

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211448Orig1s000

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:	April 15, 2025
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 211448
Product Name, Dosage Form, and Strengths:	Mezofy (aripiprazole) oral films, 5 mg, 10 mg, and 15 mg
Applicant Name:	CMG Pharmaceutical Co., Ltd
FDA Received Date:	April 14, 2025
TTT ID #:	2024-11376-1
DMEPA 1 Safety Evaluator:	Loretta Holmes, BSN, PharmD
DMEPA 1 Associate Director for Nomenclature and Labeling:	Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

CMG Pharmaceutical Co., Ltd submitted revised container labels and carton labeling received on April 14, 2025 and April 15, 2025, respectively, for Mezofy. The Division of Psychiatry (DP) requested that we review the revised container label and carton labeling for Mezofy (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^a and a follow up recommendation provided via email communication on April 14, 2025^b.

2 CONCLUSION

CMG Pharmaceutical Co., Ltd implemented all of our recommendations and we have no additional recommendations at this time.

^a Holmes, L. Labels and Labeling Review for Mezofy (NDA 211448). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2025 Apr 09. TTT ID: 2024-11376.

^b We provided the following recommendation via email for the carton labeling: Relocate the strength statement to follow the established name. As currently presented it is placed between the proprietary name and established name. There must not be intervening written, printed, or graphic matter between the proprietary name and established name (21 CFR 201.10(a)).

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
04/15/2025 02:39:42 PM

YEVGENIYA M KOGAN
04/15/2025 02:45:27 PM

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:	April 9, 2025
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 211448
Product Name, Dosage Form, and Strengths:	Mezofy (aripiprazole) oral films, 5 mg, 10 mg, and 15 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	CMG Pharmaceutical Co., Ltd
FDA Received Date:	March 31, 2025
TTT ID #:	2024-11376
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 Mezofy (aripiprazole) oral films, the Division of Psychiatry (DP) requested that we review the proposed Mezofy Prescribing Information (PI), 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

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

2 MATERIALS CONSIDERED

This section lists the materials considered for our review.

Materials Considered	Appendix Section
Relevant Product Information	A
Labels and Labeling	B
Previous DMEPA Reviews	C

3 CONCLUSION

We evaluated the proposed Mezofy Prescribing Information (PI) and determined that it is acceptable from a medication error perspective. We note that the Patient Labeling Team has completed a review of the Instructions for Use. We defer to their recommendations.

However, the proposed Mezofy container labels, and carton labeling 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 CMG Pharmaceutical Co., Ltd in Section 4.

4 RECOMMENDATIONS FOR CMG PHARMACEUTICAL CO., LTD

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels and Carton Labeling			
1.	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	Revise the established name to be in accordance with 21 CFR 201.10(g)(2).

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

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		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.	
2.	The strength 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.).

Table 2. Identified Issues and Recommendations for CMG Pharmaceutical Co., Ltd (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
3.	The terminology within the statement of dosage (i.e., (b) (4) is inconsistent with the terminology in the Prescribing Information.	There should be consistency with the terminology in the Prescribing Information.	We recommend revising the statement of dosage to read, "Recommended Dosage: See Prescribing Information."
4.	There are areas where the "How to Use" instructions can be improved.	Providing clarity will help to minimize product administration errors.	Revise the How to Use instructions as follows (the revisions are in red text and strikethrough): Keep the MEZOFY film in the foil pouch until ready to use. Open the pouch by gently pulling the sides apart. Remove the MEZOFY film from the pouch. Put the MEZOFY film on top of (b) (4) the tongue where it will dissolve. Swallow after it dissolves completely. Do not chew the MEZOFY film. Do not swallow the undissolved MEZOFY film. See Instructions for Use for (b) (4) complete instructions.
5.	There are some inconsistencies with the NDC numbers presentation.	Inconsistencies with the NDC numbers presentation may lead to confusion and product misidentification.	Ensure that the NDC numbers are consistent and appropriate on all container labels and carton labeling.
Container Labels			
1.	The linear barcode appears to be missing on the container labels.	The drug barcode is often used as an additional verification during the medication use process; therefore, it is an important safety feature that should be part of the label and is a requirement per 21 CFR 201.25(c)(2).	Add the product's linear barcode to each individual container label in accordance with 21CFR 201.25(c)(2). The bar code should be placed in a conspicuous location where it will not be difficult to read because of distorted text. Additionally, the barcode should

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

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			be placed in an area where it will not be damaged because it appears at the point of label separation (e.g., perforation).
2.	There are no directions showing where the foil pouch should be opened.	Directions showing where the pouch should be opened may help to minimize potential damage to the film when the pouch is opened.	Consider providing directional arrows that point to where the pouch should be opened along with brief instructions on how to open the pouch.
3.	On the back panel, the white font against the colored background is difficult to read due to the lack of sufficient contrast and the small font size.	The lack of contrast impairs the readability of the text.	Consider changing the text to a black font and placing it in a white background text box (or use other means to improve readability of the text).
Carton Labeling			
1.	The strength lacks adequate spacing between the number and the unit of measure.	Lack of adequate spacing may impact readability and might result in wrong strength errors. For example, the “m” in mg can sometimes be mistaken as a zero or two zeros.	We recommend placing adequate space between the numerical dose and unit of measure (e.g., 10 mg instead of 10mg) to improve readability.
2.	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

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

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			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 <i>Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021)</i>.
3.	There appears to be two placeholders for the 2D barcode.	It is not clear where the 2D barcode will be placed so we are unable to assess its placement.	Show the intended location of the 2D barcode.
4.	On the Principal Display Panel (PDP) and back panel, the net quantity statement is enclosed in a color block.	As currently presented the net quantity statement is too prominent and may be confused as the strength.	Consider moving the net quantity statement out of the color block and decreasing the size of the statement.

APPENDICES: MATERIALS CONSIDERED FOR THIS REVIEW

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 3 presents relevant product information for Mezofy received on March 31, 2025 from CMG Pharmaceutical Co., Ltd.

Table 3. Relevant product information for Mezofy																									
Product Name	Mezofy																								
Initial Approval Date	N/A																								
Active Ingredient	aripiprazole																								
Indication	Treatment of schizophrenia in adult and pediatric patients 13 years and older.																								
Dosage Form	Oral Films																								
Strengths	5 mg, 10 mg, and 15 mg																								
Route of Administration	Oral																								
Dose and Frequency	<u>Adults</u> The recommended starting and recommended dosage for Mezofy is 10 mg or 15 mg taken orally once daily. Aripiprazole has been shown to be effective in a dosage range of 10 mg to 30 mg daily; however, dosages higher than 10 mg or 15 mg daily were not more effective. Dosage increases should generally not be made before 2 weeks, the time needed to achieve steady-state. <u>Pediatric Patients 13 to 17 years of Age</u> The recommended starting dosage of oral aripiprazole is 2 mg once daily. Because Mezofy is not available in dosage strengths below 5 mg, patients should initiate aripiprazole treatment at the 2 mg daily dosage with another aripiprazole product (refer to the prescribing information of other aripiprazole products). After two days, the dose can be titrated to 5 mg of Mezofy once daily, and after an additional two days, the dose can be titrated to 10 mg Mezofy once daily. Subsequent dose titrations should be made in 5 mg increments according to patient tolerability. The 30 mg daily dosage was not shown to be more efficacious than 10 mg once daily.																								
How Supplied	<table border="1"> <thead> <tr> <th>Strength</th> <th>Film Color/Shape</th> <th>Print</th> <th>Pack Size</th> <th>NDC Code</th> </tr> </thead> <tbody> <tr> <td>5 mg</td> <td>white rectangular</td> <td>CMG ARF5</td> <td>one strip (film) per pouch, box of 30 pouches</td> <td>80096-101-20</td> </tr> <tr> <td>10 mg</td> <td>white rectangular</td> <td>CMG ARF10</td> <td>one strip (film) per pouch, box of 30 pouches</td> <td>80096-102-20</td> </tr> <tr> <td>15 mg</td> <td>white rectangular</td> <td>CMG ARF15</td> <td>one strip (film) per pouch, box of 30 pouches</td> <td>80096-103-20</td> </tr> </tbody> </table>					Strength	Film Color/Shape	Print	Pack Size	NDC Code	5 mg	white rectangular	CMG ARF5	one strip (film) per pouch, box of 30 pouches	80096-101-20	10 mg	white rectangular	CMG ARF10	one strip (film) per pouch, box of 30 pouches	80096-102-20	15 mg	white rectangular	CMG ARF15	one strip (film) per pouch, box of 30 pouches	80096-103-20
Strength	Film Color/Shape	Print	Pack Size	NDC Code																					
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15 mg	white rectangular	CMG ARF15	one strip (film) per pouch, box of 30 pouches	80096-103-20																					

Table 3. Relevant product information for Mezofy	
Product Name	Mezofy
Storage	Store at 20° to 25°C (68° to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [USP controlled room temperature].

Table 4 presents relevant product information for the Listed Drug (LD).

Table 4. Relevant Product Information for the Listed Drug (LD).																																								
Product Name	Abilify ^a (NDA 021436)																																							
Initial Approval Date	11/15/2002																																							
Active Ingredient	aripiprazole																																							
Indication	Treatment of: • Schizophrenia • Acute Treatment of Manic and Mixed Episodes associated with Bipolar I Disorder • Adjunctive Treatment of Major Depressive Disorder • Irritability Associated with Autistic Disorder • Treatment of Tourette's Disorder																																							
Dosage Form	Tablets																																							
Strengths	2 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg																																							
Route of Administration	Oral																																							
Dose and Frequency	Administer once daily without regard to meals. <table border="1" data-bbox="446 1304 1533 1768"> <thead> <tr> <th></th> <th>Initial Dose</th> <th>Recommended Dose</th> <th>Maximum Dose</th> </tr> </thead> <tbody> <tr> <td>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>Schizophrenia – adolescents</td> <td>2 mg/day</td> <td>10 mg/day</td> <td>30 mg/day</td> </tr> <tr> <td>Bipolar mania – adults: monotherapy</td> <td>15 mg/day</td> <td>15 mg/day</td> <td>30 mg/day</td> </tr> <tr> <td>Bipolar mania – adults: adjunct to lithium or valproate</td> <td>10 to 15 mg/day</td> <td>15 mg/day</td> <td>30 mg/day</td> </tr> <tr> <td>Bipolar mania – pediatric patients: monotherapy or as an adjunct to lithium or valproate</td> <td>2 mg/day</td> <td>10 mg/day</td> <td>30 mg/day</td> </tr> <tr> <td>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>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>10 mg/day</td> </tr> <tr> <td>Patients ≥50 kg</td> <td>2 mg/day</td> <td>20 mg/day</td> </tr> </tbody> </table>		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	10 mg/day	Patients ≥50 kg	2 mg/day	20 mg/day
	Initial Dose	Recommended Dose	Maximum Dose																																					
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^a DailyMed. U.S. National Library of Medicine. Jan 2025. [Cited 2025 Apr 04]. 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 ^a (NDA 021436)				
How Supplied	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
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].				

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,^b along with postmarket medication error data, we reviewed the following Mezofy labels and labeling submitted by CMG Pharmaceutical Co., Ltd.

- Prescribing Information received on March 31, 2025, available from <\\Cdsub1\evsprod\NDA211448\0041\m1\us>
- Instructions for Use received on March 5, 2025, available from <\\CDSESUB1\EVSPROD\nda211448\0040\m1\us\114-labeling\draft\labeling\label-ifu.pdf>
- Container labels received on March 31, 2025, available from <\\Cdsub1\evsprod\NDA211448\0041\m1\us>
- Carton labeling received on March 31, 2025, available from <\\Cdsub1\evsprod\NDA211448\0041\m1\us>

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

Container Labels:



^b Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

LORETTA HOLMES
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YEVGENIYA M KOGAN
04/09/2025 03:22:35 PM

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

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

Memorandum

Date: April 1, 2025

To: Pawanprit (Pinky) Singh, PharmD, Regulatory Project Manager, Division of Psychiatry (DP)
Anna Weissman, MD, Clinical Reviewer, DP

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

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

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

NDA: 211448

Background:

In response to DP's consult request dated January 6, 2025, OPDP has reviewed the proposed carton and container labeling for the original NDA submission for MEZOFY (aripiprazole) oral film.

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 1, 2025, and our comments are provided below.

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

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

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/s/

RACHAEL O OYEWOLE
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**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

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

Memorandum

Date: March 27, 2025

To: Pawanprit (Pinky) Singh, PharmD, Regulatory Project Manager, Division of Psychiatry (DP)

Anna Weissman, MD, DP

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

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

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

NDA: 211448

Background:

In response to DP's consult request dated January 6, 2025, OPDP has reviewed the proposed Prescribing Information (PI) and Instructions for Use (IFU) for the original NDA submission for MEZOFY (aripiprazole) oral film.

PI/IFU:

OPDP's review of the proposed PI is based on the draft labeling accessed from SharePoint on March 26, 2025, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed IFU, and comments were sent under separate cover on March 25, 2025.

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

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/s/

RACHAEL O OYEWOLE
03/27/2025 03:59:10 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: March 24, 2025

To: Pawanprit (Pinky) Singh, PharmD
Regulatory Project Manager
Division of Psychiatry (DP)

Through: Barbara Fuller, MSN, BSN, RN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Laurie Buonaccorsi, PharmD
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Rachael Oyewole, PharmD
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): MEZOFY (aripiprazole)

Dosage Form and Route: oral film

Application Type/Number: NDA 211448

Applicant: CMG Pharmaceutical Co.
c/o Premier Consulting

1 INTRODUCTION

On October 15, 2024, in response to the Agency's Complete Response letter dated August 18, 2020, CMG Pharmaceutical Co. c/o Premier Consulting resubmitted for the Agency's review an original New Drug Application (NDA) 211448 for MEZOFY (aripiprazole) oral film. This 505(b)(2) NDA references ABILIFY (aripiprazole) tablets (NDA 021436) and proposes an indication for the treatment of schizophrenia.

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 January 6, 2025 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for MEZOFY (aripiprazole) oral film. On February 26, 2025, DMPP and OPDP were notified by DP that a MG would not be required for MEZOFY (aripiprazole) oral film because the Applicant did not propose an indication for Major Depressive Disorder (MDD) and therefore risk regarding MDD was being removed from the Prescribing Information (PI).

2 MATERIAL REVIEWED

- Draft MEZOFY (aripiprazole) oral film IFU received on October 15, 2024, revised throughout the review cycle, and received electronically via a Sharepoint link by DMPP and OPDP on March 14, 2025.
- Draft MEZOFY (aripiprazole) oral film PI received on October 15, 2024, revised by the Review Division throughout the review cycle, and received electronically via a Sharepoint link by DMPP and OPDP on March 14, 2025.
- Approved OPIPZA (aripiprazole) oral film labeling dated July 22, 2024.

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 APFont to make medical information more accessible for patients with vision loss.

In our collaborative review of the IFU we:

- simplified wording and clarified concepts where possible
- ensured that the IFU is consistent with the PI
- removed unnecessary or redundant information

- ensured that the IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language
- 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 IFU is consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The IFU is 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 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 IFU.

Please let us know if you have any questions.

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

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/s/

LAURIE J BUONACCORSI
03/24/2025 12:46:45 PM

RACHAEL O OYEWOLE
03/24/2025 02:34:36 PM

BARBARA A FULLER
03/24/2025 02:36:54 PM

MEMORANDUM
REVIEW OF REVISED LABELS AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: August 17, 2020
Requesting Office or Division: Division of Psychiatry (DP)
Application Type and Number: NDA 211448
Product Name and Strength: (b) (4) (aripiprazole) oral film, 5 mg, 10 mg, and 15 mg
Applicant/Sponsor Name: CMG Pharmaceutical Co., Ltd
OSE RCM #: 2019-2176-1
DMEPA Safety Evaluator: Loretta Holmes, BSN, PharmD
DMEPA Team Leader: Sevan Kolejian, PharmD, MBA, BCPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised pouch labels and carton labeling received on August 14, 2020 for (b) (4). The Division of Psychiatry (DP) requested that we review the revised pouch labels and carton labeling for (b) (4) (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, labeling, and Use Related Risk Analysis review^a and in follow-up email correspondence with the Applicant.

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time. We note the following comments from the Applicant:
A place-holder NDC number (i.e., NDC XXXX-XXXX-XXX) is currently in the draft labeling and labels. The labeler code has been requested and the NDC number will be submitted in revised labeling following FDA's assignment of the labeler code. The final package will also include serialization information as required by the Drug Supply Chain Security Act (Global Trade Item Number (GTIN) and Serial Number (SN)), expiration date, and lot number.

^aHolmes, L. Labels Labeling and URRR Review for (b) (4) (NDA 211448). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Jun 22. RCM No.: 2019-2176 and 2019-2192.

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/s/

LORETTA HOLMES
08/17/2020 02:53:45 PM

SEVAN H KOLEJIAN
08/17/2020 03:12:07 PM

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

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

Memorandum

Date: July 27, 2020

To: Pawanprit (Pinky) Singh, Regulatory Project Manager
Division of Psychiatry (DP)

Kim Updegraff, Associate Director for Labeling, (DP)

From: Christine Bradshaw, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, Team Leader, OPDP

Subject: OPDP Labeling Comments for [REDACTED] (b) (4) (aripiprazole) oral film

NDA: 211448

In response to DP's consult request dated December 4, 2019, OPDP has reviewed the proposed product labeling (PI), Instructions for Use (IFU), and carton and container labeling for the original NDA submission for [REDACTED] (b) (4) (aripiprazole) oral film [REDACTED] (b) (4)

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DP (Singh) on July 17, 2020, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed IFU were sent under separate cover on July 27, 2020.

Carton and Container Labeling:

OPDP has reviewed the attached proposed carton and container labeling uploaded to SharePoint by DP (Singh) on July 21, 2020, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Christine Bradshaw at (301) 796-6796 or Christine.bradshaw@fda.hhs.gov.

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/s/

CHRISTINE J BRADSHAW
07/27/2020 02:33:26 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: July 27, 2020

To: Singh (Pinky) Pawanprit, RPM
Regulatory Project Officer
Division of Psychiatry (DP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Shawna Hutchins, MPH, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Domenic D'Alessandro, PharmD, MBA, CDE
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Instructions for Use (IFU)

Drug Name (established name): (b) (4) (aripiprazole)

Dosage Form and Route: oral film, for oral use

Application Type/Number: NDA 211448

Applicant: CMG Pharmaceutical CO, LTD.

1 INTRODUCTION

On October 18, 2019, CMG Pharmaceutical CO, LTD., submitted for the Agency's review an original New Drug Application (NDA) for [REDACTED]^{(b) (4)} (aripiprazole) oral film, for oral use, for the proposed indication of use for the treatment of Schizophrenia.

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 December 27, 2019 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for [REDACTED]^{(b) (4)} (aripiprazole) oral film, for oral use. On July 17, 2020, it was determined by DP that the DMPP and OPDP review of the proposed Medication Guide (MG) would not be required.

2 MATERIAL REVIEWED

- Draft [REDACTED]^{(b) (4)} (aripiprazole) IFU received on October 18, 2019, and received by DMPP and OPDP on July 17, 2020.
- Draft [REDACTED]^{(b) (4)} (aripiprazole) Prescribing Information (PI) received on October 18, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 17, 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.

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 APFont to make medical information more accessible for patients with vision loss. We reformatted the IFU documents using the Arial font, size 10.

In our collaborative review of the IFU we:

- simplified wording and clarified concepts where possible
- ensured that the IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The IFU is 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 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 IFU.

Please let us know if you have any questions.

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

SHAWNA L HUTCHINS
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ALINE M MOUKHTARA
07/27/2020 11:46:25 AM

LASHAWN M GRIFFITHS
07/27/2020 11:48:02 AM

LABELS LABELING AND URRRA REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
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 22, 2020
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 211448
Product Name and Strength:	(b) (4) (aripiprazole) oral film, 5 mg, 10 mg, and 15 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	CMG Pharmaceutical Co., Ltd
FDA Received Date:	October 18, 2019
OSE RCM #:	2019-2176 and 2019-2192
DMEPA Safety Evaluator:	Loretta Holmes, BSN, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA

1 PURPOSE OF REVIEW

As part of the NDA approval process for (b) (4) (aripiprazole) oral film, 5 mg, 10 mg, and 15 mg, the Division of Psychiatry (DP) requested that we review the proposed labels and labeling for areas that may lead to medication errors. NDA 211448 is a 505() (2) submission. The listed drug product (Abilify oral tablets, NDA 021436) was approved on November 15, 2002. The Applicant, CMG Pharmaceutical Co., also submitted an updated Human Factors Use Related Risk Analysis (URRA) for this product for our review. The updated URRA was submitted in response to a recommendation we provided in our review^b of the URRA that was submitted on May 31, 2018 under IND 119610.

2 MATERIALS REVIEWED

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B (N/A)
ISMP Newsletters	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Other (updated Human Factors Use Related Risk Analysis)	E
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Table 2, below, includes the identified medication error issues with the submitted pouch labels and carton labeling, DMEPA's rationale for concern, and the proposed recommendations to minimize the risk for medication error.

We also reviewed the proposed Prescribing Information and noted areas where the language in Section 2 Dosage and Administration of the Full Prescribing Information could be improved for clarity and conciseness. We collaborated with the Division to revise the language.

^a The proposed proprietary name (b) (4) was found conditionally acceptable in the following review: Holmes, L. Proprietary Name Review for (b) (4) aripiprazole) NDA 211448. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Jan 07. RCM No.: 2019-35234392.

^b Stewart, J. Human Factors Use-Related Risk Analysis Review Aripiprazole Oral Soluble Film IND 119610. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Jul 20. RCM No.: 2018-1167.

Furthermore, we reviewed the updated Human Factors Use Related Risk Analysis (URRA). We note that the recommendation we provided in our review of the URRA submitted on May 31, 2018 under IND 119610 was followed (see Appendix E). We continue to agree with CMG Pharmaceutical Company's justification that a human factors (HF) validation study is not necessary for aripiprazole oral film. We find the updated URRA acceptable and have no additional comments.

Table 2: Identified Issues and Recommendations for CMG Pharmaceutical Co., (entire table to be conveyed to the Applicant)

General Comment
We note that you submitted two different color schemes for the (b) (4) pouch labels and carton labeling. We acknowledge your January 17, 2020 response to our Information Request (dated January 10, 2020) in which you stated the two different color schemes were proposed for consideration and feedback from the Agency in an effort to reduce medication errors. You also stated that in the second proposed scheme, the strengths are distinguished by the variety of background color, with the product strength font corresponding in color. Furthermore, you stated that you prefer the second proposed scheme that differentiates product strength by background color and font color. We recommend use of the second proposed color scheme because it provides better strength differentiation as represented here by those proposed pouch labels: (b) (4)  Additionally, we note that you have submitted two versions of the back panel of the pouches, one with a predominately white font (as shown below) and one with an all-black font. We recommend use of the predominately white font color because it appears to provide comparatively better contrast against the colored background and improves readability. (b) (4) 

Pouch Labels and Carton Labeling			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The established name and dosage form are presented as follows: "(Aripiprazole Oral (b) (4) Film)".	As presented, the established name and dosage form are not consistent with the proposed Prescribing Information.	For consistency with the proposed prescribing information, revise the established name and dosage form to read as follows: "(aripiprazole) oral film".
2.	The NDC number is represented by a placeholder (i.e., XXXX-XXXX-XXX).	We are unable to evaluate the actual NDC number.	Replace the NDC number placeholder with the actual NDC number.
3.	The established name does not appear to be at least ½ the size of the proprietary name.	The size of the established name does not appear to comply with 21 CFR 201.10(g)(2).	Revise the established name so that it is at least ½ the size of the proprietary name as required per 21 CFR 201.10(g)(2).
4.	There is no space between the numerical strength and unit of measure (e.g., 5mg) in the statement of strength.	The lack of space between the numerical strength and unit of measure impairs the readability of the statement of strength.	To improve the readability of the statement of strength, place adequate space between the numerical dose and unit of measure (e.g., 5 mg).
5.	There is no linear barcode present.	The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label whenever possible.	Add the product's linear barcode to each individual pouch and carton as required per 21 CFR 201.25(c)(2).

6.	The storage statement is not consistent with the storage statement in Section 16 of the Prescribing Information (PI).	Storage statements that are inconsistent between the PI and other labels/labeling components may lead to confusion.	Update the storage statement to ensure that it is consistent with the storage statement in Section 16 of the PI.

Pouch Labels

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The expiration date number segments are separated by a period (i.e., YYYY.MM.DD).	The use of periods may impair the readability of the expiration date.	For improved readability, we recommend using a space to separate the number segments of the expiration (i.e., YYYY MM DD).
2.	The NDC number is located on the back panel.	The NDC number lacks sufficient prominence due to its location on the back panel. The NDC number is a component of the product identifying information and should be easily located.	Relocate the NDC number to the front panel (principal display panel).
3.	“How to Use” instructions are missing on the pouch labels.	The lack of instructions for use on the pouch labels may contribute to product administration errors.	Provide abbreviated “How to Use” instructions on the back panel of the pouch labels.

Carton Labeling

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	A 2D data matrix barcode is not present.	A 2D data matrix barcode is used for tracking and tracing purposes.	In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act. ¹ The Act requires manufacturers and repackagers, respectively, 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 beginning November 27, 2017, and November 27, 2018, respectively. We recommend that

			you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. ¹The draft guidance is available at: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf. If a 2D barcode is added, show its location on the carton labeling.
2.	The lot number location and expiration date location and format are not shown on the carton labeling.	We are unable to comment on the location of the lot number and expiration date. Additionally, we are unable to evaluate the expiration date format.	Show the lot number and expiration date location. Provide the proposed expiration date format.
3.	The Rx statement is too prominent.	The prominence of the Rx statement draws attention away from important information on the principal display panel.	Remove the box from the "Rx only" statement.
4.	"How to Use" instructions are missing on the carton labeling.	The lack of instructions for use on the carton labeling may contribute to product administration errors.	Provide abbreviated "How to Use" instructions on the carton labeling.
5.	The statement of strength is on one of the side panels but there is no other product identifying information (i.e., proprietary name, established name, dosage form) present.	The statement of strength is presented without other product identifying information that would provide context.	Delete the statement of strength from the side panel.
6.	The carton labeling has a Medication Guide (MG) statement.	This product will not have a MG.	Delete the MG statement.

4 CONCLUSION

Our evaluation of the proposed pouch labels and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Applicant (CMG Pharmaceutical Company). We ask that the Division convey Table 2 in its entirety to the Applicant so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for (b) (4) that CMG Pharmaceutical Co. submitted on October 18, 2019, and the listed drug (LD).

Product Name	Abilify ^c	(b) (4)
Initial Approval Date	November 15, 2002	N/A
Active Ingredient	aripiprazole	aripiprazole
Indication	Schizophrenia, Acute Treatment of Manic and Mixed Episodes associated with Bipolar I, Adjunctive Treatment of Major Depressive Disorder, Irritability Associated with Autistic Disorder, and Treatment of Tourette's disorder	Treatment of Schizophrenia
Route of Administration	Oral	Oral
Dosage Form	Tablets	Oral Film
Strengths	2 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg	5 mg, 10 mg, and 15 mg
Dose and Frequency	The dosage range is 2 mg to 30 mg (depending on the indication) orally once daily.	The dosage range is 10 mg to 30 mg orally once daily. Adolescents: Start treatment with (b) (4) (b) (4), the daily dose can be titrated with (b) (4) to 5 mg after 2 days and to the target dose of 10 mg after 2 additional days. Subsequent dose increases should be administered in 5 mg increments.
How Supplied	30-count bottle; Blister of 100	One strip (film) per pouch, box of 30 pouches
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].	Store at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [USP controlled room temperature].

^c The Abilify prescribing information was obtained from DailyMed, accessed online on 06/08/2020 at: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c040bd1d-45b7-49f2-93ea-aed7220b30ac>.

APPENDIX E. UPDATED HUMAN FACTORS USE RELATED RISK ANALYSIS (URRA)

In our review of the URRA submitted on May 31, 2018 under IND 119610, we provided the following recommendation (summarized here): *“Include an updated URRA as part of your NDA submission to revise your analysis of the use error related to placement of the OSF in the wrong location of the mouth.”*

The updated URRA, submitted on October 18, 2019, can be accessed via the Electronic Document Room with these links:

- [Application 211448 - Sequence 0001 - ura-2018-01-use-related-risk-analysis](#)
- [\\cdsesub1\evsprod\nda211448\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\schizophrenia\5354-other-stud-rep\use-related-risk\ura-2018-01-use-related-risk-analysis.pdf](#)

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^d along with postmarket medication error data, we reviewed the following (b) (4) labels and labeling submitted by CMG Pharmaceutical Co., Ltd on October 18, 2019.

- Pouch Labels and Carton Labeling

(links: [\\cdsesub1\evsprod\nda211448\0001\m1\us\114-labeling\114a-draft-label\ \(b\) \(4\) packaging.pdf](\\cdsesub1\evsprod\nda211448\0001\m1\us\114-labeling\114a-draft-label\ (b) (4) packaging.pdf) or [Application 211448 - Sequence 0001 - \(b\) \(4\) packaging](#))

- Prescribing Information (image not shown)

(links: <\\cdsesub1\evsprod\nda211448\0001\m1\us\114-labeling\114a-draft-label\labeling-insert-draft.pdf> or [Application 211448 - Sequence 0001 - labeling-insert-draft](#))

F.2 Labels and Labeling Images

Pouch Labels (front)



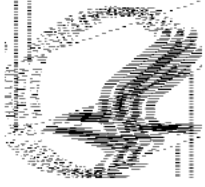
^d Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

LORETTA HOLMES
06/22/2020 04:07:22 PM

SEVAN H KOLEJIAN
06/22/2020 04:58:05 PM



Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
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Division of Pediatric and Maternal Health Review

Date: June 1, 2020 **Date consulted:** May 13, 2020

From: Jean Limpert, MD, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

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

To: Pawanprit (Pinky) Singh, Regulatory Project Manager (RPM)
Division of Psychiatry Products (DPP)

Drug: (b) (4) (aripiprazole) oral soluble film

NDA: 211448

Applicant: CMG Pharmaceutical Co., Ltd (CMG)

Subject: Clinical Relevance of Proposed Animal Data for Section 8.1 of Labeling

Indication: Schizophrenia

Materials Reviewed:

- Applicant's submission for NDA 211448, submitted October 18, 2019.
- May 13, 2020, DPMH consult form for (b) (4) (aripiprazole), DARRTS Reference ID 4608094
- DPMH review of ABILIFY (aripiprazole) NDA 21436/S-043, 21713/S034, 21729/S026, 21866/S028, Catherine Roca, MD, 9/26/2018. DARRTS Reference ID 4326481

Consult Question: “We would like to know DPMH thoughts regarding the value of this information in this drug label.”

BACKGROUND

On October 18, 2019, CMG submitted an original NDA for Aripiprazole oral soluble film (OSF). On May 13, 2020, DPP consulted DPMH to provide input on the relevance of a published article (b) (4) of labeling. The NDA submission is currently under review by DPP.

The NDA submission was submitted under the 505(b)(2) pathway. The sponsor submitted studies demonstrating bioequivalence between Aripiprazole OSF and Abilify oral tablets (NDA # 021436) and is relying upon approved labeling for Abilify tablets.

Aripiprazole OSF is an oral dissolving film designed to dissolve on the tongue within a few seconds. The product was developed to assist noncompliant patients and patients with swallowing difficulties who may otherwise be unable to take aripiprazole.¹

Question for DPMH

“We are asking for a DPMH consult regarding the value of some information in (b) (4) drug labeling based on a published article (b) (4). We would like to know DPMH thoughts regarding the value of this information in the drug label.”

The sponsor is proposing to add the following language to the animal section data of 8.1.



¹ Applicant’s submission, section 2.2

Comments from DPP in the consult request:



Pharmacology-Toxicology Input

Reviewer comment: The final review from Pharmacology Toxicology is not yet finalized.

The following email communication regarding this consult was provided from the Pharmacology-Toxicology reviewer Dr. Tabacova:



REVIEW

Cholesterol biosynthesis is needed during pregnancy and alterations in this metabolic pathway are linked to a variety of neurodevelopmental disorders. Antipsychotics, including aripiprazole, have been found to affect cholesterol biosynthesis through inhibition of DHCR7, which converts 7-dehydrocholesterol (7-DHC) to cholesterol. Inhibition of DHCR7 leads to elevated levels of 7-DHC, a compound that is toxic to cells and affects neuronal viability and growth.² A literature review of pharmaceuticals that target cholesterol biosynthesis found an association of certain antipsychotics (i.e., haloperidol, clozapine) and negative pregnancy outcomes though aripiprazole was not specifically evaluated.³

Smith-Lemli-Opitz Syndrome (SLOS) is a rare autosomal recessive disorder (1 in 20,000 to 60,000 newborns) caused by mutations in the DHCR7 gene. Mutations in DHCR7 prevent cells from making enough cholesterol and also result in the accumulation of toxic byproducts including 7-DHC. It is not completely understood how either abnormality leads to the specific features of SLOS.⁴ SLOS has a wide clinical spectrum and is characterized by prenatal and postnatal growth restriction, microcephaly, intellectual disabilities, behavioral problems, and multiple major and minor malformations. The malformations include distinctive facial features, cleft palate, cardiac defects, underdeveloped external genitalia in males, postaxial polydactyly, and 2-3 syndactyly of the toes.⁵

Psychiatric and behavioral issues are routinely assessed and managed in SLOS patients though schizophrenia is not specifically described as a co-morbid condition. Many patients with SLOS, however, are treated with psychotropic medications. There are no published consensus clinical guidelines for SLOS but use of psychotropic drugs that elevate 7-DHC may be used on a case by case basis with close monitoring of clinical symptoms and serum concentrations of 7-DHC levels.⁶

Given the effect of Aripiprazole on 7-DHC levels, its use in patients with SLOS who become pregnant may be deleterious. Currently, there are no current guidelines for the management of pregnant women with SLOS due to the lack of reported cases.⁷ There is one published case report of an affected SLOS woman with a successful pregnancy and in this case, aripiprazole was not taken during her pregnancy.⁸

(b) (4)

The effects of maternal exposure to aripiprazole may be exacerbated in the context of single-allele DHCR7 mutations, but there are currently no clinical data to assess this interaction. Heterozygous DHCR7 mutation carriers are healthy individuals and comprise 1-1.5% of the general population. Animal data has demonstrated that pregnant mice with single-allele DHCR7 mutations demonstrated higher 7-DHC levels compared to aripiprazole treated controls.⁹ Additionally, limited evaluation of human cell lines has assessed the vulnerability of individuals with a DHCR7+/- genotype and found that exposure to aripiprazole led to higher levels of 7-DHC in those with DHCR7+/- mutation compared to normal cells.¹⁰ At this time, there is no clinical evidence to evaluate the effect of pregnant women taking aripiprazole who may have DHCR7 mutations.

DATA REVIEW

Applicant's review of literature

The applicant does not provide results of the pregnancy registry.

Reviewer comment: This submission is a 505b(2) submission and the applicant does not have access to pregnancy registry results for Abilify.

The applicant provided a summary of safety information for aripiprazole from the published literature using the search term "aripiprazole." The applicant searched PubMed on July 12, 2019.

Reviewer comment: The applicant included two publications related to pregnancy. These were previously reviewed by DPMH and these publications do not provide clinical information related to the consult question.

DPMH literature review

In the 2018 DPMH review for Abilify, human data did not demonstrate a clear risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. See 2018 DPMH review for Abilify for full details of the literature review.¹¹

This reviewer conducted an interim literature search in PubMed and Embase using the search terms "aripiprazole and pregnancy," and "aripiprazole and congenital anomalies/congenital malformations/birth defects/stillbirth/ spontaneous abortion."

⁹ Mirnics K, Korade Z. Vulnerability of dhcr7+/-mutation carriers to aripiprazole exposure. Neuropsychopharmacology (2017) 43 Supplement 1 (S507-S508).

¹⁰ Korade Z, Genaro-Mattos TC, Tallman KA, Liu W, Garbett KA, Koczok K, et al. Vulnerability of DHCR7(+I-) mutation carriers to aripiprazole and trazodone exposure. J Lipid Res. 2017;58:2139-46.

¹¹ DPMH review of ABILIFY (aripiprazole) NDA 21436/S-043, Catherine Roca, MD, 9/26/2018. DARRTS Reference ID 4326481.

Interim published literature results do not provide additional clinical information relevant to the consult question.

DISCUSSION/CONCLUSIONS

The animal data proposed by the applicant has a number of limitations from the nonclinical perspective. In terms of clinical relevance, pregnancy in patients with SLOS is rare; there is only one published case report of pregnancy in a patient with SLOS. Healthy patients with single DHCR7 mutations who become pregnant may be more vulnerable to the effects of aripiprazole and other antipsychotics that increase 7-DHC. There are no clinical data, however, to assess the potential effect of maternal aripiprazole exposure and single DHCR7 mutations on pregnancy outcomes.

RECOMMENDATIONS

DPMH agrees with DPP that the proposed animal data findings have limited clinical relevance and concurs with the recommendation (b) (4)

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/s/

JEAN L LIMPERT
06/08/2020 12:51:25 PM

MIRIAM C DINATALE
06/08/2020 05:35:16 PM

LYNNE P YAO
06/11/2020 01:57:59 PM

MEMORANDUM

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

DATE: 12/18/2019

TO: Division of Psychiatry Products
Office of Drug Evaluation I

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

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

RE: NDA 211448

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the sites listed below. The rationale for this decision is noted below.

Rationale

The clinical sites were inspected in June and July 2019 and the analytical site was inspected in (b) (4) (b) (4) which falls within the surveillance interval. The inspections were conducted under the following submissions: NDAs NON-RESPONSIVE and ANDAs NON-RESPONSIVE and NON-RESPONSIVE

The final classification for the inspections was No Action Indicated (NAI).

Therefore, based on the rationale described above, an inspection is not warranted at this time.

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	inVentiv Health Clinique, Inc.	2500 rue Einstein, Quebec City, Quebec, Canada
Analytical	(b) (4)	
Analytical		

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/

FOLAREMI ADEYEMO
12/18/2019 02:39:39 PM