominent.	The net quantity statement distracts from other important information on the panel.	Remove the colored banner background from the net quantity statement.
3.	The statement (b) (4) is on the principal display panel (PDP).	The pouches, each containing a single film, will be contained in a carton so the rationale for this statement is not clear.	Delete the statement (b) (4) " and consider adding the statement "KEEP PRODUCT IN FOIL POUCH UNTIL READY TO USE."
4.	The NDC number is too prominent.	The NDC number should not compete in size and prominence with critical information on the PDP.	Decrease the size of the NDC number.
5.	Under the "To Open" instructions, the punctuation at the end of the sentences is incorrect or missing (see below): 1. Fold along the dotted line, 2. Tear at the arrow	For clarity, the punctuation should be corrected.	For step 1, delete the comma and replace it with a period. For step 2, add a period to the end of the sentence.
6.	The "Rx only" statement is too prominent.	The "Rx only" statement should not compete in size and prominence with critical information on the PDP.	Decrease the size of the "Rx Only" statement and unbold "Rx".

Table 2. Identified Issues and Recommendations for Xiamen LP Pharmaceutical Co., Ltd. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
7.	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 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).*
8.	The terminology within the statement of dosage (i.e., "(b) (4)" and "(b) (4)") is inconsistent with the	The statement of dosage should be consistent with the terminology in the Prescribing Information.	Revise the statement of dosage to read, "Recommended Dosage: See Prescribing Information."

Table 2. Identified Issues and Recommendations for Xiamen LP Pharmaceutical Co., Ltd. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
	terminology in the Prescribing Information.		
Carton Labeling			
1.	The strength statement on the Principal Display Panel (PDP) lacks prominence.	Lack of prominence of the strength statement may contribute to product selection medication errors. See 21CFR201.15(a)(6) which states a word, statement, or other information required by or under authority of the act to appear on the label may lack that prominence and conspicuousness required by section 502(c) of the act by reason, among other reasons, of: smallness or style of type in which such word, statement, or information appears, insufficient background contrast, obscuring designs or vignettes, or crowding with other written, printed, or graphic matter.	Increase the prominence of the strength statement in accordance with 21 CFR 201.15(a)(6). Take into account all pertinent factors including font size, type, and color; background contrast; and statement location. If necessary, consider decreasing the prominence of other information that is not critical (e.g., net quantity statement, NDC code, etc.).
2.	The strength statement on the PDP is in white font on colored banner whereas the strength statement on the side panels is (b) (4) (b) (4)	The (b) (4) (b) (4) for the strength statement on the side panels may lead to product selection errors.	Revise the strength statement on the side panels so that it is consistent with the presentation on the PDP (i.e., white font on colored banner).
3.	The net quantity statement is too prominent.	The net quantity statement should not compete in size and prominence with	Decrease the size of the net quantity statement. Additionally, consider moving the net quantity statement to a

Table 2. Identified Issues and Recommendations for Xiamen LP Pharmaceutical Co., Ltd. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		critical information on the PDP.	position below the Medication Guide statement.
4.	The statement (b) (4) is on the PDP.	The statement is duplicative. It is also on the back panel under the "(b) (4) (b) (4)" instructions.	Delete the statement "(b) (4) (b) (4)" from the PDP.
5.	Under "How to Use" some of the statements are not clear.	The lack of clarity of some of the statements may lead to confusion.	Revise the statement "(b) (4) (b) (4)" to read "Do not chew or swallow whole." Revise the statement (b) (4) " to read "Take only as directed by your healthcare provider."
6.	The "Rx only" statement is too prominent.	The "Rx only" statement should not compete in size and prominence with critical information on the PDP.	Decrease the size of the "Rx Only" statement and unbold "Rx Only". Additionally, move the statement to a location that is not in close proximity to the strength statement or other critical information on the PDP.
7.	The statement "Do not cut or chew the oral film" is not on the PDP.	The film should not be cut or chewed so this information should be on the PDP.	Add the following statement to the PDP: "Do not cut or chew the oral film". Additionally, delete the statement "(b) (4) (b) (4)" from the back panel.
8.	The statement of dosage is missing from the carton labeling.	Requirement per 21 CFR 201.55 that labels for prescription drugs bear a statement of the recommended dosage.	Add the following statement of dosage to the back panel "Recommended Dosage: See Prescribing Information".
Packaging			
1.	The cartons contain (b) (4) oral films.	The cartons do not contain a full month's (typically 28 or 30 days) supply of oral films.	Consider providing the oral films in cartons that contain a full month's supply.

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APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. RELEVANT PRODUCT INFORMATION

Tables 3 and 4 presents relevant product information for Aripiprazole oral film received on April 19, 2024 from Xiamen LP Pharmaceutical Co., Ltd., and the Listed Drug (LD), respectively.

<table>
<tr><th colspan="2">Table 3. Relevant Product Information for Aripiprazole oral film</th></tr>
<tr><td>Product Name</td><td>Aripiprazole</td></tr>
<tr><td>Initial Approval Date</td><td>N/A</td></tr>
<tr><td>Active Ingredient</td><td>Aripiprazole</td></tr>
<tr><td>Indication</td><td>• Schizophrenia
• Adjunctive Treatment of Major Depressive Disorder
• Irritability Associated with Autistic Disorder
• Treatment of Tourette’s disorder</td></tr>
<tr><td>Dosage Form</td><td>oral film</td></tr>
<tr><td>Strengths</td><td>2 mg, 5 mg, and 10 mg</td></tr>
<tr><td>Route of Administration</td><td>Oral</td></tr>
<tr><td>Dose and Frequency</td><td>Oral Soluble Film: Administer once daily without regard to meals. Do not cut or divide film. (b) (4).
<table>
<tr><th></th><th></th><th>Initial Dose</th><th>Recommended Dose</th><th>Maximum Dose</th></tr>
<tr><td colspan="2">Schizophrenia – adults</td><td>10 to 15 mg/day</td><td>10 to 15 mg/day</td><td>30 mg/day</td></tr>
<tr><td colspan="2">Schizophrenia – adolescents</td><td>2 mg/day</td><td>10 mg/day</td><td>30 mg/day</td></tr>
<tr><td colspan="2">Major Depressive Disorder – Adults adjunct to antidepressants</td><td>2 to 5 mg/day</td><td>5 to 10 mg/day</td><td>15 mg/day</td></tr>
<tr><td colspan="2">Irritability associated with autistic disorder – pediatric patients</td><td>2 mg/day</td><td>5 to 10 mg/day</td><td>15 mg/day</td></tr>
<tr><td rowspan="2">Tourette’s disorder –</td><td>Patients < 50 kg</td><td>2 mg/day</td><td>5 mg/day</td><td>10 mg/day</td></tr>
<tr><td>Patients ≥ 50 kg</td><td>2 mg/day</td><td>10 mg/day</td><td>20 mg/day</td></tr>
</table>
Known CYP2D6 poor metabolizers: Half of the usual dose, (b) (4) (b) (4).</td></tr>
</table>

Table 3. Relevant Product Information for Aripiprazole oral film					
Product Name	**Aripiprazole**				
How Supplied	**Strength**	**Film Color/Shape**	**Printed Blue Mark**	**Pack Size**	**NDC Code**
	2 mg	1 cm × 1.2 cm Rectangular thin white film	A2	(b) (4)	71034-016 (b) (4)
	5 mg	2 cm × 1.5 cm Rectangular thin white film	A5		71034-010
	10 mg	2 cm × 3 cm Rectangular thin white film	A10		71034-011
Storage	Store at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].				

Table 4. Relevant Product Information for the Listed Drug (LD).	
Product Name	**Abilify**[d] (NDA 021436)
Initial Approval Date	11/15/2002
Active Ingredient	aripiprazole
Indication	The oral formulations are indicated for: • Schizophrenia • Acute Treatment of Manic and Mixed Episodes associated with Bipolar I • Adjunctive Treatment of Major Depressive Disorder • Irritability Associated with Autistic Disorder • Treatment of Tourette's disorder The injection is indicated for: • Agitation associated with schizophrenia or bipolar mania
Dosage Forms	Tablets, Orally Disintegrating Tablets, Oral Solution, and Injection
Strengths	Tablets: 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg Orally Disintegrating Tablets: 10 mg and 15 mg Oral Solution: 1 mg/mL Injection: 9.75 mg/1.3 mL single-dose vial
Route of Administration	Oral; Intramuscular

[d] Abilify [Prescribing Information] DailyMed. U.S. National Library of Medicine. Nov 2022. [Cited 2023 Jun 11]. Available from: https://dailymed.nlm.nih.gov/dailymed/getFile.cfm?setid=c040bd1d-45b7-49f2-93ea-aed7220b30ac&type=pdf.

Table 4. Relevant Product Information for the Listed Drug (LD).

Product Name	Abilify[d] (NDA 021436)
Dose and Frequency	Oral formulations: Administer once daily without regard to meals IM injection: Wait at least 2 hours between doses. Maximum daily dose 30 mg Known CYP2D6 poor metabolizers: Half of the usual dose

		Initial Dose	Recommended Dose	Maximum Dose
Schizophrenia – adults		10 to 15 mg/day	10 to 15 mg/day	30 mg/day
Schizophrenia – adolescents		2 mg/day	10 mg/day	30 mg/day
Bipolar mania – adults: monotherapy		15 mg/day	15 mg/day	30 mg/day
Bipolar mania – adults: adjunct to lithium or valproate		10 to 15 mg/day	15 mg/day	30 mg/day
Bipolar mania – pediatric patients: monotherapy or as an adjunct to lithium or valproate		2 mg/day	10 mg/day	30 mg/day
Major Depressive Disorder – adults: adjunct to antidepressants		2 to 5 mg/day	5 to 10 mg/day	15 mg/day
Irritability associated with autistic disorder – pediatric patients		2 mg/day	5 to 10 mg/day	15 mg/day
Tourette's disorder	Patients <50 kg	2 mg/day	5 mg/day	10 mg/day
	Patients ≥50 kg	2 mg/day	10 mg/day	20 mg/day
Agitation associated with schizophrenia or bipolar mania – adults		9.75 mg /1.3 mL injected IM		30 mg/day injected IM

How Supplied

ABILIFY Tablet Presentations

Tablet Strength	Tablet Color/Shape	Tablet Markings	Pack Size	NDC Code
2 mg	green modified rectangle	"A-006" and "2"	Bottle of 30	59148-006-13
5 mg	blue modified rectangle	"A-007" and "5"	Bottle of 30 Blister of 100	59148-007-13 59148-007-35
10 mg	pink modified rectangle	"A-008" and "10"	Bottle of 30 Blister of 100	59148-008-13 59148-008-35
15 mg	yellow round	"A-009" and "15"	Bottle of 30 Blister of 100	59148-009-13 59148-009-35
20 mg	white round	"A-010" and "20"	Bottle of 30 Blister of 100	59148-010-13 59148-010-35
30 mg	pink round	"A-011" and "30"	Bottle of 30 Blister of 100	59148-011-13 59148-011-35

ABILIFY DISCMELT Orally Disintegrating Tablet Presentations

Tablet Strength	Tablet Color	Tablet Markings	Pack Size	NDC Code
10 mg	pink (with scattered specks)	"A" and "640" "10"	Blister of 30	59148-640-23
15 mg	yellow (with scattered specks)	"A" and "641" "15"	Blister of 30	59148-641-23

ABILIFY (aripiprazole) Oral Solution (1 mg/mL) is supplied in child-resistant bottles along with a calibrated oral dosing cup. ABILIFY Oral Solution is available as follows: 150 mL bottle NDC 59148-013-15

ABILIFY (aripiprazole) Injection for intramuscular use is available as a ready-to-use, 9.75 mg/1.3 mL (7.5 mg/mL) solution in clear, Type 1 glass vials as follows: 9.75 mg/1.3 mL single-dose vial NDC 59148-016-65

Table 4. Relevant Product Information for the Listed Drug (LD).	
Product Name	Abilify[d] (NDA 021436)
Storage	Tablets Store at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Oral Solution Store at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Opened bottles of ABILIFY Oral Solution can be used for up to 6 months after opening, but not beyond the expiration date on the bottle. The bottle and its contents should be discarded after the expiration date. Injection Store at 25ºC (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from light by storing in the original container. Retain in carton until time of use.

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,[e] along with postmarket medication error data, we reviewed the following Aripiprazole labels and labeling submitted by Xiamen LP Pharmaceutical Co., Ltd. received on April 19, 2024

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

The above labels and labeling are available from:
\\Cdsesub1\evsprod\NDA216655\0017\m1\us.

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

Container Labels

(b) (4)

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

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

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/s/

LORETTA HOLMES
06/24/2024 11:04:10 AM

YEVGENIYA M KOGAN
06/24/2024 02:10:12 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:	June 20, 2024
To:	Shin-Ye (Sandy) Chang, PharmD Senior 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)** Lindsay McCann, PharmD, BCCCP 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):	TRADENAME (aripiprazole)
Dosage Form and Route:	oral film
Application Type/Number:	NDA 216655
Applicant:	Xiamen LP Pharmaceutical Co., Ltd. c/o LP Pharmaceuticals, Inc. (USA)

1 INTRODUCTION

On September 19, 2023, in response to the Agency's Refuse to File letter dated October 21, 2022, Xiamen LP Pharmaceutical Co., Ltd. c/o LP Pharmaceuticals, Inc. (USA) resubmitted for the Agency's review a New Drug Application (NDA) 216655 for TRADENAME (aripiprazole) oral film. This 505(b)(2) NDA references ABILIFY (aripiprazole) tablets (NDA 021436) and proposes the following indications for TRADENAME (aripiprazole) oral film:

- schizophrenia
- adjunctive treatment of major depressive disorder (MDD)
- irritability associated with autistic disorder
- treatment of Tourette's disorder

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 November 21, 2023 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for TRADENAME (aripiprazole) oral film. On March 6, 2024, DP requested that the Applicant revise the MG to remove detailed instructions and illustrations regarding the preparation and administration of aripiprazole oral film and develop a separate Instructions for Use (IFU). The Applicant submitted a revised MG and an IFU on March 20, 2024, and resubmitted the MG and IFU with further revisions on April 19, 2024.

3 MATERIAL REVIEWED

- Draft TRADENAME (aripiprazole) oral film MG and IFU received on April 19, 2024, and received by DMPP and OPDP on June 13, 2024.
- Draft TRADENAME (aripiprazole) oral film Prescribing Information (PI) received on September 19, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 13, 2024.
- Approved ABILIFY (aripiprazole) tablets, ABILIFY ASIMTUFII (aripiprazole) extended-release injectable suspension, and REXULTI (brexpiprazole) tablets labeling dated November 30, 2022, July 27, 2023, and May 24, 2024, respectively.

4 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 MG and IFU documents using the Arial font, size 10 and 11, respectively.

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
- 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 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 MG and IFU are consistent with the approved comparator labeling where applicable

5 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

6 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG 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 MG and IFU.

Please let us know if you have any questions.

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

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06/20/2024 01:43:49 PM

LASHAWN M GRIFFITHS
06/20/2024 02:12:49 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: April 17, 2024

TO: Tiffany Farchione, MD
Director
Division of Psychiatry (DP)
Office of Neuroscience (ON)
Office of New Drugs (OND)

FROM: Sri Rama Krishnaiah Yellela, Ph.D.
Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Director
DNDSI, OSIS

SUBJECT: Remote regulatory assessment (RRA) of Phase I Clinical Trial Center – Xiamen Lotus Hospital, Xiamen, Fujian, China

1. RRA Summary

OSIS arranged a remote regulatory assessment (RRA)[1] of two clinical studies (#LP088-20-09 and #LP088-20-10) conducted at Phase I Clinical Trial Center – Xiamen Lotus Hospital, Xiamen, Fujian, China in support of NDA 216655 (Aripiprazole oral soluble film 5 mg and 10 mg). The studies were conducted under IND 150931.

No objectionable conditions were observed and no discussion items were conveyed during the conclusion of the RRA. However, the RRA report notes that an external statistical company created a randomization sheet which identified the bottles that were subsequently retained as reserve samples by the clinical site. The finding is a protocol deviation because the protocol specified that the clinical site was supposed to randomly select reserve samples from investigation products (IP) supplied by sponsor for the studies.

Based on the review of RRA report and post-RRA correspondence received from the ORA investigator, I conclude that the protocol

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[1] One set of tools for oversight of regulated products used during the pandemic has been remote regulatory assessments (RRAs). The term "RRA" describes a category of activities for which FDA may use different terminologies, but all are considered to be types of RRAs, including "remote record reviews" and "remote interactive evaluations."

deviation did not impact clinical data from both studies because the study sponsor was required to retain reserves in accordance with 21 CFR 312.57(d). Based on information collected during the RRA, it is unclear if the sponsor retained reserve samples for the studies. In addition, the RRA report does not mention whether the responsibility of retaining reserve samples was explicitly transferred by the sponsor to the clinical site.

2. Reviewed Studies

NDA 216655

Study Number: LP088-20-09
Study Title: "*A randomized, open-label, single-dose, two-treatment, two-period, crossover study to assess the bioequivalence of aripiprazole tablets 10 mg and aripiprazole oral soluble film 10 mg administered under fasting conditions in healthy adult human subjects*"
Dates of study conduct: 12/26/2020 – 03/03/2021

Study Number: LP088-20-10
Study Title: "*A randomized, open-label, single-dose, two-treatment, two-period, crossover study to assess the bioequivalence of aripiprazole tablets 10 mg and aripiprazole oral soluble film 10 mg administered under fed conditions in healthy adult human subjects*"
Dates of study conduct: 12/13/2020 – 02/18/2021

Clinical Investigator: Zhiqing Huang, M.D., Ph.D.
Phase I Clinical Trial Center – Xiamen Lotus Hospital
8006 Xiangan South Road, Xiangan
Xiamen, Fujian, China 36112
FEI #3029756672

Clinical site: Phase I Clinical Trial Center – Xiamen Lotus Hospital
8006 Xiangan South Road, Xiangan
Xiamen, Fujian, China 36112
FEI #3029987977

3. Scope of RRA

ORA Investigator Scott B. Laufenberg reviewed the clinical portion of the above studies conducted at Phase I Clinical Trial Center – Xiamen Lotus Hospital, Xiamen, Fujian, China on February 26th, 28th and 29th 2024 and March 4th, 6th and 8th 2024.

The clinical site has no inspectional (or RRA) history under the BA/BE program.

The records reviewed during the current RRA included but were not limited to informed consent (IC) documents and processes, ethics committee approvals and correspondence, investigational product accountability/dispensation/dosing/retention/storage, reserve samples, inclusion/exclusion criteria adherence, protocol adherence, subject randomization, adverse events, concomitant medications, and collection, processing, and handling of biological samples. The RRA also included interviews with the firm's management and staff.

4. RRA Observations

At the conclusion of the RRA, Investigator Laufenberg did not observe any objectionable conditions and did not discuss items with site management. However, DNDSI staff noted a protocol deviation in the RRA report regarding selection and retention of BE reserve samples for RLD and test products [***Attachment #1***]. DNDSI contacted Investigator Laufenberg post-RRA for information regarding reserve samples. The protocol deviation and my assessment are presented below.

Finding not discussed during RRA: The clinical site did not randomly select BE reserve samples of test and RLD supplied by sponsor as required in Section 9.2.4 of study protocol [***Attachment #2***]. Specifically, the protocol states that the clinical site was supposed to randomly select reserve samples from investigation products supplied by the sponsor. Instead, the site selected BE reserve samples which were already identified on a randomization list created by an external statistical/data management company called (b) (4) (b) (4) [page 17, ***Attachment #1***].

OSIS Evaluation: The finding is a protocol deviation and regulatory violation of 21 CFR 312.60. However, the sponsor, and not the site, is required to retain BE reserve samples per applicable regulation 21 CFR 312.57(d). Based on information collected during the RRA, it is unclear if the sponsor retained reserve samples for the studies. In addition, the RRA report

does not mention whether the responsibility of retaining reserve samples was explicitly transferred by the sponsor to the clinical site.

In the absence of information regarding the transfer of reserve sample requirements from Sponsor to clinical site, I cannot evaluate whether the reserve samples selected and retained by the site are valid. In addition, I cannot determine if the Sponsor retained reserve samples for the studies. Therefore, the protocol deviation is not likely to impact the reliability of clinical data generated from the reviewed studies.

Sri Rama Krishnaiah Yellela, Ph.D.
Pharmacologist

Attachment #1: RRA report-Dr. Zhiqing Huang Fujian, Phase I Clinical Trial Center, China
Attachment #2: Protocol requirement on selection and retention of BE retention samples

Draft: SRKY 4/12/2024; 4/15/2024; 4/15/2024; 4/16/2024; 4/17/2024
Edit: RCA 4/15/2024; 4/15/2024, 4/16/2024; AD 04/16/2024

OSIS File #: BE 10066 (NDA 216655)
eNSpect Assignment ID: 236449
eNSpect OpID: 274344

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

DATE: 12/4/2023

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

FROM: Office of Study Integrity and Surveillance (OSIS)

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

RE: NDA 216655

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

Rationale

OSIS conducted a Remote Regulatory Assessment (RRA) for the site in March 2023. The RRA was conducted under the following submissions: NDAs (b) (4) and (b) (4).

OSIS concluded that data from the reviewed studies were reliable.

Site

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

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/s/

JAMES J LUMALCURI
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