HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use MEZOFY safely and effectively. See full prescribing information for MEZOFY.

MEZOFY™ (aripiprazole) oral film
Initial U.S. Approval: 2002

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS
See full prescribing information for complete boxed warning

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. MEZOFY is not approved for the treatment of patients with dementia-related psychosis. (5.1)**

---------- INDICATIONS AND USAGE ----------
MEZOFY is an atypical antipsychotic indicated for the treatment of schizophrenia in adult and pediatric patients ages 13 years and older (1)

---------- DOSAGE AND ADMINISTRATION ----------

	Starting Dosage	Recommended Dosage	Maximum Dosage
Adults (2.1)	10 mg/day to 15 mg/day	10 mg/day to 15 mg/day	30 mg/day
Pediatric patients* (13 to 17 years) (2.1)	2 mg/day*	10 mg/day	30 mg/day
*Initiate the 2 mg daily dosage with another aripiprazole product			

- Administer once daily with or without food (2.1)
- See section 2.1 for titration recommendations
- Pediatric patients (13 to 17 years): Initiate the 2 mg once daily recommended starting dosage with another aripiprazole product
- Dosage adjustments requiring dosage strengths below 5 mg require the use of another aripiprazole product (2.3)

---------- DOSAGE FORMS AND STRENGTHS ----------
- Oral Film: 5 mg, 10 mg, 15 mg (3)

----------CONTRAINDICATIONS----------
- Known hypersensitivity to aripiprazole (4)

---------- WARNINGS AND PRECAUTIONS ----------
- *Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis:* Increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack, including fatalities) (5.2)
- *Neuroleptic Malignant Syndrome:* Manage with immediate discontinuation and close monitoring (5.3)
- *Tardive Dyskinesia:* Discontinue if clinically appropriate (5.4)
- *Metabolic Changes:* Monitor for hyperglycemia/diabetes mellitus, dyslipidemia, and weight gain (5.5)
- *Pathological Gambling and Other Compulsive Behaviors:* Consider dose reduction or discontinuation (5.6)
- *Orthostatic Hypotension:* Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease, and risk of dehydration or syncope (5.7)
- *Leukopenia, Neutropenia, and Agranulocytosis:* Perform complete blood cell counts in patients with a history of a clinically significant low white blood cell count (WBC)/absolute neutrophil count (ANC). Consider discontinuing MEZOFY if clinically significant decline in WBC/ANC in the absence of other causative factors (5.9)
- *Seizures:* Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold (5.10)
- *Potential for Cognitive and Motor Impairment:* Use caution when operating machinery (5.11)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions with aripiprazole (incidence ≥ 5% and at least twice that for placebo) are (6.1):

- Adult patients with schizophrenia: akathisia
- Pediatric patients (13 to 17 years) with schizophrenia: extrapyramidal disorder, somnolence, and tremor

To report SUSPECTED ADVERSE REACTIONS, contact CMG Pharmaceutical Co., Ltd. at 82-31-881-7678 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------
Dosage adjustments due to drug interactions (2.3, 7):

Factors	**Dosage Adjustments for MEZOFY**
Known CYP2D6 Poor Metabolizers	Administer half the recommended dose
Known CYP2D6 Poor Metabolizers taking concomitant strong CYP3A4 inhibitors	Administer a quarter the recommended dose*
Strong CYP2D6 **or** CYP3A4 inhibitors	Administer half of recommended dose
Strong CYP2D6 **and** CYP3A4 inhibitors	Administer a quarter of recommended dose*
Strong CYP3A4 inducers	Double recommended dose over 1 to 2 weeks
* Dosage adjustments requiring dosage strengths below 5 mg require the use of another aripiprazole product	

---------- USE IN SPECIFIC POPULATIONS ----------
Pregnancy: May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 04/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. MEZOFY is not approved for the treatment of patients with dementia-related psychosis *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

MEZOFY is indicated for the treatment of schizophrenia in adult and pediatric patients 13 years and older.

2 DOSAGE AND ADMINISTRATION

2.1 Schizophrenia

Adults

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 *[see Clinical Studies (14)]*.

Pediatric Patients 13 to 17 years of Age

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 *[see Clinical Studies (14)]*.

2.2 Important Administration Instructions

Instruct patients and/or caregivers to read the “Instructions for Use” carefully for complete directions on how to properly dose and administer MEZOFY oral film.

Apply MEZOFY on top of the tongue where it adheres and dissolves. The patient should refrain from chewing the film and should not swallow undissolved MEZOFY. MEZOFY should not be cut.

Swallow after the film completely dissolves. The dissolved film may be swallowed with or without water.

MEZOFY can be taken with or without food *[see Clinical Pharmacology (12.3)]*.

Only one oral film should be taken at a time; if a second film is needed to complete the dosage, it should not be taken until the first film has completely dissolved and swallowed.

2.3 Dosage Modifications for Use with CYP2D6 Inhibitors, CYP3A4 Inhibitors and Inducers, and in Patients Who Are Known CYP2D6 Poor Metabolizers

Dosage adjustments are recommended in patients who are known CYP2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors or strong CYP3A4 inducers (see Table 1) *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

When the concomitant drug is withdrawn from the combination therapy, MEZOFY dosage should be adjusted to its original level. When the concomitant use of CYP3A4 inducer is withdrawn, MEZOFY dosage should be reduced to the original level over 1 to 2 weeks. For patients receiving a combination of strong, moderate, and weak inhibitors of CYP3A4 and CYP2D6 (e.g., a strong CYP3A4 inhibitor and a moderate CYP2D6 inhibitor or a moderate CYP3A4 inhibitor with a moderate CYP2D6 inhibitor), the dosage may be reduced to a quarter (25%) of the recommended daily dosage and adjusted based on clinical response.

Because MEZOFY is not available in dosage strengths below 5 mg, dosage reduction of aripiprazole to a quarter (25%) of the recommended daily dosage requires the use of another aripiprazole product.

Table 1 Dose Adjustment Recommendations for MEZOFY When Used Concomitantly in Patients Who Are Known CYP2D6 Poor Metabolizers and Patients Taking Concomitant CYP2D6 Inhibitors, CYP3A4 Inhibitors, and/or CYP3A4 Inducers

Factors	Dosage Adjustments for MEZOFY
Known CYP2D6 Poor Metabolizers	Administer half the recommended dose
Known CYP2D6 Poor Metabolizers receiving concomitant strong CYP3A4 inhibitors	Administer a quarter of the recommended dose*
Strong CYP2D6 **or** CYP3A4 inhibitors	Administer half of the recommended dose
Strong CYP2D6 **and** CYP3A4 inhibitors	Administer a quarter the recommended dose*
Strong CYP3A4 inducers	Double the recommended dose over 1 to 2 weeks
*Dosage adjustments requiring dosage strengths below 5 mg require the use of another aripiprazole product (refer to prescribing information for other aripiprazole products).	

3 DOSAGE FORMS AND STRENGTHS

MEZOFY Oral Film is available as:

- 5 mg white, rectangular-shaped, oral film with “CMG ARF5” printed in red on one side.
- 10 mg white, rectangular-shaped, oral film with “CMG ARF10” printed in red on one side.
- 15 mg white, rectangular-shaped, oral film with “CMG ARF15” printed in red on one side.

4 CONTRAINDICATIONS

MEZOFY is contraindicated in patients with a history of a hypersensitivity reaction to aripiprazole. Reactions have ranged from pruritus/urticaria to anaphylaxis *[see Adverse Reactions (6)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated

patients. Over the course of a typical 10-week controlled trial, the rate of death in drug treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group.

Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. MEZOFY is not approved for the treatment of patients with dementia-related psychosis *[see* Boxed Warning*, Warnings and Precautions (5.2)]*.

5.2 Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia-Related Psychosis

In placebo-controlled clinical studies (two flexible dose and one fixed dose study) of dementia-related psychosis, there was an increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, in aripiprazole-treated patients (mean age: 84 years; range: 78-88 years). In the fixed-dose study, there was a statistically significant dose response relationship for cerebrovascular adverse events in patients treated with aripiprazole. MEZOFY is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning]*.

5.3 Neuroleptic Malignant Syndrome (NMS)

Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex, has been reported in association with administration of antipsychotic drugs, including aripiprazole. Rare cases of NMS have been reported during aripiprazole treatment in the global clinical database.

Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, delirium, and autonomic instability. Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

If NMS is suspected, immediately discontinue MEZOFY and provide intensive symptomatic treatment and monitoring.

5.4 Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. The risk appears to be highest among the elderly, especially elderly women, but it is not possible to predict which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible increase with the duration of treatment and the cumulative dose. The syndrome can develop, after a relatively brief treatment period, even at low doses. It may also occur after discontinuation of treatment.

Tardive dyskinesia may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and, thereby, may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, MEZOFY should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients: 1) who suffer from a chronic illness that is known to respond to antipsychotic drugs; and 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do

require chronic treatment, use the lowest dose and the shortest duration of treatment producing a satisfactory clinical response. Periodically reassess the need for continued treatment.

If signs and symptoms of tardive dyskinesia appear in a patient on MEZOFY, drug discontinuation should be considered. However, some patients may require treatment with MEZOFY despite the presence of the syndrome.

5.5 Metabolic Changes

Atypical antipsychotic drugs have been associated with metabolic changes, including hyperglycemia, diabetes mellitus, dyslipidemia, and weight gain. Although all drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

Hyperglycemia/Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. There have been reports of hyperglycemia in patients treated with aripiprazole *[see Adverse Reactions (6.1, 6.2)]*. Assess fasting plasma glucose before or soon after initiation of antipsychotic medication and monitor periodically during long-term treatment.

Adults

In an analysis of 13 placebo-controlled monotherapy trials in adults, primarily with schizophrenia or another indication, the mean change in fasting glucose in aripiprazole-treated patients (+4.4 mg/dL; median exposure 25 days; N=1057) was not significantly different than in placebo-treated patients (+2.5 mg/dL; median exposure 22 days; N=799). Table 2 shows the proportion of aripiprazole -treated patients with normal and borderline fasting glucose at baseline (median exposure 25 days) that had treatment-emergent high fasting glucose measurements compared to placebo-treated patients (median exposure 22 days).

Table 2 Changes in Fasting Glucose from Placebo-Controlled Monotherapy Trials in Adult Patients

	Category Change (at least once) from Baseline	Treatment Arm	n/N	%
Fasting Glucose	Normal to High (<100 mg/dL to ≥126 mg/dL)	Aripiprazole	31/822	3.8
		Placebo	22/605	3.6
	Borderline to High (≥100 mg/dL and <126 mg/dL to ≥126 mg/dL)	Aripiprazole	31/176	17.6
		Placebo	13/142	9.2

At 24 weeks, the mean change in fasting glucose in aripiprazole-treated patients was not significantly different than in placebo-treated patients [+2.2 mg/dL (n=42) and +9.6 mg/dL (n=28), respectively].

Pediatric Patients

In an analysis of two placebo-controlled trials of 4- to 6-weeks duration in pediatric patients with schizophrenia (13 to 17 years) and another indication, the mean change in fasting glucose in aripiprazole-treated patients (+4.8 mg/dL; with a median exposure of 43 days; N=259) was not significantly different than in placebo-treated patients (+1.7 mg/dL; with a median exposure of 42 days; N=123).

At 12 weeks in pooled trials in pediatric schizophrenia and another indication, the mean change in fasting glucose in aripiprazole-treated patients was not significantly different than in placebo-treated patients [+2.4 mg/dL (n=81) and +0.1 mg/dL (n=15), respectively].

Dyslipidemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

There were no significant differences between aripiprazole- and placebo-treated patients in the proportion with changes from normal to clinically significant levels for fasting/nonfasting total cholesterol, fasting triglycerides, fasting LDLs, and fasting/nonfasting HDLs. Analyses of patients with at least 12 or 24 weeks of exposure were limited by small numbers of patients.

Adults

Table 3 shows the proportion of adult patients, primarily from pooled schizophrenia and another indication monotherapy placebo-controlled trials, with changes in total cholesterol (pooled from 17 trials; median exposure 21 to 25 days), fasting triglycerides (pooled from eight trials; median exposure 42 days), fasting LDL cholesterol (pooled from eight trials; median exposure 39 to 45 days, except for placebo-treated patients with baseline normal fasting LDL measurements, who had median treatment exposure of 24 days) and HDL cholesterol (pooled from nine trials; median exposure 40 to 42 days).

Table 3 Changes in Blood Lipid Parameters from Placebo-Controlled Monotherapy Trials in Adults

	Treatment Arm	n/N	%
Total Cholesterol Normal to High (<200 mg/dL to ≥240 mg/dL)	Aripiprazole	34/1357	2.5
	Placebo	27/973	2.8
Fasting Triglycerides Normal to High (<150 mg/dL to ≥200 mg/dL)	Aripiprazole	40/539	7.4
	Placebo	30/431	7.0
Fasting LDL Cholesterol Normal to High (<100 mg/dL to ≥160 mg/dL)	Aripiprazole	2/332	0.6
	Placebo	2/268	0.7
HDL Cholesterol Normal to Low (≥40 mg/dL to <40 mg/dL)	Aripiprazole	121/1066	11.4
	Placebo	99/794	12.5

In monotherapy trials in adults, the proportion of patients at 12 weeks and 24 weeks with changes from Normal to High in total cholesterol (fasting/nonfasting), fasting triglycerides, and fasting LDL cholesterol were similar between aripiprazole- and placebo-treated patients: at 12 weeks, Total Cholesterol (fasting/nonfasting), 1/71 (1.4%) vs. 3/74 (4.1%); Fasting Triglycerides, 8/62 (12.9%) vs. 5/37 (13.5%); Fasting LDL Cholesterol, 0/34 (0%) vs. 1/25 (4.0%), respectively; and at 24 weeks, Total Cholesterol (fasting/nonfasting), 1/42 (2.4%) vs. 3/37 (8.1%); Fasting Triglycerides, 5/34 (14.7%) vs. 5/20 (25%); Fasting LDL Cholesterol, 0/22 (0%) vs. 1/18 (5.6%), respectively.

Pediatric Patients

In monotherapy trials of pediatric patients with schizophrenia and another indication, the proportion of patients at 12 weeks and 24 weeks with changes from Normal to High in total cholesterol (fasting/nonfasting), fasting triglycerides, and fasting LDL cholesterol were similar between aripiprazole- and placebo-treated patients: at 12 weeks, Total Cholesterol (fasting/nonfasting), 0/57 (0%) vs. 0/15 (0%); Fasting Triglycerides, 2/72 (2.8%) vs. 1/14 (7.1%), respectively; and at 24 weeks, Total Cholesterol (fasting/nonfasting), 0/36 (0%) vs. 0/12 (0%); Fasting Triglycerides, 1/47 (2.1%) vs. 1/10 (10.0%), respectively.

Weight Gain

Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Adults

In an analysis of 13 placebo-controlled monotherapy trials, primarily from pooled schizophrenia and another indication with a median exposure of 21 to 25 days, the mean change in body weight in aripiprazole-treated patients was +0.3 kg (N=1673) compared to –0.1 kg (N=1100) in placebo-controlled patients. At 24 weeks, the mean change from baseline in body weight in aripiprazole-treated patients was –1.5 kg (n=73) compared to –0.2 kg (n=46) in placebo-treated patients.

In trials of adjunctive aripiprazole for another indication, patients first received 8 weeks of treatment with another medication followed by 6 weeks of adjunctive aripiprazole or placebo in addition to their ongoing treatment. The mean change in body weight in patients receiving adjunctive aripiprazole was +1.7 kg (N=347) compared to +0.4 kg (N=330) in patients receiving adjunctive placebo.

Table 4 shows the percentage of adult patients with weight gain ≥7% of body weight by indication.

Table 4 Percentage of Patients from Placebo-Controlled Trials in Adult Patients with Weight Gain ≥7% of Body Weight

	Indication	Treatment Arm	n/N	Patients n (%)
Weight gain ≥7% of body weight	Schizophrenia (4- to 6-week duration)	Aripiprazole	852	69 (8.1)
		Placebo	379	12 (3.2)
	Other Indication (3-week duration)	Aripiprazole	719	16 (2.2)
		Placebo	598	16 (2.7)
	Other Indication (6-week duration)	Aripiprazole	347	18 (5.2)
		Placebo	330	2 (0.6)

Pediatric Patients

In an analysis of two placebo-controlled trials in pediatric patients with schizophrenia (13 to 17 years) and another indication (10 to 17 years) with median exposure of 42 to 43 days, the mean change in body weight in aripiprazole -treated patients was +1.6 kg (N=381) compared to +0.3 kg (N=187) in placebo-treated patients. At 24 weeks, the mean change from baseline in body weight in aripiprazole-treated patients was +5.8 kg (n=62) compared to +1.4 kg (n=13) in placebo-treated patients.

In two short-term, placebo-controlled trials in patients (6 to 17 years) in another indication with median exposure of 56 days, the mean change in body weight in aripiprazole-treated patients was +1.6 kg (n=209) compared to +0.4 kg (n=98) in placebo-treated patients.

Table 5shows the percentage of pediatric patients with weight gain ≥7% of body weight by indication.

Table 5 Percentage of Patients from Placebo-Controlled Monotherapy Trials in Pediatric Patients with Weight Gain ≥7% of Body Weight

	Indication	Treatment Arm	n/N	Patients n (%)
Weight gain ≥7% of body weight	Pooled Schizophrenia and Another Indication (4- to 6-week duration)	Aripiprazole	381	20 (5.2)
		Placebo	187	3 (1.6)
	Another Indication (8-week duration)	Aripiprazole	209	55 (26.3)
		Placebo	98	7 (7.1)

In an open-label trial that enrolled patients from the two placebo-controlled trials of pediatric patients with schizophrenia (13 to 17 years) and another indication (10 to 17 years), 73.2% of patients (238/325) completed

26 weeks of therapy with aripiprazole. After 26 weeks, 32.8% of patients gained ≥7% of their body weight, not adjusted for normal growth. To adjust for normal growth, z-scores were derived (measured in standard deviations [SD]), which normalize for the natural growth of pediatric patients by comparisons to age- and gender-matched population standards. A z-score change <0.5 SD is considered not clinically significant. After 26 weeks, the mean change in z-score was 0.09 SD.

When treating pediatric patients, weight gain should be monitored and assessed against that expected for normal growth.

MEZOFY is not approved for use in pediatric patients less than 13 years of age *[Use in Specific Populations (8.4)]*.

5.6 Pathological Gambling and Other Compulsive Behaviors

Postmarketing reports with aripiprazole suggest that patients can experience intense urges, particularly for gambling, and the inability to control these urges while taking aripiprazole. Other compulsive urges, reported less frequently, include: sexual urges, shopping, eating or binge eating, and other impulsive or compulsive behaviors. Because patients may not recognize these behaviors as abnormal, it is important for prescribers to ask patients or their caregivers specifically about the development of new or intense gambling urges, compulsive sexual urges, compulsive shopping, binge or compulsive eating, or other urges while being treated with MEZOFY. It should be noted that impulse-control symptoms can be associated with the underlying disorder. In some cases, although not all, urges were reported to have stopped when the dose was reduced, or the medication was discontinued. Compulsive behaviors may result in harm to the patient and others if not recognized. Consider dose reduction or stopping the medication if a patient develops such urges.

5.7 Orthostatic Hypotension and Syncope

MEZOFY may cause orthostatic hypotension and syncope, perhaps due to its α_1-adrenergic receptor antagonism. Generally, the risk is greatest during initial dose titration and when increasing the dose. The incidence of orthostatic hypotension-associated reactions from short-term, placebo-controlled trials of adult patients on oral aripiprazole (n=2467) included (aripiprazole incidence, placebo incidence) orthostatic hypotension (1%, 0.3%), postural dizziness (0.5%, 0.3%), and syncope (0.5%, 0.4%); of pediatric patients 6 to 17 years of age (n=611) on oral aripiprazole included orthostatic hypotension (0.5%, 0%), postural dizziness (0.3%, 0%), and syncope (0.2%, 0%) *[see Adverse Reactions (6.1)]*.

The incidence of a significant orthostatic change in blood pressure (defined as a decrease in systolic blood pressure ≥20 mmHg accompanied by an increase in heart rate ≥25 bpm when comparing standing to supine values) for aripiprazole was not meaningfully different from placebo (aripiprazole incidence, placebo incidence): in adult oral aripiprazole-treated patients (4%, 2%), in pediatric oral aripiprazole-treated patients aged 6 to 17 years (0.2%, 1%).

MEZOFY is not approved for use in pediatric patients less than 13 years of age *[Use in Specific Populations (8.4)]*.

Use MEZOFY with caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease, or conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications) [see Drug Interactions (7.1)]. Orthostatic vital signs should be monitored in patients who are vulnerable to hypotension.

5.8 Falls

Antipsychotics, including MEZOFY, may cause somnolence, postural hypotension, motor and sensory instability, which may lead to falls and, consequently, fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating antipsychotic treatment and periodically during long-term therapy.

5.9 Leukopenia, Neutropenia, and Agranulocytosis

Leukopenia and neutropenia have been reported during treatment with antipsychotic agents, including aripiprazole. Agranulocytosis has also been reported.

Possible risk factors for leukopenia and neutropenia include pre-existing low white blood cell count (WBC) or absolute neutrophil count (ANC) and history of drug-induced leukopenia/neutropenia. In patients with a pre-existing WBC or ANC or history of drug-induced leukopenia or neutropenia, perform a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of MEZOFY at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue MEZOFY in patients with absolute neutrophil count <1000/mm^3 and follow their WBC until recovery.

5.10 Seizures

Like other antipsychotics, MEZOFY may cause seizures. The risk is greatest in patients with a history of seizures or with conditions that lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in older patients.

In short-term, placebo-controlled trials, patients with a history of seizures excluded seizures/convulsions occurred in 0.1% (3/2467) of undiagnosed adult patients treated with oral aripiprazole, and in 0.2% (1/611) of pediatric patients (6 to 17 years).

MEZOFY is not approved for use in pediatric patients less than 13 years of age *[Use in Specific Populations (8.4)]*.

5.11 Potential for Cognitive and Motor Impairment

MEZOFY, like other antipsychotics, may cause somnolence and has the potential to impair judgment, thinking, or motor skills. In short-term, placebo-controlled clinical trials, somnolence (including sedation) was reported as follows (aripiprazole incidence, placebo incidence): in adult patients (n=2467) treated with oral aripiprazole (11%, 6%), and in pediatric patients ages 6 to 17 (n=611) (24%, 6%). Somnolence (including sedation) led to discontinuation in 0.3% (8/2467) of adult patients and 3% (15/611) of pediatric patients (6 to 17 years) on oral aripiprazole in short-term, placebo-controlled trials.

MEZOFY is not approved for use in pediatric patients less than 13 years of age *[Use in Specific Populations (8.4)]*.

Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that therapy with MEZOFY does not affect them adversely.

5.12 Body Temperature Dysregulation

Atypical antipsychotics may disrupt the body's ability to reduce core body temperature. Strenuous exercise, exposure to extreme heat, dehydration, and anticholinergic medications may contribute to an elevation in core body temperature; use MEZOFY with caution in patients who may experience these conditions.

5.13 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use, including aripiprazole. Antipsychotic drugs, including MEZOFY, should be used cautiously in patients at risk for aspiration.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Increased Mortality in Elderly Patients with Dementia-Related Psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Cerebrovascular Adverse Events, Including Stroke, In Elderly Patients with Dementia-Related Psychosis *[see Warnings and Precautions (5.2)]*
- Neuroleptic Malignant Syndrome (NMS) *[see Warnings and Precautions (5.3)]*
- Tardive Dyskinesia *[see Warnings and Precautions (5.4)]*
- Metabolic Changes *[see Warnings and Precautions (5.5)]*
- Pathological Gambling and Other Compulsive Behaviors *[see Warnings and Precautions (5.6)]*
- Orthostatic Hypotension and Syncope *[see Warnings and Precautions (5.7)]*
- Falls *[see Warnings and Precautions (5.8)]*
- Leukopenia, Neutropenia, and Agranulocytosis *[see Warnings and Precautions (5.9)]*
- Seizures *[see Warnings and Precautions (5.10)]*
- Potential for Cognitive and Motor Impairment *[see Warnings and Precautions (5.11)]*
- Body Temperature Dysregulation *[see Warnings and Precautions (5.12)]*
- Dysphagia *[see Warnings and Precautions (5.13)]*

6.1 Clinical Trials Experience

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.

The safety of MEZOFY for the treatment of schizophrenia in adults and pediatric patients 13 to 17 years is based on clinical trials of oral aripiprazole, including 12,794 adult patients who participated in multiple-dose, clinical trials in schizophrenia and other indications. A total of 3390 patients were treated with oral aripiprazole for at least 180 days and 1933 patients treated with oral aripiprazole had at least 1 year of exposure.

Aripiprazole has been evaluated for safety in 920 pediatric patients who participated in multiple-dose, clinical trials in schizophrenia and other indications and who had approximately 517 patient-years of exposure to oral aripiprazole. A total of 465 pediatric patients were treated with oral aripiprazole for at least 180 days and 117 pediatric patients treated with oral aripiprazole had at least 1 year of exposure.

The most common adverse reactions in adult patients in clinical trials (≥10%) were nausea, vomiting, constipation, headache, dizziness, akathisia, anxiety, insomnia, and restlessness.

The most common adverse reactions in the pediatric clinical trials (≥10%) were somnolence, headache, vomiting, extrapyramidal disorder, fatigue, increased appetite, insomnia, nausea, nasopharyngitis, and weight increased.

Adult Patients with Schizophrenia

The following findings are based on a pool of five placebo-controlled trials (four 4-week and one 6-week) in which oral aripiprazole was administered in doses ranging from 2 mg to 30 mg per day.

The most common adverse reaction associated with the use of aripiprazole in patients with schizophrenia (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) was akathisia (aripiprazole 8%; placebo 4%).

Table 6 enumerates the pooled incidence, of adverse reactions that occurred during acute therapy (up to 6 weeks in schizophrenia and up to 3 weeks in another indication), including only those reactions that occurred in 2% or more of patients treated with aripiprazole (doses ≥2 mg/day) and for which the incidence in patients treated with aripiprazole was greater than the incidence in patients treated with placebo in the combined dataset.

Table 6 Adverse Reactions in Adult Patients Treated with Oral Aripiprazole in Short-Term, Placebo-Controlled Trials in Schizophrenia and Another Indication

System Organ Class Preferred Term	Percentage of Patients Reporting Reactions[a]	
	Aripiprazole (n = 1843)	Placebo (n = 1166)
Eye Disorders		
Blurred Vision	3	1
Gastrointestinal Disorders		
Nausea	15	11
Constipation	11	7
Vomiting	11	6
Dyspepsia	9	7
Dry Mouth	5	4
Toothache	4	3
Abdominal Discomfort	3	2
Stomach Discomfort	3	2
General Disorders and Administration Site Conditions		
Fatigue	6	4
Pain	3	2
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal Stiffness	4	3
Pain in Extremity	4	2
Myalgia	2	1
Muscle Spasms	2	1
Nervous System Disorders		
Headache	27	23
Dizziness	10	7
Akathisia	10	4

Sedation	7	4
Extrapyramidal Disorder	5	3
Tremor	5	3
Somnolence	5	3
Psychiatric Disorders		
Agitation	19	17
Insomnia	18	13
Anxiety	17	13
Restlessness	5	3
Respiratory, Thoracic, and Mediastinal Disorders		
Pharyngolaryngeal Pain	3	2
Cough	3	2

[a] Adverse reactions reported by at least 2% of patients treated with oral aripiprazole, except adverse reactions with an incidence equal to or less than placebo

An examination of population subgroups did not reveal any clear evidence of differential adverse reaction incidence on the basis of age, gender, or race.

Pediatric Patients (13 to 17 years) with Schizophrenia

The following findings are based on one 6-week, placebo-controlled trial in which oral aripiprazole was administered in doses ranging from 2 mg to 30 mg per day.

The incidence of discontinuation due to adverse reactions between aripiprazole-treated and placebo-treated pediatric patients (13 to 17 years) was 5% and 2%, respectively.

The most common adverse reactions associated with the use of aripiprazole in pediatric patients (13 to 17 years) with schizophrenia (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) were extrapyramidal disorder, somnolence, and tremor.

Adverse Reactions in Pediatric Patients (6 to 17 years) with Schizophrenia and Other Indications

Table 7 enumerates the pooled incidence, rounded to the nearest percent, of adverse reactions that occurred during acute therapy for schizophrenia and other indications, including only those reactions that occurred in 1% or more of pediatric patients treated with aripiprazole (doses ≥2 mg/day) and for which the incidence in patients treated with aripiprazole was greater than the incidence in patients treated with placebo.

MEZOFY is not approved for use in pediatric patients less than 13 years of age *[Use in Specific Populations (8.4)]*.

Table 7 Adverse Reactions in Pediatric Patients (6 to 17 years)[a] Treated with Oral Aripiprazole in Short-Term, Placebo-Controlled Trials of Schizophrenia and Other Indications

System Organ Class Preferred Term	Percentage of Patients Reporting Reactions[b]	
	Aripiprazole (n = 611)	Placebo (n = 298)
Eye Disorders		
Blurred Vision	3	0
Gastrointestinal Disorders		
Vomiting	9	7
Nausea	8	4

Diarrhea	5	3
Salivary Hypersecretion	4	1
Abdominal Pain Upper	3	2
Constipation	3	2
Dry Mouth	1	0
General Disorders and Administration Site Conditions		
Fatigue	10	2
Pyrexia	5	1
Irritability	1	0
Thirst	1	0
Infections and Infestations		
Nasopharyngitis	6	3
Investigations		
Weight Increased	2	1
Metabolism and Nutrition Disorders		
Increased Appetite	7	3
Decreased Appetite	4	2
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	1	0
Musculoskeletal Stiffness	1	0
Nervous System Disorders		
Somnolence	16	4
Headache	13	12
Sedation	8	1
Tremor	6	1
Extrapyramidal Disorder	14	2
Akathisia	6	1
Drooling	4	0
Lethargy	2	0
Dizziness	3	1
Dystonia	1	0
Dyskinesia	1	0
Hypersomnia	1	0
Reproductive System and Breast Disorders		
Dysmenorrhea[c]	2	1
Respiratory, Thoracic, and Mediastinal Disorders		
Rhinorrhoea	2	1
Skin and Subcutaneous Tissue Disorders		
Rash	2	1

[a]MEZOFY is not approved for use in pediatric patients less than 13 years of age.

[b]Adverse reactions reported by at least 2% of patients treated with oral aripiprazole, except adverse reactions with an incidence equal to or less than placebo.

[c] Adjusted for gender.

Dose-Related Adverse Reactions

Dose response relationships for the incidence of treatment-emergent adverse events were evaluated from four trials in adult patients with schizophrenia comparing various fixed doses (2 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg/day) of oral aripiprazole to placebo. This analysis, stratified by study, indicated that the only adverse reaction to have a possible dose response relationship, and then most prominent only with 30 mg, was somnolence [including sedation]; (incidences were placebo, 7.1%; 10 mg, 8.5%; 15 mg, 8.7%; 20 mg, 7.5%; 30 mg, 12.6%).

In the study of pediatric patients (13 to 17 years of age) with schizophrenia, three common adverse reactions appeared to have a possible dose response relationship: extrapyramidal disorder (incidences were placebo, 5%; 10 mg, 13%; 30 mg, 21.6%); somnolence (incidences were placebo, 6%; 10 mg, 11%; 30 mg, 21.6%); and tremor (incidences were placebo, 2%; 10 mg, 2%; 30 mg, 11.8%).

Extrapyramidal Symptoms

In short-term, placebo-controlled trials in schizophrenia in adults, the incidence of reported EPS-related events, excluding events related to akathisia, for aripiprazole-treated patients was 13% vs. 12% for placebo; and the incidence of akathisia-related events for aripiprazole-treated patients was 8% vs. 4% for placebo. In the short-term, placebo-controlled trial of schizophrenia in pediatric patients (13 to 17 years), the incidence of reported EPS-related events, excluding events related to akathisia, for aripiprazole-treated patients was 25% vs. 7% for placebo; and the incidence of akathisia-related events for aripiprazole-treated patients was 9% vs. 6% for placebo.

Objectively collected data from those trials was collected on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia), and the Assessments of Involuntary Movement Scales (for dyskinesias). In the adult schizophrenia trials, the objectively collected data did not show a difference between aripiprazole and placebo, with the exception of the Barnes Akathisia Scale (aripiprazole, 0.08; placebo, –0.05). In the pediatric (13 to 17 years) schizophrenia trial, the objectively collected data did not show a difference between aripiprazole and placebo, with the exception of the Simpson Angus Rating Scale (aripiprazole, 0.24; placebo, –0.29).

Similarly, in a long-term (26-week), placebo-controlled trial of schizophrenia in adults, objectively collected data on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia), and the Assessments of Involuntary Movement Scales (for dyskinesias) did not show a difference between aripiprazole and placebo.

Dystonia

Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first-generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Additional Findings Observed in Clinical Trials

Adverse Reactions in Long-Term, Double-Blind, Placebo-Controlled Trials

The adverse reactions reported in a 26-week, double-blind trial comparing oral aripiprazole and placebo in patients with schizophrenia were generally consistent with those reported in the short-term, placebo-controlled trials, except for a higher incidence of tremor [8% (12/153) for aripiprazole vs. 2% (3/153) for placebo]. In this study, the majority of the cases of tremor were of mild intensity (8/12 mild and 4/12 moderate), occurred early in therapy (9/12 ≤49 days), and were of limited duration (7/12 ≤10 days). Tremor infrequently led to discontinuation (<1%) of aripiprazole. In addition, in a long-term (52 week), active-controlled study, the incidence of tremor was 5% (40/859) for aripiprazole.

Other Adverse Reactions Observed During Clinical Trial Evaluation of Aripiprazole

Other adverse reactions associated with aripiprazole are presented below. The following listing does not include reactions: 1) already listed in previous tables or elsewhere in labeling, 2) for which a drug cause was remote, 3) which were so general as to be uninformative, 4) which were not considered to have significant clinical implications, or 5) which occurred at a rate equal to or less than placebo.

Reactions are categorized by body system according to the following definitions: *frequent* adverse reactions are those occurring in at least 1/100 patients; *infrequent* adverse reactions are those occurring in 1/100 to 1/1000 patients; *rare reactions* are those occurring in fewer than 1/1000 patients:

Adults - Oral Administration

Blood and Lymphatic System Disorders:

rare - thrombocytopenia

Cardiac Disorders:

infrequent – bradycardia, palpitations, *rare* – atrial flutter, cardiorespiratory arrest, atrioventricular block, atrial fibrillation, angina pectoris, myocardial ischemia, myocardial infarction, cardiopulmonary failure

Eye Disorders:

infrequent – photophobia; rare - diplopia

Gastrointestinal Disorders:

infrequent - gastroesophageal reflux disease

General Disorders and Administration Site Conditions:

frequent - asthenia; infrequent – peripheral edema, chest pain; rare – face edema

Hepatobiliary Disorders:

rare - hepatitis, jaundice

Immune System Disorders:

rare - hypersensitivity

Injury, Poisoning, and Procedural Complications:

infrequent - fall; rare - heat stroke

Investigations:

frequent - weight decreased, *infrequent* - hepatic enzyme increased, blood glucose increased, blood lactate dehydrogenase increased, gamma glutamyl transferase increased; *rare* – blood prolactin increased, blood urea increased, blood creatinine increased, blood bilirubin increased, electrocardiogram QT prolonged, glycosylated hemoglobin increased

Metabolism and Nutrition Disorders:

frequent – anorexia;

rare - hypokalemia, hyponatremia, hypoglycemia

Musculoskeletal and Connective Tissue Disorders:

infrequent - muscular weakness, muscle tightness; *rare* – rhabdomyolysis, mobility decreased

Nervous System Disorders:

infrequent - parkinsonism, memory impairment, cogwheel rigidity, hypokinesia, bradykinesia; *rare* – akinesia, myoclonus, coordination abnormal, speech disorder, Grand Mal convulsion; *<1/10,000 patients* - choreoathetosis

Psychiatric Disorders:

infrequent – aggression, loss of libido, delirium; *rare* – libido increased, anorgasmia, tic, homicidal ideation, catatonia, sleep walking

Renal and Urinary Disorders:

rare - urinary retention, nocturia

Reproductive System and Breast Disorders:

infrequent - erectile dysfunction; *rare* – gynaecomastia, menstruation irregular, amenorrhea, breast pain, priapism

Respiratory, Thoracic, and Mediastinal Disorders:

infrequent - nasal congestion, dyspnea

Skin and Subcutaneous Tissue Disorders:

infrequent - rash, hyperhidrosis pruritus, photosensitivity reaction, alopecia; *rare* - urticaria

Vascular Disorders:

infrequent - hypotension, hypertension

Pediatric Patients - Oral Administration

Most adverse events observed in the pooled database of 1,686 pediatric patients, were also observed in the adult population. Additional adverse reactions observed in the pediatric population are listed below.

Eye Disorders

infrequent - oculogyric crisis

Gastrointestinal Disorders:

infrequent - tongue dry, tongue spasm

Investigations:

frequent - blood insulin increased

Nervous System Disorders:

infrequent - sleep talking

Renal and Urinary Disorders

frequent - enuresis

Skin and Subcutaneous Tissue Disorders:

infrequent – hirsutism

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of aripiprazole. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to establish a causal relationship to drug exposure: occurrences of allergic reaction (anaphylactic reaction, angioedema, laryngospasm, pruritus/urticaria, or oropharyngeal spasm), pathological gambling, hiccups and blood glucose fluctuation, oculogyric crisis, and drug reaction with eosinophilia and systemic symptoms (DRESS).

7 DRUG INTERACTIONS

7.1 Clinically Significant Drug Interactions on MEZOFY

Table 8 Clinically Significant Drug Interactions with MEZOFY

Strong CYP3A4 Inhibitors or Strong CYP2D6 Inhibitors	
Prevention or Management	Reduce the MEZOFY dosage with concomitant use of a strong CYP3A4 inhibitor or CYP2D6 inhibitor *[see Dosage and Administration (2.3)]*.
Clinical Effect(s)	Concomitant use of aripiprazole with a strong CYP3A4 or CYP2D6 inhibitor increased the exposure of aripiprazole compared to the use of aripiprazole alone *[see Clinical Pharmacology (12.3)]*.
Strong CYP3A4 Inducers	
Prevention or Management	Increasing the MEZOFY dosage with concomitant use of a strong CYP3A4 inducer *[see Dosage and Administration (2.3)]*.
Clinical Effect(s)	Concomitant use of aripiprazole and a strong CYP3A4 inducer decreased the exposure of aripiprazole compared to the use of aripiprazole alone *[see Clinical Pharmacology (12.3)]*.
Antihypertensive Drugs	
Prevention or Management	Monitor blood pressure and adjust dose accordingly *[see Warnings and Precautions (5.7)]*.
Clinical Effect(s)	Due to its alpha adrenergic antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.
Lorazepam	
Prevention or Management	Monitor sedation and blood pressure and adjust dose accordingly.
Clinical Effect(s)	The intensity of sedation was greater with the combination of oral aripiprazole and lorazepam as compared to that observed with aripiprazole alone. The orthostatic hypotension observed was greater with the

	combination as compared to that observed with lorazepam alone *[see Warnings and Precautions (5.7)]*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to atypical antipsychotics, including MEZOFY, during pregnancy. Healthcare providers are encouraged to register patients by contacting the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or visit https://womensmentalhealth.org/clinical-and-research-programs-pregnancyregistry/.

Risk Summary

Neonates exposed to antipsychotic drugs (including aripiprazole) during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery *(see Clinical considerations)*. Overall available data from published epidemiologic studies of pregnant women exposed to aripiprazole have not established a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes *(see Data)*. There are risks to the mother associated with untreated schizophrenia and with exposure to antipsychotics, including MEZOFY, during pregnancy *(see Clinical Considerations)*.

In animal reproduction studies, oral and intravenous aripiprazole administration during organogenesis in rats and/or rabbits at doses 10 and 19 times, respectively, the maximum recommended human dose (MRHD) of 30 mg/day based on mg/m^2 body surface area, produced fetal death, decreased fetal weight, undescended testicles, delayed skeletal ossification, skeletal abnormalities, and diaphragmatic hernia. Oral and intravenous aripiprazole administration during the pre- and postnatal period in rats at doses 10 times the MRHD based on mg/m^2 body surface area, produced prolonged gestation, stillbirths, decreased pup weight, and decreased pup survival *(see Data)*.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

There is a risk to the mother from untreated schizophrenia, including increased risk of relapse, hospitalization, and suicide. Schizophrenia is associated with increased adverse perinatal outcomes, including preterm birth. It is not known if this is a direct result of the illness or other comorbid factors.

Fetal/Neonatal Adverse Reactions

Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder have been reported in neonates who were exposed to antipsychotic drugs (including aripiprazole) during the third trimester of pregnancy. These symptoms have varied in severity. Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization.

Data

Human data

Published data from observational studies, birth registries, and case reports on the use of atypical antipsychotics during pregnancy do not report a clear association with antipsychotics and major birth defects. A retrospective study from a Medicaid database of 9258 women exposed to antipsychotics during pregnancy did not indicate an overall increased risk for major birth defects.

Animal Data

In animal studies, aripiprazole demonstrated developmental toxicity, including possible teratogenic effects in rats, rabbits and mice.

In pregnant rats treated orally with aripiprazole during organogenesis at doses of 3, 10, and 30 mg/kg/day, which are approximately 1, 3 and 10 times the MRHD of 30 mg/day based on mg/m^2 body surface area, a slight prolongation of gestation and delay in fetal development, as evidenced by decreased fetal weight and undescended testes, were observed at 10 times the MRHD. Delayed skeletal ossification was observed at 3 and 10 times the MRHD. Delivered offspring had increased incidences of hepatodiaphragmatic nodules and diaphragmatic hernia were observed at 10 times the MRHD (the other dose groups were not examined for these findings). Postnatally, delayed vaginal opening was seen at 3 and 10 times the MRHD. Impaired reproductive performance (decreased fertility rate, corpora lutea, implants, live fetuses, and increased post-implantation loss, likely mediated through effects on female offspring) were observed at 10 times the MRHD; however, there was no evidence to suggest that these developmental effects were secondary to maternal toxicity.

In pregnant rats injected intravenously with aripiprazole during organogenesis at doses of 3, 9, and 27 mg/kg/day, which are 1, 3, and 9 times the MRHD of 30 mg/day based on mg/m^2 body surface area, decreased fetal weight and delayed skeletal ossification were observed at 9 times the MRHD; this dose also caused maternal toxicity.

In pregnant rabbits treated orally with aripiprazole during organogenesis at doses of 10, 30, and 100 mg/kg/day which are 6, 19, and 65 times the MRHD of 30 mg/day based on mg/m^2 body surface area, decreased maternal food consumption, and increased abortions as well as increased fetal mortality were observed at 65 times the MHRD. Decreased fetal weight and increased incidence of fused sternebrae were observed at 19 and 65 times the MRHD.

In pregnant rabbits injected intravenously with aripiprazole during organogenesis at doses of 3, 10, and 30 mg/kg/day, which are 2, 6, and 19 times the MRHD of 30 mg/day based on mg/m^2 body surface area, decreased fetal weight, increased fetal abnormalities (primarily skeletal), and decreased fetal skeletal ossification were observed at 19 times the MRHD; this dose also caused maternal toxicity. The fetal no-effect dose was 10 mg/kg/day, which is 6 times the MRHD.

In rats treated orally with aripiprazole peri- and post-natally from gestation day 17 through postpartum day 21 at doses of 3, 10, and 30 mg/kg/day which are 1, 3, and 10 times the MRHD of 30 mg/day based on mg/m^2 body surface area slight maternal toxicity and slightly prolonged gestation were observed at 10 times the MHRD. An increase in stillbirths and, decreases in pup weight (persisting into adulthood) and survival were also seen at this dose.

In rats injected intravenously with aripiprazole from gestation day 6 through lactation day 20 at doses of 3, 8, and 20 mg/kg/day, which are 1, 3, and 6 times the MRHD of 30 mg/day based on mg/m^2 body surface area, increased stillbirths were observed at 3 and 6 times the MRHD; and decreases in early postnatal pup weight and survival were observed at 6 times the MRHD; these doses also caused some maternal toxicity. There were no effects on postnatal behavioral and reproductive development.

8.2 Lactation

Risk Summary

Limited data from published literature report the presence of aripiprazole in human breast milk, at relative infant doses ranging between 0.7% to 8.3% of the maternal weight-adjusted dosage. There are reports of poor weight gain in breastfed infants exposed to aripiprazole and reports of inadequate milk supply in lactating women taking aripiprazole.

The development and health benefits of breastfeeding should be considered along with the mother's clinical need for MEZOFY and any potential adverse effects on the breastfed infant from MEZOFY or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of MEZOFY have been established for the treatment of schizophrenia in pediatric patients 13 to 17 years of age. Use of MEZOFY for this age group is based on a 6-week, trial in 202 pediatric patients that compared two fixed doses (10 mg or 30 mg daily) of another oral aripiprazole formulation to placebo. Both doses of aripiprazole were superior to placebo in the PANSS total score. *[see Dosage and Administration (2.1), Adverse Reactions (6.1), and Clinical Studies (14)]*. Although maintenance efficacy in pediatric patients has not been systematically evaluated, maintenance efficacy can be extrapolated from adult data along with comparisons of aripiprazole pharmacokinetic parameters in adult and pediatric patients.

Safety and effectiveness in pediatric patients with agitation associated with schizophrenia have not been established.

The pharmacokinetics of aripiprazole and dehydro-aripiprazole in pediatric patients, 10 to 17 years of age, were similar to those in adults after correcting for the differences in body weight *[see Clinical Pharmacology (12.3)]*.

The safety and effectiveness of MEZOFY have not been established in pediatric patients less than 13 years of age.

Juvenile Animal Toxicity Data

Aripiprazole in juvenile rats caused mortality, CNS clinical signs, impaired memory and learning, and delayed sexual maturation when administered at oral doses of 10, 20, 40 mg/kg/day from weaning (21 days old) through maturity (80 days old). At 40 mg/kg/day, mortality, decreased activity, splayed hind limbs, hunched posture, ataxia, tremors and other CNS signs were observed in both genders. In addition, delayed sexual maturation was observed in males. At all doses and in a dose-dependent manner, impaired memory and learning, increased motor activity, and histopathology changes in the pituitary (atrophy), adrenals (adrenocortical hypertrophy), mammary glands (hyperplasia and increased secretion), and female reproductive organs (vaginal mucification, endometrial atrophy, decrease in ovarian corpora lutea) were observed. The changes in female reproductive organs were considered secondary to the increase in prolactin serum levels. A No Observed Adverse Effect Level (NOAEL) could not be determined and, at the lowest tested dose of 10 mg/kg/day, there is no safety margin relative to the systemic exposures (AUC_{0-24}) for aripiprazole or its major active metabolite in adolescents at the maximum recommended pediatric dose of 15 mg/day. All drug-related effects were reversible after a 2-month recovery period, and most of the drug effects in juvenile rats were also observed in adult rats from previously conducted studies.

Aripiprazole in juvenile dogs (2 months old) caused CNS clinical signs of tremors, hypoactivity, ataxia, recumbency and limited use of hind limbs when administered orally for 6 months at 3, 10, 30 mg/kg/day. Mean body weight and weight gain were decreased up to 18% in females in all drug groups relative to control values. A NOAEL could not be determined and, at the lowest tested dose of 3 mg/kg/day, there is no safety margin

relative to the systemic exposures (AUC_{0-24}) for aripiprazole or its major active metabolite in adolescents at the maximum recommended pediatric dose of 15 mg/day. All drug-related effects were reversible after a 2-month recovery period.

8.5 Geriatric Use

No dosage adjustment is recommended for elderly patients *[see Boxed Warning, Warnings and Precautions (5.1), and Clinical Pharmacology (12.3)]*.

Of the 13,543 patients treated with oral aripiprazole in clinical trials, 1073 (8%) were ≥65 years old and 799 (6%) were ≥75 years old. Placebo-controlled studies of oral aripiprazole in schizophrenia and other conditions did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Antipsychotic drugs increase the risk of death in elderly patients with dementia-related psychosis. MEZOFY is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*.

8.6 CYP2D6 Poor Metabolizers

Dosage adjustment is recommended in known CYP2D6 poor metabolizers due to high aripiprazole concentrations. Approximately 8% of Caucasians and 3–8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers (PM) *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

MEZOFY contains aripiprazole, which is not a controlled substance.

9.2 Abuse

MEZOFY has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of MEZOFY misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

9.3 Dependence

In physical dependence studies in monkeys, withdrawal symptoms were observed upon abrupt cessation of dosing. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed.

10 OVERDOSAGE

10.1 Human Experience

In clinical trials and in postmarketing experience, adverse reactions of deliberate or accidental overdosage with oral aripiprazole have been reported worldwide. These include overdoses with oral aripiprazole alone and in combination with other substances.

Common adverse reactions (reported in at least 5% of all overdose cases) reported with oral aripiprazole overdosage (alone or in combination with other substances) include vomiting, somnolence, and tremor. Other clinically important signs and symptoms observed in one or more patients with aripiprazole overdoses (alone or with other substances) include acidosis, aggression, aspartate aminotransferase increased, atrial fibrillation, bradycardia, coma, confusional state, convulsion, blood creatine phosphokinase increased, depressed level of consciousness, hypertension, hypokalemia, hypotension, lethargy, loss of consciousness, QRS complex prolonged, QT prolonged, pneumonia aspiration, respiratory arrest, status epilepticus, and tachycardia.

10.2 Management of Overdosage

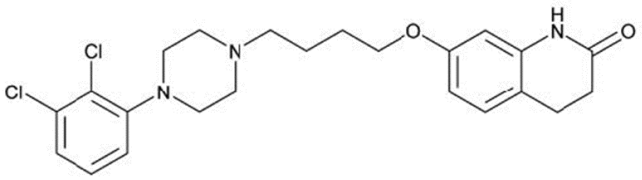
No specific information is available on the treatment of overdose with aripiprazole. Consult a Certified Poison Control Center (1-800-222-1222 or www.poison.org) for up-to-date guidance and advice for treatment of overdosage. An electrocardiogram should be obtained in case of overdosage and if QT interval prolongation is present, cardiac monitoring should be instituted. Otherwise, management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. Close medical supervision and monitoring should continue until the patient recovers.

Charcoal: In the event of an overdose of aripiprazole, an early charcoal administration may be useful in partially preventing the absorption of aripiprazole. Administration of 50 g of activated charcoal, one hour after a single 15 mg oral dose of aripiprazole, decreased the mean AUC and C_{max} of aripiprazole by 50%.

Hemodialysis: Although there is no information on the effect of hemodialysis in treating an overdose with aripiprazole, hemodialysis is unlikely to be useful in overdose management since aripiprazole is highly bound to plasma proteins.

11 DESCRIPTION

MEZOFY contains aripiprazole, an atypical antipsychotic. The chemical name of aripiprazole is 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyril. The molecular formula is $C_{23}H_{27}Cl_2N_3O_2$ and its molecular weight is 448.38. The structural formula is:



Aripiprazole is white to off-white crystalline powder. It has a melting point of 140 ±40°C, and is freely soluble in dichloromethane, sparingly soluble in toluene, insoluble in methanol and water.

MEZOFY oral film isfor oral administration and is available in 5 mg, 10 mg, and 15 mg strengths. Inactive ingredients include acesulfame potassium, citric acid, FD&C Red No. 40, glycerin, hypromellose, L-menthol, polysorbate 80, polyvinyl alcohol, sucralose, and xylitol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of aripiprazole in the treatment of schizophrenia is unclear. However, the efficacy of aripiprazole could be mediated through a combination of partial agonist activity at D_2 and 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors.

12.2 Pharmacodynamics

Aripiprazole exhibits high affinity for dopamine D_2 and D_3, serotonin 5-HT_{1A} and 5-HT_{2A} receptors (K_i values of 0.34 nM, 0.8 nM, 1.7 nM, and 3.4 nM, respectively), moderate affinity for dopamine D_4, serotonin 5-HT_{2C} and 5-HT_7, alpha1-adrenergic and histamine H_1 receptors (K_i values of 44 nM, 15 nM, 39 nM, 57 nM, and 61 nM, respectively), and moderate affinity for the serotonin reuptake site (K_i=98 nM). Aripiprazole has no appreciable affinity for cholinergic muscarinic receptors (IC_{50} > 1000 nM).

MEZOFY activity is presumably primarily due to the parent drug, aripiprazole, and to a lesser extent, to its major metabolite, dehydro-aripiprazole, which has been shown to have affinities for D_2 receptors similar to the parent drug.

12.3 Pharmacokinetics

The single-dose pharmacokinetics of oral aripiprazole is linear and dose-proportional between the doses of 5 mg (0.5 times the lowest recommended starting dose) to 30 mg. Steady-state concentrations are attained within 14 days of dosing for both active moieties. At steady-state, the pharmacokinetics of aripiprazole is dose-proportional. No clinically significant difference in aripiprazole exposure was observed following administration of either MEZOFY or aripiprazole immediate release tablets.

Absorption

The absolute oral bioavailability of the tablet formulation is 87%. The median time to maximum plasma concentration (T_{max}) of aripiprazole is 2 to 2.5 hours.

Effect of Food

No clinically significant differences in pharmacokinetics were observed following administration of a high-fat meal (1000 calories, 50% fat), but T_{max} was delayed by 3 hours for aripiprazole. No significant effect of food on T_{max} of dehydro-aripiprazole was observed.

Effect of Drinking Water

No clinically significant differences in pharmacokinetics of aripiprazole and dehydroaripiprazole were observed following administration of MEZOFY with and without water.

Distribution

The steady-state volume of distribution of aripiprazole following intravenous administration is 404 L or 4.9 L/kg, indicating extensive extravascular distribution. At therapeutic concentrations, aripiprazole and its major metabolite are greater than 99% bound to serum proteins, primarily to albumin. In healthy human volunteers administered 0.5 to 30 mcg/day aripiprazole for 14 days, there was dose-dependent D_2 receptor occupancy indicating brain penetration of aripiprazole in humans.

Elimination

The mean elimination half-lives are about 75 hours for aripiprazole and 94 hours for dehydro-aripiprazole. For CYP2D6 poor metabolizers, the mean elimination half-life for aripiprazole is about 146 hours.

Metabolism

Aripiprazole is metabolized primarily by three biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation. Based on *in vitro* studies, CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole, and CYP3A4 enzymes are responsible for N-dealkylation.

Aripiprazole is the predominant drug moiety in the systemic circulation. At steady-state, dehydro-aripiprazole, the active metabolite, represents about 40% of aripiprazole AUC in plasma.

Excretion

Following a single oral dose of [^{14}C]-labeled aripiprazole, the radioactivity recovery was approximately 25% in the urine and 55% in the feces of the administered radioactivity. Less than 1% of unchanged aripiprazole was excreted in the urine and approximately 18% of the oral dose was recovered unchanged in the feces.

Specific Populations

Exposures of aripiprazole and dehydro-aripiprazole in specific populations are summarized in Figure 1, and Figure 2 respectively. In addition, in pediatric patients (10 to 17 years of age) administered with aripiprazole (20 mg to 30 mg), the body weight corrected aripiprazole clearance was similar to the adults.

Figure 1 Effects of Intrinsic Factors on Aripiprazole Pharmacokinetics

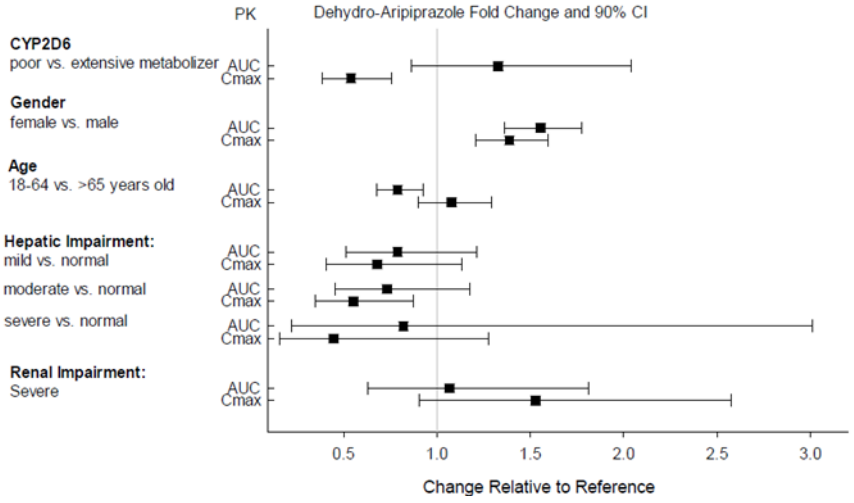
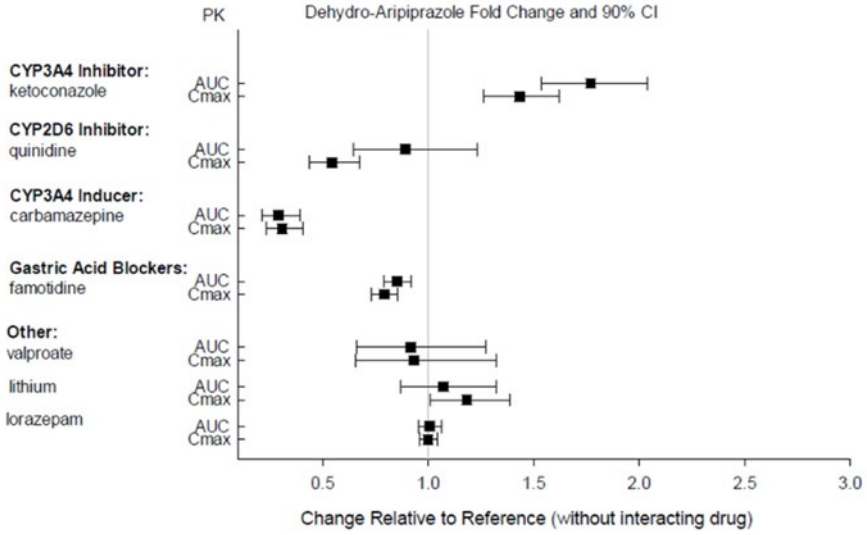


Figure 2 Effects of Intrinsic Factors on Dehydro-aripiprazole Pharmacokinetics



Clinical Drug Interaction Studies and Model-Informed Approaches

Effects of other drugs on the exposures of aripiprazole and dehydro-aripiprazole are summarized in, Figure 3 and Figure 4 respectively.

Figure 3 The Effects of Other Drugs on Aripiprazole Pharmacokinetics

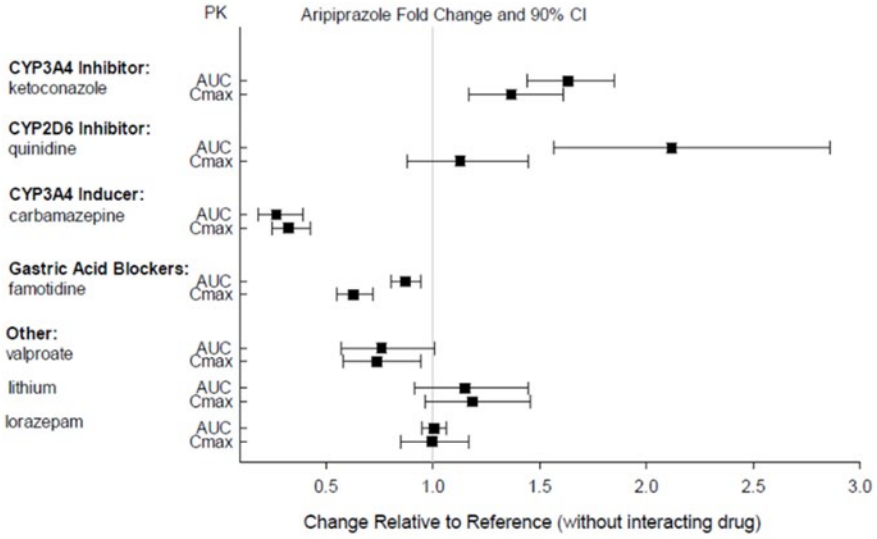
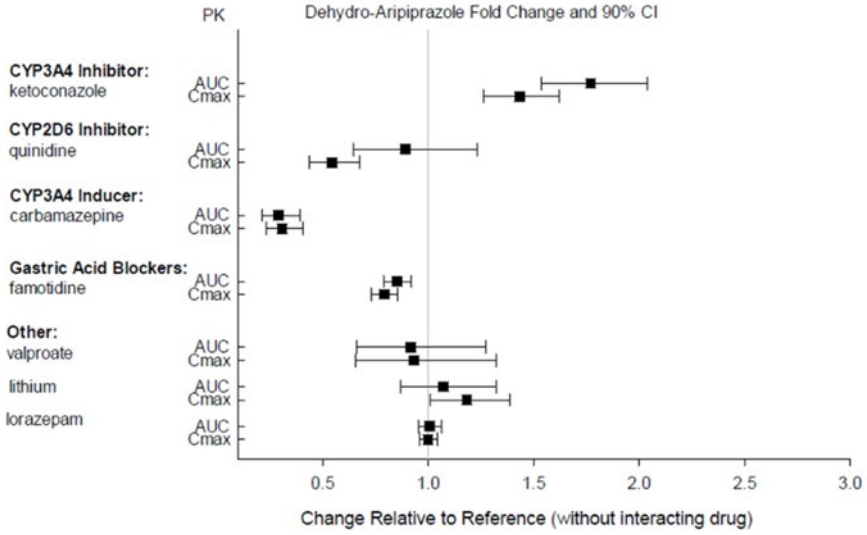


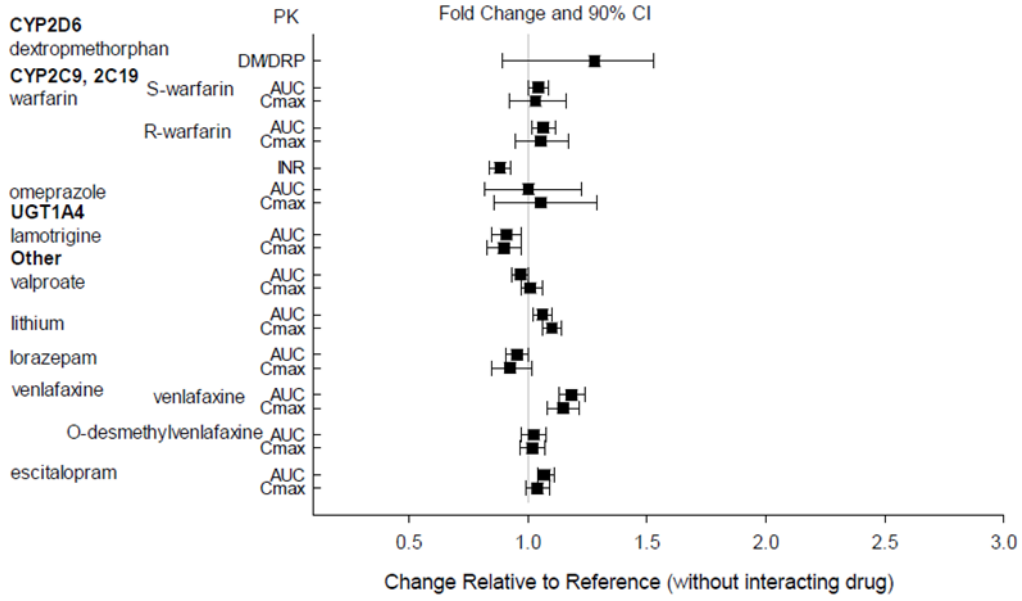
Figure 4 The Effects of Other Drugs on Dehydro-aripiprazole Pharmacokinetics



Based on simulation, a 4.5-fold increase in mean Cmax and AUC values at steady-state is expected when extensive metabolizers of CYP2D6 are administered with both strong CYP2D6 and CYP3A4 inhibitors. A 3-fold increase in mean Cmax and AUC values at steady-state is expected in poor metabolizers of CYP2D6 administered with strong CYP3A4 inhibitors.

The effects of aripiprazole on the exposures of other drugs are summarized in Figure 5.

Figure 5 The Effects of Aripiprazole on Pharmacokinetics of Other Drugs



A population PK analysis in patients with another indication showed that aripiprazole did not change the plasma concentrations of fluoxetine (20 or 40 mg/day), paroxetine CR (37.5 or 50 mg/day), or sertraline (100 or 150 mg/day) dosed to steady-state. The steady-state plasma concentrations of fluoxetine increased by about 18% and norfluoxetine increased by about 36%, and concentrations of paroxetine decreased by about 27%. The steady-state plasma concentrations of sertraline and desmethylsertraline were not substantially changed when these antidepressant therapies were concomitantly used with aripiprazole.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Lifetime carcinogenicity studies were conducted in ICR mice, F344 rats, and Sprague-Dawley (SD) rats. Aripiprazole was administered for 2 years in the diet at doses of 1, 3, 10, and 30 mg/kg/day to ICR mice and 1, 3, and 10 mg/kg/day to F344 rats (0.2, 0.5, 2 and 5 times and 0.3, 1 and 3 times the MRHD of 30 mg/day based on mg/m^2 body surface area, respectively). In addition, SD rats were dosed orally for 2 years at 10, 20, 40, and 60 mg/kg/day, which are 3, 6, 13 and 19 times the MRHD based on mg/m^2 body surface area. Aripiprazole did not induce tumors in male mice or male rats. In female mice, the incidences of pituitary gland adenomas and mammary gland adenocarcinomas and adenoacanthomas were increased at dietary doses of 3 to 30 mg/kg/day (0.5 to 5 times the MRHD). In female rats, the incidence of mammary gland fibroadenomas was increased at a dietary dose of 10 mg/kg/day (3 times the MRHD); and the incidences of adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas were increased at an oral dose of 60 mg/kg/day (19 times the MRHD).

An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be mediated by prolonged dopamine D_2-receptor antagonism and hyperprolactinemia. Serum prolactin was not measured in the aripiprazole carcinogenicity studies. However, increases in serum prolactin levels were observed in female mice in a 13-week dietary study at the doses associated with mammary gland and pituitary tumors. Serum prolactin was not

increased in female rats in 4-week and 13-week dietary studies at the dose associated with mammary gland tumors. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unclear.

Mutagenesis

The mutagenic potential of aripiprazole was tested in the *in vitro* bacterial reverse-mutation assay, the *in vitro* bacterial DNA repair assay, the *in vitro* forward gene mutation assay in mouse lymphoma cells, the *in vitro* chromosomal aberration assay in Chinese hamster lung (CHL) cells, the *in vivo* micronucleus assay in mice, and the unscheduled DNA synthesis assay in rats. Aripiprazole and a metabolite (2,3-DCPP) were clastogenic in the *in vitro* chromosomal aberration assay in CHL cells with and without metabolic activation. The metabolite, 2,3DCPP, increased numerical aberrations in the *in vitro* assay in CHL cells in the absence of metabolic activation. A positive response was obtained in the *in vivo* micronucleus assay in mice; however, the response was due to a mechanism not considered relevant to humans.

Impairment of Fertility

Female rats were treated orally with aripiprazole from 2 weeks prior to mating through gestation day 7 at doses of 2, 6, and 20 mg/kg/day, which are 0.6, 2, and 6 times the MRHD of 30 mg/day based on mg/m^2 body surface area. Estrus cycle irregularities and increased corpora lutea were seen at all doses, but no impairment of fertility was seen. Increased pre-implantation loss was seen at 2 and 6 times the MRHD, and decreased fetal weight was seen at 6 times the MRHD.

Male rats were treated orally with aripiprazole from 9 weeks prior to mating through mating at doses of 20, 40, and 60 mg/kg/day, which are 6, 13, and 19 times the MRHD of 30 mg/day based on mg/m^2 body surface area. Disturbances in spermatogenesis were seen at 19 times the MRHD and prostate atrophy was seen at 13 and 19 times the MRHD without impairment of fertility.

13.2 Animal Toxicology and/or Pharmacology

Aripiprazole produced retinal degeneration in albino rats in a 26-week chronic toxicity study at a dose of 60 mg/kg/day and in a 2-year carcinogenicity study at doses of 40 and 60 mg/kg/day which are 13 and 19 times the MRHD of 30 mg/day based on mg/m^2 body surface area. Evaluation of the retinas of albino mice and of monkeys did not reveal evidence of retinal degeneration. Additional studies to further evaluate the mechanism have not been performed. The relevance of this finding to human risk is unknown.

14 CLINICAL STUDIES

14.1 Overview of Clinical Studies

The efficacy of MEZOFY oral film has been established based on adequate and well-controlled studies of oral aripiprazole in the treatment of schizophrenia in adult and pediatric patients ages 13 to 17 years. The information below describes the results of the adequate and well-controlled studies of oral aripiprazole in patients with schizophrenia.

14.2 Schizophrenia

Adults

The efficacy of aripiprazole in the treatment of schizophrenia was evaluated in five short-term (4-week and 6-week), placebo-controlled trials of acutely relapsed inpatients who predominantly met DSM-III/IV criteria for schizophrenia. Four of the five trials were able to distinguish aripiprazole from placebo, but one study, the smallest, did not. Three of these studies also included an active control group consisting of either risperidone

(one trial) or haloperidol (two trials), but they were not designed to allow for a comparison of aripiprazole and the active comparators.

In the four positive trials for aripiprazole, four primary measures were used for assessing psychiatric signs and symptoms. Efficacy was evaluated using the total score on the Positive and Negative Syndrome Scale (PANSS). The PANSS is a 30-item scale that measures positive symptoms of schizophrenia (7 items), negative symptoms of schizophrenia (7 items), and general psychopathology (16 items), each rated on a scale of 1 (absent) to 7 (extreme); total PANSS scores range from 30 to 210. The Clinical Global Impression (CGI) assessment reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient.

In a 4-week trial (n=414) comparing two fixed doses of aripiprazole (15 or 30 mg/day) to placebo, both doses of aripiprazole were superior to placebo in the PANSS total score (Study 1 in Table 9), PANSS positive subscale, and CGI-severity score. In addition, the 15 mg dose was superior to placebo in the PANSS negative subscale.

In a 4-week trial (n=404) comparing two fixed doses of aripiprazole (20 or 30 mg/day) to placebo, both doses of aripiprazole were superior to placebo in the PANSS total score (Study 2 in Table 9), PANSS positive subscale, PANSS negative subscale, and CGI-severity score.

In a 6-week trial (n=420) comparing three fixed doses of aripiprazole (10, 15, or 20 mg/day) to placebo, all three doses of aripiprazole were superior to placebo in the PANSS total score (Study 3 in Table 9), PANSS positive subscale, and the PANSS negative subscale.

In a 6-week trial (n=367) comparing three fixed doses of aripiprazole (2, 5, or 10 mg/day) to placebo, the 10 mg dose of aripiprazole was superior to placebo in the PANSS total score (Study 4 in Table 9), the primary outcome measure of the study. The 2 and 5 mg doses did not demonstrate superiority to placebo on the primary outcome measure.

Thus, the efficacy of 10, 15, 20, and 30 mg daily doses was established in two studies for each dose. Among these doses, there was no evidence that the higher dose groups offered any advantage over the lowest dose group of these studies.

An examination of population subgroups did not reveal any clear evidence of differential responsiveness on the basis of age, gender, or race.

A longer-term trial enrolled 310 inpatients or outpatients meeting DSM-IV criteria for schizophrenia who were, by history, symptomatically stable on other antipsychotic medications for periods of 3 months or longer. These patients were discontinued from their antipsychotic medications and randomized to aripiprazole 15 mg/day or placebo for up to 26 weeks of observation for relapse. Relapse during the double-blind phase was defined as CGI-Improvement score of ≥5 (minimally worse), scores ≥5 (moderately severe) on the hostility or uncooperativeness items of the PANSS, or ≥20% increase in the PANSS total score. Patients receiving aripiprazole 15 mg/day experienced a significantly longer time to relapse over the subsequent 26 weeks compared to those receiving placebo (Study 5 in Figure 6).

Pediatric Patients (13 to 17 years)

The efficacy of aripiprazole in the treatment of schizophrenia in pediatric patients (13 to 17 years of age) was evaluated in one 6-week, placebo-controlled trial of outpatients who met DSM-IV criteria for schizophrenia and had a PANSS score ≥70 at baseline. In this trial (n=302) comparing two fixed doses of aripiprazole (10 or 30 mg/day) to placebo, aripiprazole was titrated starting from 2 mg/day to the target dose in 5 days in the 10 mg/day treatment arm and in 11 days in the 30 mg/day treatment arm. Both doses of aripiprazole were superior to placebo in the PANSS total score (Study 6 in Table 9), the primary outcome measure of the study. The 30 mg/day dosage was not shown to be more efficacious than the 10 mg/day dose. Although maintenance efficacy

in pediatric patients has not been systematically evaluated, maintenance efficacy can be extrapolated from adult data along with comparisons of aripiprazole pharmacokinetic parameters in adult and pediatric patients.

Table 9 Schizophrenia Studies (Adults and Pediatric Patients 13 to 17 years)

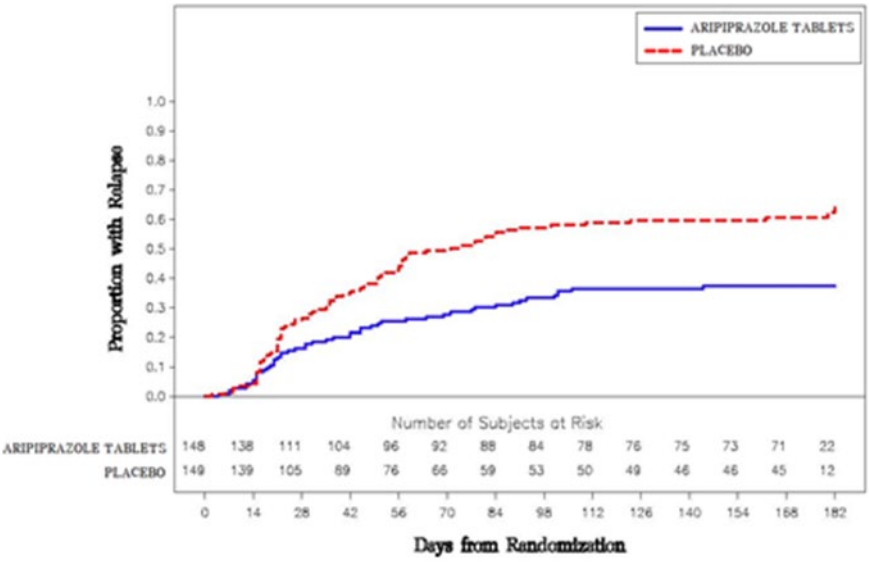
Study Number	Treatment Group	Primary Efficacy Measure: PANSS		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Study 1	Aripiprazole (15 mg/day)*	98.5 (17.2)	-15.5 (2.40)	-12.6 (-18.9, -6.2)
	Aripiprazole (30 mg/day)*	99.0 (19.2)	-11.4 (2.39)	-8.5 (-14.8, -2.1)
	Placebo	100.2 (16.5)	-2.9 (2.36)	--
Study 2	Aripiprazole (20 mg/day)*	92.6 (19.5)	-14.5 (2.23)	-9.6 (-15.4, -3.8)
	Aripiprazole (30 mg/day)*	94.2 (18.5)	-13.9 (2.24)	-9.0 (-14.8, -3.1)
	Placebo	94.3 (18.5)	-5.0 (2.17)	--
Study 3	Aripiprazole (10 mg/day)*	92.7 (19.5)	-15.0 (2.38)	-12.7 (-19.00, -6.41)
	Aripiprazole (15 mg/day)*	93.2 (21.6)	-11.7 (2.38)	-9.4 (-15.71, -3.08)
	Aripiprazole (20 mg/day)*	92.5 (20.9)	-14.4 (2.45)	-12.1 (-18.53, -5.68)
	Placebo	92.3 (21.8)	-2.3 (2.35)	--
Study 4	Aripiprazole (2 mg/day)	90.7 (14.5)	-8.2 (1.90)	-2.9 (-8.29, 2.47)
	Aripiprazole (5 mg/day)	92.0 (12.6)	-10.6 (1.93)	-5.2 (-10.7, 0.19)
	Aripiprazole (10 mg/day)*	90.0 (11.9)	-11.3 (1.88)	-5.9 (-11.3, -0.58
	Placebo	90.8 (13.3)	-5.3 (1.97)	--
Study 6 (Pediatric, 13-17 years)	Aripiprazole (10 mg/day)*	93.6 (15.7)	-26.7 (1.91)	-5.5 (-10.7, -0.21)
	Aripiprazole (30 mg/day)*	94.0 (16.1)	-28.6 (1.92)	-7.4 (-12.7, -2.13)
	Placebo	94.6 (15.6)	-21.2 (1.93)	--

SD = Standard deviation; SE = Standard error; LS Mean = Least-squares mean; CI = Unadjusted confidence interval; PANSS = Positive and Negative Syndrome Scale

[a] Difference (drug minus placebo) in least-squares mean change from baseline

* Doses statistically significantly superior to placebo

Figure 6 Kaplan-Meier Estimation of Cumulative Proportion of Adults with Relapse (Schizophrenia Study 5)



16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

MEZOFY (aripiprazole) oral film is supplied as white film with markings in red edible ink and is available in the presentations listed in Table 10.

Table 10 MEZOFY Presentations

Strength	Film Color/Shape	Markings	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

16.2 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].

17 PATIENT COUNSELING INFORMATION

Advise patient to read the FDA-approved patient labeling (Instructions for Use).

Administration Instructions
Advise patients to keep MEZOFY in the foil pouch until ready to use. Instruct patients to place MEZOFY on top of the tongue where it will dissolve with or without water. Advise patients to swallow MEZOFY after it dissolves completely and do not to chew. If the dosage requires administration of multiple films, the next film can be administered as soon as the prior film has dissolved and been swallowed.

Neuroleptic Malignant Syndrome
Counsel patients about a potentially fatal adverse reaction, Neuroleptic Malignant Syndrome (NMS), that has been reported in association with administration of antipsychotic drugs. Advise patients to contact a healthcare provider or report to the emergency room if they experience signs or symptoms of NMS *[see Warnings and Precautions (5.3)]*.

Tardive Dyskinesia
Counsel patients to notify their health care provider if they notice any movements which they cannot control in their face, tongue, or other body part *[see Warnings and Precautions (5.4)]*.

Metabolic Changes
Educate patients about the risk of metabolic changes, how to recognize symptoms of hyperglycemia and diabetes mellitus, and the need for specific monitoring, including blood glucose, lipids, and weight *[see Warnings and Precautions (5.5)]*.

Pathological Gambling and Other Compulsive Behaviors
Advise patients and their caregivers of the possibility that they may experience compulsive urges to shop, intense urges to gamble, compulsive sexual urges, binge eating and/or other compulsive urges and the inability to control these urges while taking aripiprazole. In some cases, but not all, the urges were reported to have stopped when the dose was reduced or stopped *[see Warnings and Precautions (5.6)]*.

Orthostatic Hypotension and Syncope
Educate patients about the risk of orthostatic hypotension and syncope, especially early in treatment, and also at times of re-initiating treatment *[see Warnings and Precautions (5.7)]*.

Leukopenia/Neutropenia
Advise patients with a pre-existing low WBC or a history of drug induced leukopenia/ neutropenia they should have their CBC monitored while taking MEZOFY *[see Warnings and Precautions (5.9)]*.

Interference with Cognitive and Motor Performance
Caution patients about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that MEZOFY therapy does not affect them adversely *[see Warnings and Precautions (5.11)]*.

Heat Exposure and Dehydration
Educate patients regarding appropriate care in avoiding overheating and dehydration *[see Warnings and Precautions (5.12)]*.

Concomitant Medications
Advise to inform their health care providers of any changes to their current prescription or over-the-counter medications because there is a potential for interactions *[see Drug Interactions (7)]*.

Pregnancy
Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with MEZOFY. Advise patients that MEZOFY used during the third trimester may cause extrapyramidal and/or withdrawal symptoms (agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder) in the neonate *[see Use in Specific Populations (8.1)]*.

Lactation
Advise patients that there is a pregnancy registry that monitors pregnancy outcomes in women exposed to MEZOFY during pregnancy *[see Use in Specific Populations (8.2)]*.

MEZOFY manufactured by

Labtec Company GmbH
Heykenaukamp 10 21147 Hamburg
Germany

Distributed and marketed by

CMG Pharmaceutical Co., Ltd,
Suite 306, 170, Hakdong-ro, Gangnam-gu,
Seoul, 06112, Republic of Korea

MEZOFY is a trademark of CMG Pharmaceutical Co., Ltd.

INSTRUCTIONS FOR USE
MEZOFY™ (meh zoe fye)
(aripiprazole) oral film

This Instructions for Use contains information on how to take MEZOFY.

Figure A

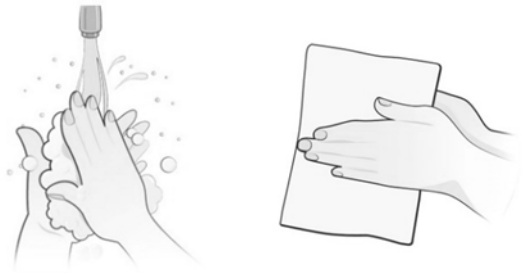
Important Information You Need to Know Before Taking MEZOFY.

- MEZOFY is for oral use only (taken by mouth).
- Do not take or give MEZOFY until you have read and understand this Instructions for Use.
- Each MEZOFY comes in a foil pouch. Keep the MEZOFY in the foil pouch until ready to take or give it.
- Take or give MEZOFY right away after you remove it from the foil pouch.
- Do not chew the film or swallow it whole.
- Do not cut the film.
- Take or give MEZOFY with or without food.
- Check the expiration date printed on the carton and the foil pouch. **Do not** take MEZOFY if it is expired.

Step 1: Preparing to take MEZOFY

- Wash and dry your hands before handling and taking MEZOFY (**see Figure B**)
- Check the dose prescribed by the healthcare provider. Remove the number of pouches from the MEZOFY carton that you need for the prescribed the dose.

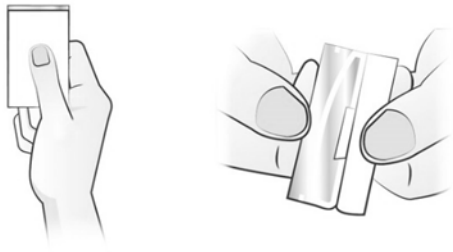
Figure B



Step 2: Opening the MEZOFY foil pouch

- Make sure your hands are completely dry before you open the foil pouch.
- Open the MEZOFY foil pouch by holding each flap at the top of the pouch with both hands and pulling the sides apart (see **Figure C**).
- If you need to take or give more than 1 MEZOFY for the prescribed dose, open only 1 pouch and take or give only 1 film at a time.

Figure C



Step 3: Removing the MEZOFY from the pouch

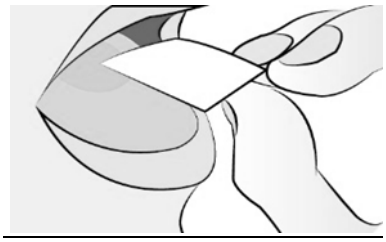
- Make sure your hands are completely dry before removing the film from the foil pouch.
- Carefully remove the MEZOFY from the foil pouch (see **Figure D**).
- Do not cut MEFOZY.

Figure D

Step 4: Placing MEZOFY on the tongue

- Place MEZOFY on top of the tongue. The film will stick to the tongue (See **Figure E**).
- Let the film dissolve completely on the tongue.
  - **Do not swallow the undissolved MEZOFY.**
  - **Do not chew MEZOFY.**

Figure E



Step 5: Swallowing the dissolved MEZOFY

- Swallow MEZOFY **after** it completely dissolves on the tongue.
- You may swallow the dissolved MEZOFY with or without water.
- If you need more than 1 MEZOFY film for the prescribed dose, wait until after the first film has completely dissolved and is swallowed before you take or give another MEZOFY film. Repeat steps 1 through 5 with each film needed to complete the prescribed dose.

Step 6: Wash your hands well with soap and water.

Disposing of MEZOFY

- Throw away (dispose of) any unused or expired MEZOFY in your household trash.
- Throw away the empty pouches in your household trash.

Storing MEZOFY

- Store MEZOFY at room temperature between 68°F to 77°F (20°C to 25°C).
- Do not use MEZOFY after the expiration date on the foil pouch or carton.

Keep MEZOFY and all medicines out of the reach of children.

Manufactured by
Labtec Company GmbH.
Heykenaukamp 10 21147 Hamburg, Germany

Distributed and marketed by
CMG Pharmaceutical Co., Ltd.
Suite 306, 170, Hakdong-ro, Gangnam-gu, Seoul, 06112, Republic of Korea
For more information or support about MEZOFY: Call 82-31-881-7678
This Instructions for Use has been approved by the U.S. Food and Drug Administration. Approved 04/2025