# Cross-Disciplinary Review Memo

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| **Application Type** | NDA |
| **Application Number(s)** | 211448 |
| **Priority or Standard** | Standard |
| **SDN#** | 40 |
| **Submit Date(s)** | October 14, 2024 |
| **Received Date(s)** | October 15, 2024 |
| **PDUFA Goal Date** | April 15, 2025 |
| **Division/Office** | Division of Psychiatry/Office of Neuroscience |
| **Established/Proper Name** | Aripiprazole |
| **(Proposed) Trade Name** | Mezofy |
| **Pharmacologic Class** | Atypical Antipsychotic |
| **Code name** | N/A |
| **Applicant** | CMG Pharmaceutical Co., Ltd |
| **Dosage form** | Oral Soluble Film |
| **Applicant proposed Dosing Regimen** | Starting dose of 10 mg/day to 15 mg/day, recommended dose of 10 mg/day to 15 mg/day, and maximum dose of 30 mg/day once daily for adults<br>Starting dose of 2 mg/day and recommended dose of 10 mg/day, and maximum dose of 30 mg/day once daily for pediatric patients (13 to 17 years) |
| **Applicant Proposed Indication(s)/Population(s)** | Schizophrenia |
| **Cross Disciplinary Review Teams** | Regulatory Project Manager: Pawanprit Singh, PharmD<br>Nonclinical Reviewer: Sonia Tabacova, PhD<br>Nonclinical Team Lead: Amy Avila, PhD<br>Nonclinical Supervisor: Ikram Elayan, PhD<br>Office of Clinical Pharmacology Reviewer: Li Tan, PhD<br>Office of Clinical Pharmacology Team Lead: Venkateswaran Chithambaram Pillai, PhD<br>Clinical Reviewer: Anna Weissman, MD<br>Clinical Team Lead: Martine Solages, MD<br>Statistical Reviewer: N/A<br>Statistical Team Lead: Peiling Yang, PhD<br>Cross-Disciplinary Team Lead: Martine Solages, MD |
| **Final Signatory** | Bernard Fischer, MD – Deputy Director, Division of Psychiatry |

## Executive Summary

CMG Pharmaceutical Co., Ltd has filed a Class 2 Resubmission for NDA 211448, a 505(b)(2) application for aripiprazole oral soluble film (OSF) for the treatment of schizophrenia in adults and pediatric patients 13 to 17 years of age. The Applicant relies on the Agency's previous findings of safety and effectiveness of the listed drug (LD), Abilify tablets (NDA 021436). Although the scientific bridge between the proposed aripiprazole oral soluble film and the LD was found to be adequate during review of the original application, there were some deficiencies identified during inspection of the manufacturing facility. Therefore, the Agency issued a complete response letter. In this resubmission, the Applicant addressed the deficiencies identified in the manufacturing facility. The interdisciplinary review team recommends approval of this NDA.

## Background

The Applicant first submitted NDA 211448 for aripiprazole oral film for the treatment of schizophrenia in adults and pediatric patients 13 to 17 years of age on October 18, 2019. The Applicant submitted NDA 211448 via the 505(b)(2) pathway, relying on the Agency's findings of safety and effectiveness for Abilify tablets, the LD, as well as two pharmacokinetic studies: a single-dose, crossover, three-treatment, three-sequence bioavailability (BA) study and a single-dose, crossover, food effect study.

Aripiprazole is an atypical antipsychotic indicated (as Abilify) for the treatment of schizophrenia (adults and pediatric patients 13 to 17 years), acute treatment of manic or mixed episodes associated with bipolar I disorder (adults and pediatric patients 10 to 17 years), maintenance treatment of bipolar I disorder (adults), adjunctive treatment of major depressive disorder (adults), treatment of irritability associated with autistic disorder (pediatric patients 6 to 17 years), acute treatment of agitation associated with schizophrenia or bipolar I disorder (adults), and for the treatment of Tourette's disorder. The Applicant proposed only the schizophrenia indications for this aripiprazole oral soluble film (OSF) product.

The review team found that the submitted pharmacokinetic (PK) studies demonstrated that aripiprazole OSF had comparable bioavailability to the LD, providing an adequate bridge to support approval. However, the Chemistry, Manufacturing, and Controls (CMC) team determined that deficiencies identified during inspection of the manufacturing facility precluded an approval action. As a result, the Agency sent the Sponsor a Complete Response Letter on August 18, 2020.

On November 30, 2020, the Applicant and the Agency held a Type A meeting via teleconference to discuss the deficiencies in the Complete Response Letter and to work towards successful NDA resubmission. On July 15, 2022; June 27, 2023; and August 2, 2024; the Applicant submitted requests for 12-month extensions to resubmit the application pending the resolution of the facility issues. The Agency granted these requests, ultimately extending the resubmission

deadline to August 18, 2025. On October 15, 2024, the Agency received a Class 2 Resubmission of NDA 211448.

Refer to the NDA 211448 Unireview archived on August 18, 2020, for the full multidisciplinary review of the original application. Also refer to the Integrated Quality Review archived on March 10, 2025, describing the resolution of the deficiencies identified in the August 18, 2020, Complete Response Letter.

This cross-disciplinary memo summarizes the review of the resubmission, which focused primarily on labeling.

## Proprietary Name

The Applicant originally proposed the name (b) (4), which was determined to be acceptable during the initial review cycle in 2020. In the 2024 resubmission, the Applicant again proposed the proprietary name (b) (4) However, in the interim, the Agency had approved another aripiprazole product with a similar proprietary name in 2024. The Agency determined that the Applicant's subsequently proposed proprietary name of aripiprazole oral film, Mezofy, was acceptable.

## Prescription Drug Labeling

Labeling for aripiprazole oral soluble film is generally consistent with that of Abilify. Dosage and administration guidelines have been expanded to account for new modes of administration, current class language has been included to describe warnings and precautions when appropriate, and references to the indications other than schizophrenia have been removed. Pertinent differences between the aripiprazole oral soluble film and Abilify labels are discussed below.

### HIGHLIGHTS

The Boxed Warning has been updated to align with more recently updated language about the risk of Increased Mortality in Elderly Patients with Dementia-Related Psychosis. This boxed warning indicates that elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.

The Suicidal Thoughts and Behaviors boxed warning from the label for the LD Abilify is not included in the label for aripiprazole OSF. This boxed warning applies to Abilify because of the indication for adjunctive treatment of major depressive disorder (MDD). The warning describes that there is increased risk of suicidal thinking and behavior in pediatric and young adult patients taking antidepressants and advises healthcare professionals to closely monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors. The Applicant is not pursuing the adjunctive MDD indication for aripiprazole OSF. The risks described in the antidepressant-specific boxed warning do not apply to patients with schizophrenia taking aripiprazole OSF. The boxed warning has generally not been included in

labeling for antipsychotic drugs indicated for schizophrenia only. For these reasons, the boxed warning about Suicidal Thoughts and Behaviors is not included in the label for aripiprazole OSF.

**1 INDICATIONS AND USAGE**
Aripiprazole OSF is indicated for the treatment of schizophrenia in adults and pediatric patients 13 to 17 years old. The Applicant did not seek indications for acute treatment of manic and mixed episodes associated with bipolar I, adjunctive treatment of major depressive disorder, irritability associated with autistic disorder, or treatment of Tourette's disorder.

**2 DOSAGE AND ADMINISTRATION**
Dosage and administration guidelines have been updated for clarity and concision. Dosage and administration guidelines also differ from guidelines in Abilify labeling because, for the OSF, they instruct the prescriber to refer patients and caregivers to the "Instruction for Use." The guidelines provide general instructions for use of the film, including a reminder that the film should not be cut. The recommended starting dose of 2 mg for pediatric patients 13 to 17 years old is not available for the film formulation. As a result, this section has been updated to note that use of another formulation will be required for initial dosing.

Examples in Table 1 have been removed to align with the Agency's current practice.

**3 DOSAGE FORMS AND STRENGTHS**
This section differs from the Abilify label because it includes descriptions of the appearance of each strength of film.

**5 WARNINGS AND PRECAUTIONS**
Warnings and precautions regarding neuroleptic malignant syndrome; tardive dyskinesia; metabolic changes; orthostatic hypotension and syncope; leukopenia, neutropenia, and agranulocytosis; and seizures have been revised to include the most recent class language. The warning and precaution regarding suicidal ideation and behavior has not been included, as explained above.

References to unapproved indications have been replaced with the term "another indication." Information from studies of aripiprazole for management of acute treatment of manic and mixed episodes associated with bipolar I, adjunctive treatment of major depressive disorder, irritability associated with autistic disorder, or treatment of Tourette's disorder that were not pooled with schizophrenia studies have been removed from labeling. Data on pediatric metabolic changes from trials of aripiprazole for the treatment of Tourette's disorder have been removed due to orphan exclusivity limitations.

**6 ADVERSE REACTIONS**
The beginning of this section was updated to note that because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse event data presented in Section 6 are generally unchanged from those presented in the Abilify label. However, several changes were made as a result of the Applicant pursuing only the schizophrenia indication. References to unapproved indications have been replaced with the term "another indication." Unpooled data on adverse effects from trials of oral aripiprazole for the treatment of Tourette's disorder have been removed. Tourette's disorder data were also removed from pooled data due to orphan exclusivity limitations.

A sentence was added to explain that the safety of aripiprazole OSF for the treatment of schizophrenia in adults and pediatric patients 13 to 17 years is based on clinical trials of oral aripiprazole.

**7 DRUG INTERACTIONS**

Section 7 (Drug Interactions) was revised to include only clinically significant drug interactions and such drug interactions were listed separately in two tables based on the mechanism of drug interaction (i.e., pharmacokinetic (PK)-based and pharmacodynamic (PD)-based interaction). Drugs having no clinically important interactions with aripiprazole were removed from Section 7.

**8 USE IN SPECIFIC POPULATIONS**

Section 8 (Use in Specific Populations) has been revised to replace references to unapproved indications with (b) (4) Data from trials of oral aripiprazole for the treatment of Tourette's disorder have been removed due to orphan product exclusivity limitations.

Sections (b) (4) have been removed due to lack of significant impact of (b) (4) (b) (4) of aripiprazole.

**11 DESCRIPTION**

This section has been updated to include physical description of the OSF and information about solubility and physical properties of the drug substance.

**12 CLINICAL PHARMACOLOGY**

In Section 12.3, the beginning statement related to drug activity has been moved to Section 12.2 Pharmacodynamics; the statement related to the relative abundance of the (b) (4) (b) (4) has been deleted as this information has already been described under Metabolism sub-heading. The half-life information has been moved under Elimination sub-heading. Given that the elimination pathway information has already been presented under Metabolism sub-heading, this information was deleted from (b) (4) A statement was added to inform prescribers that there are no clinically significant differences between the drug product and the listed drug.

Under the subtitle of Absorption, the (b) (4) were removed because this information is not essential for safe and effective use of the drug product. The statement regarding (b) (4) was removed due to repetition of the same information from the introductory paragraph in Section 12.3. A subtitle "Effect of food" was added for clarity. The

(b) (4) were removed. A subsection "Effect of Drinking Water" has been added to include the results from the study that evaluated the impact of water on the pharmacokinetics of drug product.

A paragraph for inclusion under the Elimination subtitle was generated and the half-life information was added from the introductory paragraph in Section 12.3.

In Section 12.3 (Specific Populations), a statement about (b) (4) was deleted as it does not relate to clinical pharmacology data and was therefore not appropriate for inclusion in this section.

In Section 12.3 (Drug Interaction), the contents were realigned to be consistent with the data presentation.

**14 CLINICAL STUDIES**

Clinical studies that evaluated the efficacy of aripiprazole for management of acute treatment of manic and mixed episodes associated with bipolar I, adjunctive treatment of major depressive disorder, irritability associated with autistic disorder, or treatment of Tourette's disorder have been removed from labeling.

**17 PATIENT COUNSELING INFORMATION**

Instructions to advise patients and caregivers to look for the emergence of suicidal thoughts and behaviors have been removed. See HIGHLIGHTS section above for rationale for not including information about antidepressant-specific risk of suicidal thoughts and behaviors.

**Other Prescription Drug Labeling**

Labeling for the LD, Abilify, includes a Medication Guide (MG). A MG was considered for aripiprazole OSF; however, the decision was made not to include one. The reason for inclusion of a MG with Abilify was because it is indicated for the adjunctive treatment of MDD. Much of the information provided in Abilify's MG concerns its use in the MDD population. Aripiprazole OSF is only approved for schizophrenia. The review team concluded that a MG focused on depression and depression-related adverse reactions would not be relevant to individuals with schizophrenia.

**Postmarketing Requirements and Commitment**

Aripiprazole OSF has been developed in 5-, 10-, and 15-mg formulations. The label for the LD, Abilify tablets, specifies that for the treatment of schizophrenia in pediatric patients 13 to 17 years of age, the starting dose should be 2 mg. It is anticipated that there will be a significant number of patients who would benefit from an aripiprazole OSF dose of 2 mg/day. We have added language to product labeling indicating another formulation of aripiprazole will need to be used prior to initiating treatment with aripiprazole OSF 5 mg. The label also specifies that the OSF should not be cut.

The Applicant must develop a 2-mg soluble film formulation of their product as a Pediatric Research Equity Act postmarketing requirement. Development of a 2-mg soluble film for use in adolescents with schizophrenia will include formulation development, associated pharmaceutical testing, generation of adequate stability data, and collection of adequate data supporting a biowaiver for this strength.

**Deputy Division Director (Signatory) Comments**

This summary review memo reflects my edits and feedback. I agree with the review team and concur with the approval decision.

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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