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

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

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS and SUICIDAL THOUGHTS AND BEHAVIORS

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. OPIPZA is not approved for the treatment of patients with dementia-related psychosis. (5.1)**
- **Increased risk of suicidal thinking and behavior in pediatric and young adult patients taking antidepressants. Closely monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors. (5.3)**

----------INDICATIONS AND USAGE----------

OPIPZA is an atypical antipsychotic indicated for:

- treatment of schizophrenia in patients ages 13 years and older (1)
- adjunctive treatment of major depressive disorder (MDD) in adults (1)
- irritability associated with autistic disorder in pediatric patients 6 years and older (1)
- treatment of Tourette's disorder in pediatric patients 6 years and older (1)

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

		Initial Starting Dosage	Recommended Dosage	Maximum Dosage
Schizophrenia (adults) (2.1)		10 to 15 mg/day	10 to 15 mg/day	30 mg/day
Schizophrenia – (pediatric patients 13 years and older) (2.1)		2 mg/day	10 mg/day	30 mg/day
Adjunctive Treatment of MDD (adults) (2.2)		2 to 5 mg/day	5 to 10 mg/day	15 mg/day
Irritability associated with autistic disorder (pediatric patients 6 years and older) (2.3)		2 mg/day	5 to 10 mg/day	15 mg/day
Tourette's disorder (pediatric patients 6 years and older) (2.4)	< 50 kg	2 mg/day	5 mg/day	10 mg/day
	≥ 50 kg	2 mg/day	10 mg/day	20 mg/day

- Dissolve on top of tongue once daily with or without food (2.4)
- Known CYP2D6 poor metabolizers: Administer half of the recommended dosage (2.6)

----------DOSAGE FORMS AND STRENGTHS----------

- Oral Film: 2 mg, 5 mg, 10 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 (5.4)
- Tardive Dyskinesia: Discontinue if clinically appropriate (5.5)
- Metabolic Changes: Monitor for hyperglycemia/diabetes mellitus, dyslipidemia, and weight gain (5.6)
- Pathological Gambling and Other Compulsive Behaviors: Consider dose reduction or discontinuation (5.7)
- Orthostatic Hypotension and Syncope: Monitor heart rate and blood pressure and caution patients with known cardiovascular or cerebrovascular disease, and risk of dehydration or syncope (5.8)
- Leukopenia, Neutropenia, and Agranulocytosis: Perform complete blood cell counts (CBC) in patients with a history of a clinically significant low white blood cell count (WBC) or a history of leukopenia or neutropenia. Consider discontinuing OPIPZA if clinically significant decline in WBC in the absence of other causative factors (5.10)
- Seizures: Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold (5.11)
- Potential for Cognitive and Motor Impairment: Use caution when operating machinery (5.12)

----------ADVERSE REACTIONS----------

Commonly observed adverse reactions (incidence ≥5% and at least twice that for placebo) were (6.1):

- Schizophrenia (adults): akathisia
- Schizophrenia (pediatric patients 13 to 17 years): extrapyramidal disorder, somnolence, and tremor
- Adjunctive treatment of MDD (adults): akathisia, restlessness, insomnia, constipation, fatigue, and blurred vision
- Irritability associated with autistic disorder (pediatric 6 years and older): sedation, fatigue, vomiting, somnolence, tremor, pyrexia, drooling, decreased appetite, salivary hypersecretion, extrapyramidal disorder, and lethargy
- Tourette's disorder (pediatric patients 6 years and older): sedation, somnolence, nausea, headache, nasopharyngitis, fatigue, increased appetite

To report SUSPECTED ADVERSE REACTIONS, contact Carwin Pharmaceutical Associates at 1-877-676-0778 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Dosage adjustments for patients taking CYP2D6 inhibitors, CYP3A4 inhibitors, or CYP3A4 inducers (7.1):

Factors	Dosage Recommendations
CYP2D6 Poor Metabolizers taking strong CYP3A4 inhibitors (7.1)	Administer a quarter of recommended dosage (2.6)
Strong CYP2D6 **or** CYP3A4 inhibitors (7.1)	Administer half of recommended dosage (2.6)
Strong CYP2D6 and CYP3A4 inhibitors (7.1)	Administer a quarter of recommended dosage (2.6)
Strong CYP3A4 inducers (7.1)	Double the recommended dosage over 1 to 2 weeks (2.6)

----------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 Medication Guide.

Revised: 8/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS and SUICIDAL THOUGHTS AND BEHAVIORS

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. OPIPZA is not approved for the treatment of patients with dementia-related psychosis *[see Warnings and Precautions (5.1)]*.

Suicidal Thoughts and Behaviors

Antidepressants increased the risk of suicidal thoughts and behavior in pediatric and young adult patients in short-term studies. Closely monitor all antidepressant-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors *[see Warnings and Precautions (5.3)]*.

1 INDICATIONS AND USAGE

OPIPZA is indicated for the:

- treatment of schizophrenia in patients ages 13 years and older
- adjunctive treatment of major depressive disorder (MDD) in adults
- treatment of irritability associated with autistic disorder in pediatric patients 6 years and older
- treatment of Tourette's disorder in pediatric patients 6 years and older

2 DOSAGE AND ADMINISTRATION

2.1 Schizophrenia in Patients 13 Years and Older

Adults

The recommended starting and target dosage of OPIPZA for the treatment of schizophrenia in adults is 10 mg or 15 mg once daily. Aripiprazole has been systematically evaluated and shown to be effective in a dose range of 10 mg to 30 mg per day; however, doses higher than 10 mg or 15 mg per day were not more effective than 10 mg or 15 mg per day. Dosage increases should generally not be made before 2 weeks, the time needed to achieve steady-state *[see Clinical Studies (14.2)]*.

Pediatric Patients Ages 13 Years and Older

The recommended starting dosage of OPIPZA for the treatment of schizophrenia in pediatric patients 13 years and older is 2 mg once daily. The recommended target dosage of OPIPZA is 10 mg once daily. Aripiprazole was studied in pediatric patients 13 to 17 years of age with schizophrenia at daily dosages of 10 mg and 30 mg. The starting daily dosage in these patients was 2 mg, which was titrated to 5 mg after 2 days and to the target dose of 10 mg after 2 additional days. Subsequent dose increases should be administered in 5 mg increments. The 30 mg per day dosage was not shown to be more efficacious than the 10 mg per day dosage.

2.2 Adjunctive Treatment of Major Depressive Disorder in Adults

The recommended starting dosage for OPIPZA as adjunctive treatment of MDD in adults already taking an antidepressant is 2 mg to 5 mg once daily. The recommended dosage range is 2 mg to 15 mg once daily. Dosage adjustments of up to 5 mg per day should occur gradually, at intervals of no less than one week *[see Clinical Studies (14.3)]*. Patients should be periodically reassessed to determine the continued need for maintenance treatment.

2.3 Irritability Associated with Autistic Disorder in Pediatric Patients 6 years and Older

The recommended dosage range for the treatment of pediatric patients 6 to 17 years with irritability associated with autistic disorder is 5 mg to 15 mg once daily.

Dosing should be initiated at 2 mg once daily. The dose should be increased to 5 mg per day, with subsequent increases to 10 mg or 15 mg per day if needed. Dose adjustments of up to 5 mg per day should occur gradually, at intervals of no less than one week *[see Clinical Studies (14.4)]*. Patients should be periodically reassessed to determine the continued need for maintenance treatment.

2.4 Tourette's Disorder in Pediatric Patients 6 years and Older

The recommended dosage range for treatment of Tourette's disorder in pediatric patients 6 years and older is 5 mg to 20 mg once daily.

For patients weighing less than 50 kg, dosage should be initiated at 2 mg once daily with a target dosage of 5 mg once daily after 2 days. The dosage can be increased to 10 mg once daily in patients who do not achieve optimal control of tics. Dosage adjustments should occur gradually at intervals of no less than one week.

For patients weighing 50 kg or more, dosing should be initiated at 2 mg once daily for 2 days, and then increased to 5 mg once daily for 5 days, with a target dosage of 10 mg once daily on Day 8. The dosage can be increased up to 20 mg once daily for patients who do not achieve optimal control of tics. Dosage adjustments should occur gradually in increments of 5 mg per day at intervals of no less than one week *[see Clinical Studies (14.5)]*.

Patients should be periodically reassessed to determine the continued need for maintenance treatment.

2.5 Important Administration Information

Instruct patients and/or caregivers to read the "Instruction for Use" carefully for complete directions on how to properly dose and administer OPIPZA.

Administer OPIPZA orally with or without food *[see Clinical Pharmacology (12.3)]*.

Apply OPIPZA on top of the tongue where it dissolves in saliva and can be swallowed in a normal manner without the need for water or other liquids.

The patient should refrain from chewing the film and should not swallow an undissolved film. Do not cut or split OPIPZA.

Administer only one oral film at a time. If an additional film is needed to complete the dosage, administer after the previous film has completely dissolved.

2.6 Dosage Recommendations and Modifications for Cytochrome P450 Considerations

Dosage recommendations and modifications for patients who are known CYP2D6 poor metabolizers and/or in patients taking concomitant CYP3A4 inhibitors, CYP2D6 inhibitors, or strong CYP3A4 inducers are described in Table 1.

When the coadministered drug is withdrawn from the combination therapy, Aripiprazole Oral Film dosage should be adjusted to its previous dose. When the coadministered CYP3A4 inducer is withdrawn, Aripiprazole Oral Film dosage should be reduced to the previous dose over 1 to 2 weeks. 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 dosing may be reduced to one-quarter (25%) of the recommended dose initially and then adjusted to achieve clinical response *[see Dosage and Administration (2.5)]*.

Table 1: Dosage Recommendations and Modifications for OPIPZA in Patients Who are Known CYP2D6 Poor Metabolizers and in Patients Taking Concomitant CYP2D6 Inhibitors and/or 3A4 Inhibitors, CYP3A4 Inducers

Patient Population	Dosage Recommendations and Modifications for OPIPZA
CYP2D6 Poor Metabolizers	
Known CYP2D6 Poor Metabolizers	Administer half of the recommended dose
Known CYP2D6 Poor Metabolizers taking concomitant strong CYP3A4 inhibitors	Administer a quarter of the recommended dose
Patients Taking OPIPZA with CYP2D6 Inhibitors and/or CYP3A4 Inhibitors, CYP3A4 Inducers	
Concomitant use of OPIPZA with strong CYP2D6 **or** CYP3A4 inhibitors	Administer half of the recommended dose
Concomitant use of OPIPZA with strong CYP2D6 **and** CYP3A4 inhibitors	Administer a quarter of the recommended dose
Concomitant use of OPIPZA with strong CYP3A4 inducers	Double the recommended dose over 1 to 2 weeks

When adjunctive OPIPZA is administered to patients with major depressive disorder, OPIPZA should be administered without dosage adjustment as specified in *Dosage and Administration (2.2)*.

3 DOSAGE FORMS AND STRENGTHS

OPIPZA is a rectangular white film in strengths of 2 mg (1 cm by 1.2 cm), 5 mg (2 cm by 1.5 cm), and 10 mg (2 cm by 3 cm) containing the markings A2, A5, and A10, respectively.

4 CONTRAINDICATIONS

OPIPZA is contraindicated in patients with a history of a hypersensitivity to aripiprazole. Hypersensitivity reactions ranging from pruritus/urticaria to anaphylaxis have been reported in patients receiving aripiprazole *[see Adverse Reactions (6.1)]*.

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.

OPIPZA is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning and Warnings and Precautions (5.2)]*

5.2 Cerebrovascular Adverse Reactions, 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 reactions (e.g., stroke, transient ischemic attack), including fatalities, in aripiprazole-treated patients (mean age: 84 years; range: 78 to 88 years). In the fixed-dose study, there was a statistically significant dose response relationship for cerebrovascular adverse reactions in patients treated with aripiprazole. OPIPZA is not approved for the treatment of patients with dementia-related psychosis *[see Warnings and Precautions (5.1)]*.

5.3 Suicidal Thoughts and Behaviors in Adolescents and Young Adults

In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients and 4,500 pediatric patients, the incidence of suicidal thoughts and behaviors in antidepressant-treated patients age 24 years and younger was greater than in placebo-treated patients. There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied. There were differences in absolute risk of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with MDD. The drug-placebo differences in the number of cases of suicidal thoughts and behaviors per 1,000 patients treated are provided in Table 2.

Table 2: Risk Differences of the Number of Patients of Suicidal Thoughts and Behavior in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric* and Adult Patients

Age Range	Drug-Placebo Difference in Number of Patients of Suicidal Thoughts or Behaviors per 1,000 Patients Treated*
	Increases Compared to Placebo
<18 years old	14 additional patients
18 to 24 years old	5 additional patients
	Decreases Compared to Placebo
25 to 64 years old	1 fewer patient
≥65 years old	6 fewer patient

*OPIPZA is not approved in pediatric patients with MDD.

It is unknown whether the risk of suicidal thoughts and behaviors in children, adolescents, and young adults extends to longer-term use, i.e., beyond four months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with MDD that antidepressants delay the recurrence of depression and that depression itself is a risk factor for suicidal thoughts and behaviors.

Monitor all antidepressant-treated patients for any indication for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy, and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing OPIPZA, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors. It should be noted that OPIPZA is not approved for use in treating depression in the pediatric population.

5.4 Neuroleptic Malignant Syndrome (NMS)

Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex has been reported with 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, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

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

5.5 Tardive Dyskinesia

Tardive dyskinesia, a syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients will 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 appear to increase as the duration of treatment and the total cumulative dose increases. However, the syndrome can develop after relatively brief treatment periods at low doses. It may also occur after discontinuation of treatment.

Tardive dyskinesia may remit, partially or completely, if antipsychotic treatment is discontinued. Antipsychotic treatment, itself may suppress (or partially suppress) the signs and symptoms of the syndrome and 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, OPIPZA 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 who suffer from a chronic illness that (1) 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, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

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

5.6 Metabolic Changes

Atypical antipsychotic drugs have been associated with metabolic changes that include hyperglycemia/diabetes mellitus, dyslipidemia, and body weight gain. While 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 diabetic ketoacidosis or hyperosmolar coma or death, have 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)]*. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of hyperglycemia-related adverse reactions in patients treated with the atypical antipsychotics.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics, including OPIPZA, should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g.,

obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the atypical antipsychotic drug.

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=1,057) was not significantly different than in placebo-treated patients (+2.5 mg/dL; median exposure 22 days; N=799). Table 3 shows the proportion of aripiprazole-treated patients with normal and borderline fasting glucose at baseline (median exposure 25 days) that had high fasting glucose measurements compared to placebo-treated patients (median exposure 22 days).

Table 3: Changes in Fasting Glucose from Placebo-Controlled Monotherapy Trials in Adults

	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].

The mean change in fasting glucose in adjunctive trials of aripiprazole-treated patients with major depressive disorder (+0.7 mg/dL; median exposure 42 days; N=241) was not significantly different than in placebo-treated patients (+0.8 mg/dL; median exposure 42 days; N=246). Table 4 shows the proportion of adult patients with changes in fasting glucose levels from two placebo-controlled, adjunctive trials (median exposure 42 days) in patients with major depressive disorder.

Table 4: Changes in Fasting Glucose from Placebo-Controlled Adjunctive Trials in Adults with Major Depressive Disorder

	Category Change (at least once) from Baseline	Treatment Arm	n/N	%
Fasting Glucose	Normal to High (<100 mg/dL to ≥126 mg/dL)	Aripiprazole	2/201	1.0
		Placebo	2/204	1.0
	Borderline to High (≥100 mg/dL and <126 mg/dL to ≥126 mg/dL)	Aripiprazole	4/34	11.8
		Placebo	3/37	8.1

Pediatric Patients 13 Years and Older

In an analysis of two placebo-controlled trials in pediatric patients 13 to 17 years with schizophrenia and pediatric patients 10 to 17 years with 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).

In an analysis of two placebo-controlled trials in pediatric patients 6 to 17 years with irritability associated with autistic disorder (6 to 17 years) with median exposure of 56 days, the mean change in fasting glucose in aripiprazole-treated patients (–0.2 mg/dL; N=83) was not significantly different than in placebo-treated patients (–0.6 mg/dL; N=33).

In an analysis of two placebo-controlled trials in pediatric patients 6 to 18 years with Tourette's disorder with median exposure of 57 days, the mean change in fasting glucose in aripiprazole-treated patients (0.79 mg/dL; N=90) was not significantly different than in placebo-treated patients (–1.66 mg/dL; N=58).

Table 5 shows the proportion of patients with changes in fasting glucose levels from the pooled pediatric patients (13 to 17 years) with schizophrenia and pediatric patients (10 to 17 years) with another indication (median exposure of 42 to 43 days), from two placebo-controlled trials in pediatric patients (6 to 17 years) with irritability associated with autistic disorder (median exposure of 56 days), and from the two placebo-controlled trials in pediatric patients (6 to 18 years) with Tourette's disorder (median exposure 57 days).

Table 5: Changes in Fasting Glucose from Placebo-Controlled Trials in Pediatric Patients 6 to 17 Years

Category Change (at least once) from Baseline	Indication	Treatment Arm	n/N	%
Fasting Glucose Normal to High (<100 mg/dL to ≥126 mg/dL)	Pooled Schizophrenia and another indication	Aripiprazole	2/236	0.8
		Placebo	2/110	1.8
	Irritability Associated with Autistic Disorder	Aripiprazole	0/73	0
		Placebo	0/32	0
	Tourette's Disorder	Aripiprazole	3/88	3.4
		Placebo	1/58	1.7
Fasting Glucose Borderline to High (≥100 mg/dL and <126 mg/dL to ≥126 mg/dL)	Pooled Schizophrenia and another indication	Aripiprazole	1/22	4.5
		Placebo	0/12	0
	Irritability Associated with Autistic Disorder	Aripiprazole	0/9	0
		Placebo	0/1	0
	Tourette's Disorder	Aripiprazole	0/11	0
		Placebo	0/4	0

In the pooled trials that enrolled pediatric patients 13 to 17 years with schizophrenia and another indication, the mean change in fasting glucose in aripiprazole-treated patients at 12 weeks 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-treated patients and patients treated with placebo 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 6 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 6: 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	34/1,357	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	121/1,066	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.

Table 7 shows the proportion of patients with changes in total cholesterol (fasting/nonfasting), fasting triglycerides, fasting LDL cholesterol, and HDL cholesterol from two placebo-controlled adjunctive trials in adults with major depressive disorder (median exposure 42 days).

Table 7: Changes in Blood Lipid Parameters from Placebo-Controlled Adjunctive Trials in Adults with Major Depressive Disorder

	Treatment Arm	n/N	%
Total Cholesterol Normal to High (<200 mg/dL to ≥240 mg/dL)	Aripiprazole	3/139	2.2
	Placebo	7/135	5.2
Fasting Triglycerides Normal to High (<150 mg/dL to ≥200 mg/dL)	Aripiprazole	14/145	9.7
	Placebo	6/147	4.1
Fasting LDL Cholesterol Normal to High (<100 mg/dL to ≥160 mg/dL)	Aripiprazole	0/54	0
	Placebo	0/73	0
HDL Cholesterol Normal to Low (≥40 mg/dL to <40 mg/dL)	Aripiprazole	17/318	5.3
	Placebo	10/286	3.5

Pediatric Patients 10 to 17 Years

Table 8 shows the proportion of pediatric patients (13 to 17 years) with schizophrenia and pediatric patients (10 to 17 years) with another indication with changes in total cholesterol and HDL cholesterol (pooled from two placebo-controlled

trials; median exposure 42 to 43 days) and fasting triglycerides (pooled from two placebo-controlled trials; median exposure 42 to 44 days).

Table 8: Changes in Blood Lipid Parameters from Placebo-Controlled Monotherapy Trials in Pediatric Patients 10 to 17 Years with Schizophrenia and another Indication

	Treatment Arm	n/N	%
Total Cholesterol Normal to High (<170 mg/dL to ≥200 mg/dL)	Aripiprazole	3/220	1.4
	Placebo	0/116	0
Fasting Triglycerides Normal to High (<150 mg/dL to ≥200 mg/dL)	Aripiprazole	7/187	3.7
	Placebo	4/85	4.7
HDL Cholesterol Normal to Low (≥40 mg/dL to <40 mg/dL)	Aripiprazole	27/236	11.4
	Placebo	22/109	20.2

In monotherapy trials of pediatric patients with schizophrenia and pediatric patients with 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.

Table 9 shows the proportion of patients with changes in total cholesterol (fasting/nonfasting) and fasting triglycerides (median exposure 56 days) and HDL cholesterol (median exposure 55 to 56 days) from two placebo-controlled trials in pediatric patients (6 to 17 years) with irritability associated with autistic disorder.

Table 9: Changes in Blood Lipid Parameters from Placebo-Controlled Trials in Pediatric Patients 6 to 17 Years with Autistic Disorder

	Treatment Arm	n/N	%
Total Cholesterol Normal to High (<170 mg/dL to ≥200 mg/dL)	Aripiprazole	1/95	1.1
	Placebo	0/34	0
Fasting Triglycerides Normal to High (<150 mg/dL to ≥200 mg/dL)	Aripiprazole	0/75	0
	Placebo	0/30	0
HDL Cholesterol Normal to Low (≥40 mg/dL to <40 mg/dL)	Aripiprazole	9/107	8.4
	Placebo	5/49	10.2

Table 10 shows the proportion of patients with changes in total cholesterol (fasting/nonfasting) and fasting triglycerides (median exposure 57 days) and HDL cholesterol (median exposure 57 days) from two placebo-controlled trials in pediatric patients (6 to 18 years) with Tourette's disorder.

Table 10: Changes in Blood Lipid Parameters from Placebo-Controlled Trials in Pediatric Patients 6 to 18 Years with Tourette's Disorder

	Treatment Arm	n/N	%
Total Cholesterol Normal to High (<170 mg/dL to ⩾200 mg/dL)	Aripiprazole	1/85	1.2
	Placebo	0/46	0
Fasting Triglycerides Normal to High (<150 mg/dL to ⩾200 mg/dL)	Aripiprazole	5/94	5.3
	Placebo	2/55	3.6
HDL Cholesterol Normal to Low (⩾40 mg/dL to <40 mg/dL)	Aripiprazole	4/108	3.7
	Placebo	2/67	3.0

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 patients treated with placebo patients.

In the trials adding aripiprazole to antidepressants, patients first received 8 weeks of antidepressant treatment followed by 6 weeks of adjunctive aripiprazole or placebo in addition to their ongoing antidepressant 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 11 shows the percentage of adult patients with weight gain ≥7% of body weight by indication.

Table 11: Percentage of Patients from Placebo-Controlled Trials in Adults with Weight Gain ≥7% of Body Weight

	Indication	Treatment Arm	N	Patients n (%)
Weight gain ≥7% of body weight	Schizophrenia*	Aripiprazole	852	69 (8.1)
		Placebo	379	12 (3.2)
	Another indication†	Aripiprazole	719	16 (2.2)
		Placebo	598	16 (2.7)
	Major Depressive Disorder (Adjunctive Therapy)‡	Aripiprazole	347	18 (5.2)
		Placebo	330	2 (0.6)

*4 to 6 weeks duration;†3 weeks duration; ‡6 weeks duration.

Pediatric Patients 6 to 17 Years

In an analysis of two placebo-controlled trials in pediatric patients 13 to 17 years with schizophrenia and pediatric patients 10 to 17 years with another indication 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 patients treated with placebo.

In two short-term, placebo-controlled trials in pediatric patients (6 to 17 years) with irritability associated with autistic disorder 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 pediatric patients treated with placebo.

In two short-term, placebo-controlled trials in pediatric patients 6 to 18 years with Tourette's disorder with median exposure of 57 days, the mean change in body weight in aripiprazole-treated patients was +1.5 kg (n=105) compared to +0.4 kg (n=66) in patients treated with placebo.

Table 12 shows the percentage of pediatric patients (6 to 17 years) with weight gain ≥7% of body weight by indication.

Table 12: Percentage of Patients from Placebo-Controlled Monotherapy Trials in Pediatric Patients 6 to 17 Years with Weight Gain ≥7% of Body Weight

	Indication	Treatment Arm	N	Patients n (%)
Weight gain ≥7% of body weight	Pooled Schizophrenia and another indication*	Aripiprazole	381	20 (5.2)
		Placebo	187	3 (1.6)
	Irritability Associated with Autistic Disorder†	Aripiprazole	209	55 (26.3)
		Placebo	98	7 (7.1)
	Tourette's Disorder‡	Aripiprazole	105	21 (20.0)
		Placebo	66	5 (7.6)

*4 to 6 weeks duration; †8 weeks duration; ‡8 to 10 weeks duration.

In an open-label trial that enrolled patients from the two placebo-controlled trials of pediatric patients 13 to 17 years with schizophrenia and pediatric patients 10 to 17 years with another indication, 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 and adolescents 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.

In an open-label trial that enrolled patients from two short-term, placebo-controlled trials, pediatric patients 6 to 17 years with irritability associated with autistic disorder, as well as de novo patients, 60.3% (199/330) completed one year of therapy with aripiprazole. The mean change in weight z-score was 0.26 SDs for patients receiving >9 months of treatment.

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

5.7 Pathological Gambling and Other Compulsive Behaviors

Post-marketing case reports 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 aripiprazole. 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.

5.8 Orthostatic Hypotension and Syncope

OPIPZA may cause orthostatic hypotension, perhaps due to its α_1-adrenergic receptor antagonism. The incidence of orthostatic hypotension-associated events from short-term, placebo-controlled trials of adult patients treated with another oral aripiprazole product (n=2,467) 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 18 years of age (n=732) on another oral aripiprazole product included orthostatic hypotension (0.5%, 0%), postural dizziness (0.4%, 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 another oral aripiprazole product was not meaningfully different from placebo (aripiprazole incidence, placebo incidence): in adults treated with another oral aripiprazole product (4%, 2%), in pediatric patients treated with another oral aripiprazole-product aged 6 to 18 years (0.4%, 1%).

Use OPIPZA 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)]*. Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension.

5.9 Falls

Antipsychotics, including OPIPZA, 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 recurrently for patients on long-term antipsychotic therapy.

5.10 Leukopenia, Neutropenia, and Agranulocytosis

In clinical trials and/or postmarketing experience, events of leukopenia and neutropenia have been reported temporally related to antipsychotic agents, including aripiprazole. Agranulocytosis has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC)/absolute neutrophil count (ANC) and history of drug-induced leukopenia/neutropenia. In patients with a history of a clinically significant low WBC/ANC or drug-induced leukopenia/neutropenia, perform a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of OPIPZA 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 OPIPZA in patients with severe neutropenia (absolute neutrophil count <1,000/mm^3) and follow their WBC counts until recovery.

5.11 Seizures

In short-term, placebo-controlled trials, patients with a history of seizures excluded seizures/convulsions occurred in 0.1% (3/2,467) of undiagnosed adult patients and in 0.1% (1/732) of pediatric patients (6 to 18 years) treated with another oral aripiprazole product.

As with other antipsychotic drugs, use OPIPZA cautiously 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 a population of 65 years or older.

5.12 Potential for Cognitive and Motor Impairment

OPIPZA, like other antipsychotics, may have the potential to impair judgment, thinking, or motor skills. For example, in short-term, placebo-controlled trials of another oral aripiprazole product, somnolence (including sedation) was reported as follows (aripiprazole incidence, placebo incidence): in adult patients (n=2,467) treated with oral aripiprazole (11%, 6%), in pediatric patients ages 6 to 17 years (n=611) (24%, 6%). Somnolence (including sedation) led to discontinuation in 0.3% (8/2,467) of adult patients and 3% (20/732) of pediatric patients (6 to 18 years) on oral aripiprazole in short-term, placebo-controlled trials.

Patients should be cautioned about operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that therapy with OPIPZA does not affect them adversely.

5.13 Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing OPIPZA for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, (e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration) *[see Adverse Reactions (6.2)]*.

5.14 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use, including aripiprazole. OPIPZA and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia *[see Warnings and Precautions (5.1)* and *Adverse Reactions (6.2)]*.

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 Reactions, Including Stroke in Elderly Patients with Dementia-Related Psychosis *[see Warnings and Precautions (5.2)]*
- Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults *[see Boxed Warning and Warnings and Precautions (5.3)]*
- Neuroleptic Malignant Syndrome (NMS) *[see Warnings and Precautions (5.4)]*
- Tardive Dyskinesia *[see Warnings and Precautions (5.5)]*
- Metabolic Changes *[see Warnings and Precautions (5.6)]*
- Pathological Gambling and Other Compulsive Behaviors *[see Warnings and Precautions (5.7)]*
- Orthostatic Hypotension *[see Warnings and Precautions (5.8)]*
- Falls *[see Warnings and Precautions (5.9)]*

- Leukopenia, Neutropenia, and Agranulocytosis *[see Warnings and Precautions (5.10)]*
- Seizures *[see Warnings and Precautions (5.11)]*
- Potential for Cognitive and Motor Impairment *[see Warnings and Precautions (5.12)]*
- Body Temperature Regulation *[see Warnings and Precautions (5.13)]*
- Dysphagia *[see Warnings and Precautions (5.14)]*

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 OPIPZA for the treatment of adults with schizophrenia in patients 13 years and older, adjunctive treatment of adults with MDD, treatment of irritability associated with autistic disorder in pediatric patients 6 years and older, and treatment of Tourette's disorder in pediatric patients 6 years and older is based on adequate and well-controlled studies of another oral aripiprazole product. Below is a display of adverse reactions of oral aripiprazole (referred to as "aripiprazole" in this section) from those adequate and well-controlled studies.

Aripiprazole has been evaluated for safety in 13,543 adult patients who participated in multiple-dose, clinical trials in schizophrenia, major depressive disorder, and other indications, and who had approximately 7,619 patient-years of exposure to oral aripiprazole. A total of 3,390 patients were treated with oral aripiprazole for at least 180 days and 1,933 patients treated with oral aripiprazole had at least one year of exposure.

Aripiprazole has been evaluated for safety in 1,686 pediatric patients (6 to 18 years) who participated in multiple-dose, clinical trials in schizophrenia, autistic disorder, Tourette's disorder or other indications who had approximately 1,342 patient-years of exposure to oral aripiprazole. A total of 959 pediatric patients were treated with oral aripiprazole for at least 180 days and 556 pediatric patients treated with oral aripiprazole had at least one year of exposure.

The conditions and duration of treatment with aripiprazole (monotherapy and adjunctive therapy with antidepressants or mood stabilizers) included (in overlapping categories) double-blind, comparative and noncomparative open-label studies, inpatient and outpatient studies, fixed- and flexible-dose studies, and short- and longer-term exposure.

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

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

Adverse Reactions in 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/day to 30 mg/day.

The commonly observed 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 13 enumerates the pooled incidence, rounded to the nearest percent, 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 13: Adverse Reactions in Short-Term, Placebo-Controlled Trials in Adult Patients Treated with Oral Aripiprazole

Preferred Term	Percentage of Patients Reporting Reaction*	
	Aripiprazole (n=1,843)	Placebo (n=1,166)
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

*Adverse reactions reported by at least 2% of patients treated with oral aripiprazole, except adverse reactions which had 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.

Adverse Reactions in 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 to 30 mg/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.

Commonly observed 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 Autistic Disorder

The following findings are based on two 8 week, placebo-controlled trials in which oral aripiprazole was administered in doses of 2 to 15 mg/day.

The incidence of discontinuation due to adverse reactions between aripiprazole-treated and placebo-treated pediatric patients (6 to 17 years) was 10% and 8%, respectively.

Commonly observed adverse reactions associated with the use of aripiprazole in pediatric patients (6 to 17 years) with autistic disorder (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) are shown in Table 14.

Table 14: Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials of Pediatric Patients (6 to 17 years) with Autistic Disorder Treated with Oral Aripiprazole

	Percentage of Patients Reporting Reaction	
Preferred Term	**Aripiprazole (n=212)**	**Placebo (n=101)**
Sedation	21	4
Fatigue	17	2
Vomiting	14	7
Somnolence	10	4
Tremor	10	0
Pyrexia	9	1
Drooling	9	0
Decreased Appetite	7	2
Salivary Hypersecretion	6	1
Extrapyramidal Disorder	6	0
Lethargy	5	0

Adverse Reactions in Pediatric Patients (6 to 18 years) with Tourette's Disorder

The following findings are based on one 8 week and one 10 week, placebo-controlled trials in which oral aripiprazole was administered in doses of 2 to 20 mg/day.

The incidence of discontinuation due to adverse reactions between aripiprazole-treated and placebo-treated pediatric patients (6 to 18 years) was 7% and 1%, respectively.

Commonly observed adverse reactions associated with the use of aripiprazole in pediatric patients (6 to 18 years) with Tourette's disorder (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) are shown in Table 15.

Table 15: Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials of Pediatric Patients (6 to 18 years) with Tourette's Disorder Treated with Oral Aripiprazole

	Percentage of Patients Reporting Reaction	
Preferred Term	**Aripiprazole (n=121)**	**Placebo (n=72)**
Sedation	13	6
Somnolence	13	1
Nausea	11	4
Headache	10	3
Nasopharyngitis	9	0
Fatigue	8	0
Increased Appetite	7	1

Table 16 enumerates the pooled incidence, rounded to the nearest percent, of adverse reactions that occurred during acute therapy (up to 6 weeks in schizophrenia, up to 4 weeks in another indication, up to 8 weeks in autistic disorder, and up to 10 weeks in Tourette’s disorder), including only those reactions that occurred in 2% 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.

Table 16: Adverse Reactions in Short-Term, Placebo-Controlled Trials of Pediatric Patients (6 to 18 years) Treated with Oral Aripiprazole

	Percentage of Patients Reporting Reaction*	
Preferred Term	**Aripiprazole (n=732)**	**Placebo (n=370)**
Eye Disorders		
Blurred Vision	3	0
Gastrointestinal Disorders		
Abdominal Discomfort	2	1
Vomiting	8	7
Nausea	8	4
Diarrhea	4	3
Salivary Hypersecretion	4	1
Abdominal Pain Upper	3	2

Constipation	2	2
General Disorders and Administration Site Conditions		
Fatigue	10	2
Pyrexia	4	1
Irritability	2	1
Asthenia	2	1
Infections and Infestations		
Nasopharyngitis	6	3
Investigations		
Weight Increased	3	1
Metabolism and Nutrition Disorders		
Increased Appetite	7	3
Decreased Appetite	5	4
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal Stiffness	2	1
Muscle Rigidity	2	1
Nervous System Disorders		
Somnolence	16	4
Headache	12	10
Sedation	9	2
Tremor	9	1
Extrapyramidal Disorder	6	1
Akathisia	6	4
Drooling	3	0
Lethargy	3	0
Dizziness	3	2
Dystonia	2	1
Respiratory, Thoracic, and Mediastinal Disorders		
Epistaxis	2	1
Skin and Subcutaneous Tissue Disorders		
Rash	2	1

*Adverse reactions reported by at least 2% of pediatric patients treated with oral aripiprazole, except adverse reactions which had an incidence equal to or less than placebo.

Adverse Reactions in Adult Patients Receiving Aripiprazole as Adjunctive Treatment of Major Depressive Disorder

The following findings are based on a pool of two placebo-controlled trials of patients with major depressive disorder in which aripiprazole was administered at doses of 2 to 20 mg as adjunctive treatment to continued antidepressant therapy.

The incidence of discontinuation due to adverse reactions was 6% for adjunctive aripiprazole-treated patients and 2% for adjunctive placebo-treated patients.

The commonly observed adverse reactions associated with the use of adjunctive aripiprazole in patients with major depressive disorder (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) were: akathisia, restlessness, insomnia, constipation, fatigue, and blurred vision.

Table 17 enumerates the pooled incidence, rounded to the nearest percent, of adverse reactions that occurred during acute therapy (up to 6 weeks), including only those adverse reactions that occurred in 2% or more of patients treated with adjunctive aripiprazole (doses ≥2 mg/day) and for which the incidence in patients treated with adjunctive aripiprazole was greater than the incidence in patients treated with adjunctive placebo in the combined dataset.

Table 17: Adverse Reactions in Short-Term, Placebo-Controlled Adjunctive Trials in Patients with Major Depressive Disorder

	Percentage of Patients Reporting Reaction*	
Preferred Term	**Aripiprazole + ADT† (n=371)**	**Placebo + ADT† (n=366)**
Eye Disorders		
Blurred Vision	6	1
Gastrointestinal Disorders		
Constipation	5	2
General Disorders and Administration Site Conditions		
Fatigue	8	4
Feeling Jittery	3	1
Infections and Infestations		
Upper Respiratory Tract Infection	6	4
Investigations		
Weight Increased	3	2
Metabolism and Nutrition Disorders		
Increased Appetite	3	2
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	4	3
Myalgia	3	1
Nervous System Disorders		
Akathisia	25	4
Somnolence	6	4
Tremor	5	4
Sedation	4	2
Dizziness	4	2
Disturbance in Attention	3	1
Extrapyramidal Disorder	2	0
Psychiatric Disorders		
Restlessness	12	2
Insomnia	8	2

*Adverse reactions reported by at least 2% of patients treated with adjunctive Aripiprazole, except adverse reactions which had an incidence equal to or less than placebo.

†Antidepressant Therapy

Dose-Related Adverse Reactions

Schizophrenia

Dose response relationships for the incidence of adverse reactions were evaluated from four trials in adult patients with schizophrenia comparing various fixed doses (2, 5, 10, 15, 20, and 30 mg/day) of oral aripiprazole to placebo. This analysis, stratified by study, indicated that the 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, 5.0%; 10 mg, 13.0%; 30 mg, 21.6%); somnolence (incidences were placebo, 6.0%; 10 mg, 11.0%; 30 mg, 21.6%); and tremor (incidences were placebo, 2.0%; 10 mg, 2.0%; 30 mg, 11.8%).

Autistic Disorder

In a study of pediatric patients (6 to 17 years of age) with autistic disorder, one common adverse reaction had a possible dose response relationship: fatigue (incidences were placebo, 0%; 5 mg, 3.8%; 10 mg, 22.0%; 15 mg, 18.5%).

Tourette's Disorder

In a study of pediatric patients (7 to 17 years of age) with Tourette's disorder, no common adverse reaction(s) had a dose response relationship.

Extrapyramidal Symptoms

Schizophrenia

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.

Major Depressive Disorder

In the short-term, placebo-controlled trials in major depressive disorder, the incidence of reported EPS-related events, excluding events related to akathisia, for adjunctive aripiprazole- treated patients was 8% vs. 5% for adjunctive placebo-treated patients; and the incidence of akathisia-related events for adjunctive aripiprazole-treated patients was 25% vs. 4%

for adjunctive placebo-treated patients.

In the major depressive disorder trials, the Simpson Angus Rating Scale and the Barnes Akathisia Scale showed a significant difference between adjunctive aripiprazole and adjunctive placebo (aripiprazole, 0.31; placebo, 0.03 and aripiprazole, 0.22; placebo, 0.02). Changes in the Assessments of Involuntary Movement Scales were similar for the adjunctive aripiprazole and adjunctive placebo groups.

Autistic Disorder

In the short-term, placebo-controlled trials in autistic disorder in pediatric patients (6 to 17 years), the incidence of reported EPS-related events, excluding events related to akathisia, for aripiprazole-treated patients was 18% vs. 2% for placebo and the incidence of akathisia-related events for aripiprazole-treated patients was 3% vs. 9% for placebo.

In the pediatric (6 to 17 years) short-term autistic disorder trials, the Simpson Angus Rating Scale showed a significant difference between aripiprazole and placebo (aripiprazole, 0.1; placebo, – 0.4). Changes in the Barnes Akathisia Scale and the Assessments of Involuntary Movement Scales were similar for the aripiprazole and placebo groups.

Tourette's Disorder

In the short-term, placebo-controlled trials in Tourette's disorder in pediatric patients (6 to 18 years), the incidence of reported EPS-related events, excluding events related to akathisia, for aripiprazole-treated patients was 7% vs. 6% for placebo and the incidence of akathisia-related events for aripiprazole-treated patients was 4% vs. 6% for placebo.

In the pediatric (6 to 18 years) short-term Tourette's disorder trials, changes in the Simpson Angus Rating Scale, Barnes Akathisia Scale and Assessments of Involuntary Movement Scale were not clinically meaningfully different for 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 tablets *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 led to discontinuation (<1%) of aripiprazole. In addition, in a long-term (52 weeks), 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 1/1,000 patients; *rare* reactions are those occurring in fewer than 1/1,000 patients:

Adults - Oral Administration

- *Blood and Lymphatic System Disorders: rare* - thrombocytopenia
- *Cardiac Disorders: infrequent* – bradycardia, palpitations, *rare* – atrial flutter, cardio-respiratory 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* - blood prolactin decreased, 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 reactions observed in the pooled database of 1,686 pediatric patients, aged 6 to 18 years, 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 reliably estimate their frequency or establish a causal relationship to drug exposure: occurrences of allergic reaction (anaphylactic reaction, angioedema, laryngospasm, pruritus/urticaria, or oropharyngeal spasm), blood glucose fluctuation, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), hiccups, oculogyric crisis, and pathological gambling.

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with OPIPZA

Table 18 includes clinically important drug interactions with OPIPZA.

Table 18: Clinically Important Drug Interactions with OPIPZA

Strong CYP3A4 Inhibitors AND/OR Strong CYP2D6 Inhibitors	
Clinical Rationale	Concomitant use of aripiprazole with strong CYP3A4 and/or CYP2D6 inhibitors increased the exposure of aripiprazole *[see Clinical Pharmacology (12.3)]*.
Clinical Recommendation	Reduce the dosage of OPIPZA when administered concomitantly with a strong CYP3A4 inhibitor and/or strong CYP2D6 inhibitor *[see Dosage and Administration (2.6)]*.
Strong CYP3A4 Inducers	
Clinical Rationale	Concomitant use of aripiprazole and carbamazepine decreased the exposure of aripiprazole *[see Clinical Pharmacology (12.3)]*.
Clinical Recommendation	Consider increasing the dosage of OPIPZA when administered concomitantly with a strong CYP3A4 inducer *[see Dosage and Administration (2.6)]*.
Antihypertensive Drugs	
Clinical Rationale	Due to its alpha-adrenergic antagonism, aripiprazole has

	the potential to enhance the effect of certain antihypertensive agents.
Clinical Recommendation	Monitor blood pressure and adjust dose accordingly *[see Warnings and Precautions (5.8)]*.
Benzodiazepines	
Clinical Rationale	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 (5.8)]*.
Clinical Recommendation	Monitor sedation and blood pressure. Adjust dose accordingly.

7.2 Drugs Having No Clinically Important Interactions with OPIPZA

Based on pharmacokinetic studies, no dosage adjustment of aripiprazole is required when administered concomitantly with famotidine, valproate, lithium, lorazepam.

In addition, no dosage adjustment is necessary for substrates of CYP2D6, CYP2C9, CYP2C19, or CYP3A4 when co-administered with OPIPZA. Additionally, no dosage adjustment is necessary for valproate, lithium, lamotrigine, lorazepam, or sertraline when co-administered with OPIPZA *[see Clinical Pharmacology (12.3)]*.

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 aripiprazole, during pregnancy. Healthcare providers are encouraged to advise patients to register by contacting the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or visiting online at http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/.

Risk Summary

Neonates exposed to antipsychotic drugs, including OPIPZA, 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, or major depressive disorder, and with exposure to antipsychotics, including OPIPZA 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 post-natal 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.

A prospective, longitudinal study followed 201 pregnant women with a history of major depressive disorder who were euthymic and taking antidepressants at the beginning of pregnancy. The women who discontinued antidepressants during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressants. Consider the risk of untreated depression when discontinuing or changing treatment with antidepressant medication during pregnancy and postpartum.

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 9,258 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 and rabbits.

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 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 MRHD. Decreased fetal weight and increased incidence of fused sternebrae were observed at 19 and 65 times the MRHD.

In rats treated orally with aripiprazole peri- and postnatally 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 MRHD. An increase in stillbirths and, decreases in pup weight (persisting into adulthood) and survival were also seen at this dose.

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 OPIPZA and any potential adverse effects on the breastfed infant from OPIPZA or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of OPIPZA in pediatric patients with major depressive disorder 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)]*.

Schizophrenia

Safety and effectiveness in pediatric patients with schizophrenia were established in a 6-week, placebo-controlled clinical trial of another oral aripiprazole product in 202 pediatric patients aged 13 to 17 years *[see Clinical Studies (14.2)]*. 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.

Irritability Associated with Autistic Disorder

Safety and effectiveness in pediatric patients demonstrating irritability associated with autistic disorder were established in two 8 week, placebo-controlled clinical trials of another oral aripiprazole product in 212 pediatric patients aged 6 to 17 years *[Clinical Studies (14.4)]*. A maintenance trial was conducted in pediatric patients (6 to 17 years of age) with irritability associated with autistic disorder. The first phase of this trial was an open-label, flexibly dosed (aripiprazole 2 to 15 mg/day) phase in which patients were stabilized (defined as > 25% improvement on the ABC-I subscale, and a CGI-I rating of "much improved" or "very much improved") on aripiprazole for 12 consecutive weeks. Overall, 85 patients were stabilized and entered the second, 16 week, double-blind phase where they were randomized to either continue aripiprazole treatment or switch to placebo. In this trial, the efficacy of aripiprazole for the maintenance treatment of irritability associated with autistic disorder was not established.

Tourette's Disorder

Safety and effectiveness of aripiprazole in pediatric patients with Tourette's Disorder were established in one 8 week (aged 7 to 17 years) and one 10-week trial (aged 6 to 18 years) of another oral aripiprazole product in 194 pediatric patients *[see Clinical Studies (14.5)]*. Maintenance efficacy in pediatric patients has not been systematically evaluated.

Juvenile Animal Studies

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 of OPIPZA is recommended for geriatric patients *[see Clinical Pharmacology (12.3)]*.

Of the 13,543 patients treated with oral aripiprazole in clinical trials, 1,073 (8%) were ≥65 years old and 799 (6%) were ≥75 years old. Placebo-controlled studies of oral aripiprazole in schizophrenia, major depressive disorder, or another indication did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. OPIPZA 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

OPIPZA dosage adjustment is recommended in known CYP2D6 poor metabolizers due to high aripiprazole concentrations. Approximately 8% of Caucasians and 3% to 8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers (PM) *[see Dosage and Administration (2.6) and Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

No dosage adjustment for OPIPZA is required on the basis of a patient's renal function (glomerular filtration rate between 15 and 90 mL/minute) *[see Clinical Pharmacology (12.3)]*.

8.8 Hepatic Impairment

No dosage adjustment for OPIPZA is required on the basis of a patient's hepatic function (Child-Pugh scores between 5 and 15) *[see Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

OPIPZA contains aripiprazole, which is not a controlled substance.

9.2 Abuse

Aripiprazole 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 aripiprazole 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

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. No fatality was reported with aripiprazole alone. The largest known dose with a known outcome involved acute ingestion of 1,260 mg of oral aripiprazole (42 times the maximum recommended daily dose) by a patient who fully recovered. Deliberate or accidental overdosage was also reported in patients age 12 years and younger involving oral aripiprazole ingestions up to 195 mg (6.5 times the maximum recommended daily dose) with no fatalities.

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.

Management of Overdosage

Consider contacting the Poison Help line (1-800-222-1222) or medical toxicologist for additional overdosage management recommendations.

No specific information is available on the treatment of overdose with OPIPZA. An electrocardiogram should be obtained

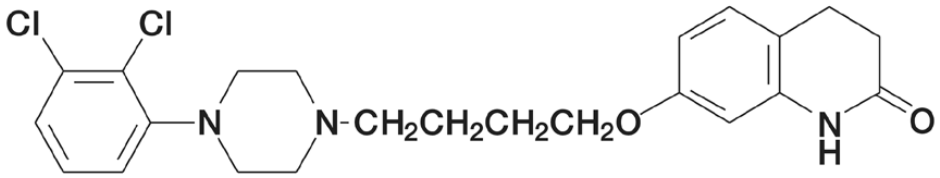
in case of overdosage and if QT interval prolongation is present, cardiac monitoring should be instituted. Otherwise, management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. Close medical supervision and monitoring should continue until the patient recovers.

Charcoal: In the event of an overdose of OPIPZA, 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 OPIPZA, hemodialysis is unlikely to be useful in overdose management since aripiprazole is highly bound to plasma proteins.

11 DESCRIPTION

OPIPZA contains aripiprazole, an atypical antipsychotic drug. Aripiprazole is 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyril. Aripiprazole has a pKa of 6.2. It is freely soluble in dichloromethane, sparingly soluble in toluene, and insoluble in methanol and water. The empirical formula is $C_{23}H_{27}Cl_2N_3O_2$ with a molecular weight of 448.38. The chemical structure is:



OPIPZA is for oral administration and is available in 2 mg, 5 mg, and 10 mg strengths. Inactive ingredients include hydroxypropyl cellulose, sodium lauryl sulfate, and sucralose. Imprinting ink contains glycerin, FD&C Blue No.1, polysorbate 20, and propylene glycol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of aripiprazole in the listed indications, is unclear. However, the efficacy of aripiprazole in the listed indications 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 (Ki values of 0.34 nM, 0.8 nM, 1.7 nM, and 3.4 nM, respectively), moderate affinity for dopamine D4, serotonin 5-HT_{2C} and 5-HT_7, alpha$_1$-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 (Ki=98 nM). Aripiprazole has no appreciable affinity for cholinergic muscarinic receptors (IC_{50}>1000 nM).

12.3 Pharmacokinetics

Aripiprazole oral film 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 and represents 40% of the parent drug exposure in plasma.

Absorption

Following administration of aripiprazole oral film, the median (range) time to reach peak plasma concentrations (T_{max}) occurs at of 1.5 (1, 6) hours. In two studies comparing the pharmacokinetics of 10 mg aripiprazole oral film to 10 mg aripiprazole tablets under fasting and fed conditions in healthy subjects, the oral film to tablet ratios of geometric mean C_{max} and AUC values under fasting conditions were 114% and 106%, respectively, the oral film to tablet ratios of geometric mean C_{max} and AUC values under fed conditions were 91% and 95%, respectively.

Steady-state concentrations are attained within 14 days of dosing for both active moieties. Aripiprazole accumulation is predictable from single-dose pharmacokinetics. At steady-state, the pharmacokinetics of aripiprazole is dose-proportional.

Effect of Food

OPIPZA can be administered with or without food. Administration of a 10 mg aripiprazole oral film with a standard high-fat (800 – 1,000 Kcal) meal did not significantly affect the C_{max} or AUC of aripiprazole, but increased median (range) T_{max} for aripiprazole from 1.5 (1, 6) to 6 (1.5, 12) hours.

Distribution

The steady-state volume of distribution of aripiprazole following intravenous administration is high (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 mg/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 and 94 hours for aripiprazole and dehydro-aripiprazole, respectively. For CYP2D6 poor metabolizers, the mean elimination half-life for aripiprazole is about 146 hours.

Metabolism

Elimination of aripiprazole is mainly through hepatic metabolism involving two P450 isozymes, CYP2D6 and CYP3A4.

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 N-dealkylation is catalyzed by CYP3A4. 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, approximately 25% and 55% of the administered radioactivity was recovered in the urine and feces, respectively. Less than 1% of unchanged aripiprazole was excreted in the urine and approximately 18% of the oral dose was recovered unchanged in the feces.

Drug Interaction Studies

Effect of other drugs on the exposures of aripiprazole and dehydro-aripiprazole are summarized in Figure 1 and Figure 2, respectively. Based on simulation, a 4.5-fold increase in mean C_{max} 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 C_{max} and AUC values at steady-state is expected in poor metabolizers of CYP2D6 administered with strong CYP3A4 inhibitors.

Figure 1: The Effect of Other Drugs on Aripiprazole Tablet Pharmacokinetics

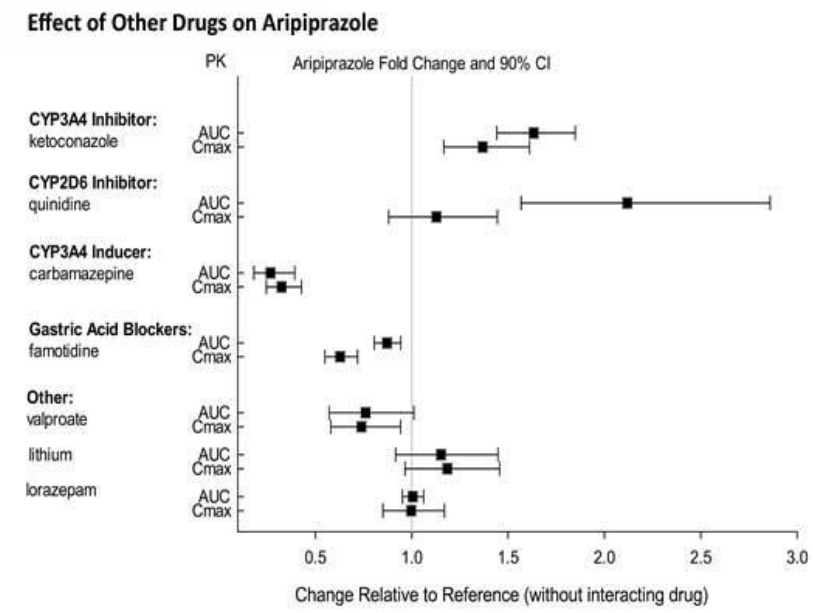
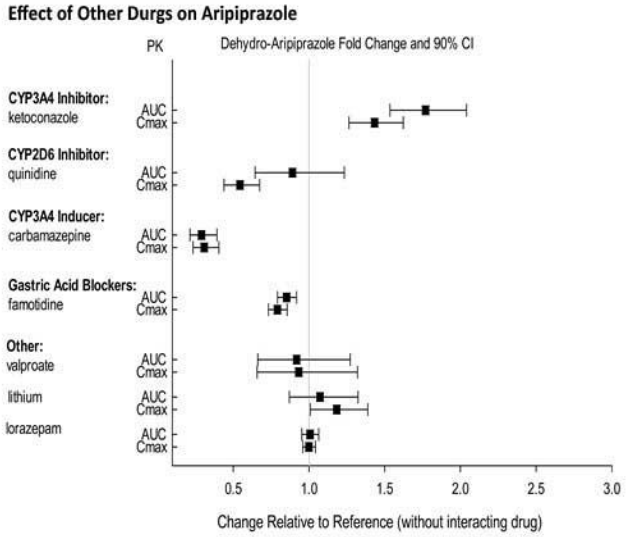
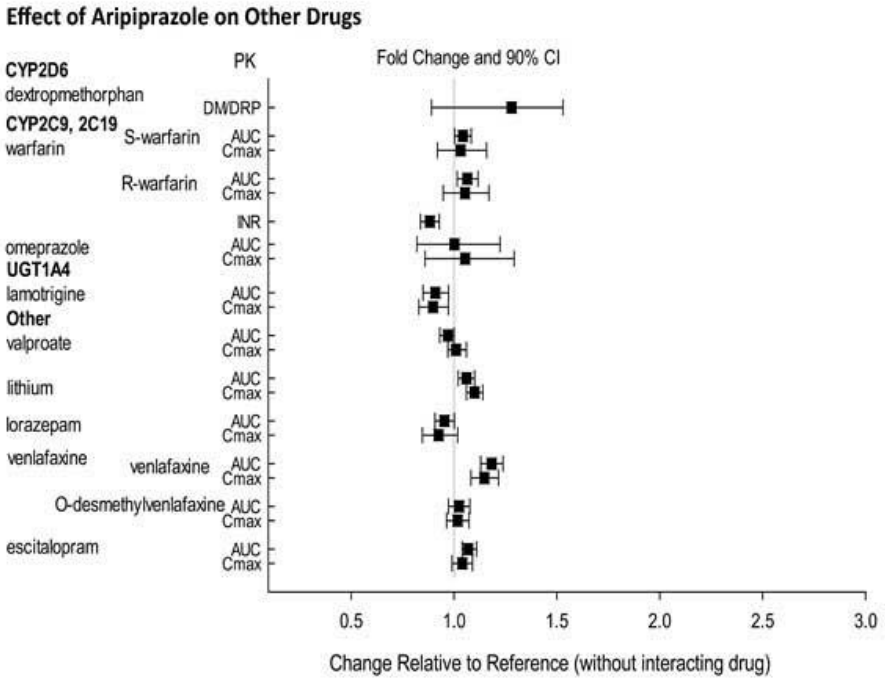


Figure 2: The Effect of Other Drugs on Dehydro-Aripiprazole Pharmacokinetics



The effect of aripiprazole on the exposures of other drugs are summarized in Figure 3. A population PK analysis in patients with major depressive disorder showed no substantial change in 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 and norfluoxetine increased by about 18% and 36%, respectively, 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 co-administered with aripiprazole.

Figure 3: The Effect of Aripiprazole on Pharmacokinetics of Other Drugs



Specific Populations

Exposure of aripiprazole and dehydro-aripiprazole in specific populations is summarized in Figure 4 and Figure 5, 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 4: Effect of Intrinsic Factors on Aripiprazole Pharmacokinetics

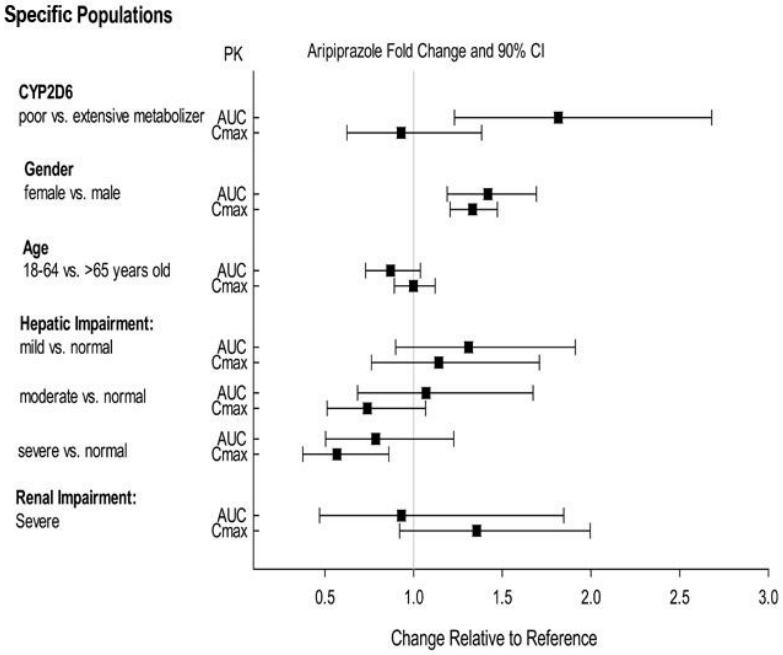
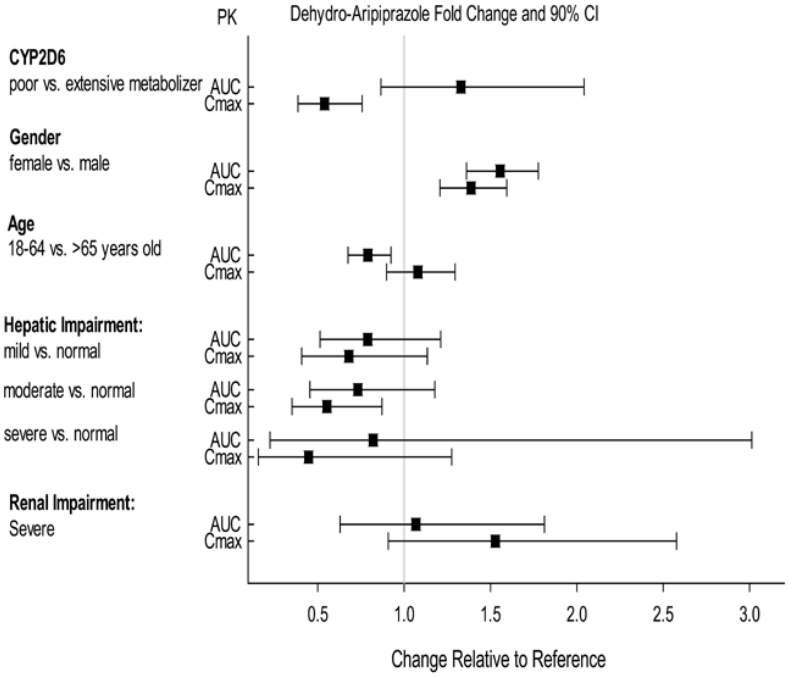


Figure 5: Effect of Intrinsic Factors on Dehydro-Aripiprazole Pharmacokinetics



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, 2,3-DCPP, 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 the Clinical Studies

The efficacy of OPIPZA for the treatment of schizophrenia in patients ages 13 to 17 years, adjunctive treatment of adults with MDD, treatment of irritability associated with autistic disorder in pediatric patients 6 years and older, and treatment of Tourette's disorder in pediatric patients 6 years and older is based on the following adequate and well-controlled studies of another oral aripiprazole product (referred to as "aripiprazole" in this section):

- Four short-term trials and one maintenance trial in adult patients and one short-term trial in pediatric patients ages 13 to 17 years with schizophrenia *[see Clinical Studies (14.1)]*
- Two short-term trials in adult patients with MDD who had an inadequate response to antidepressant therapy during the current episode *[see Clinical Studies (14.3)]*
- Two short-term trials in pediatric patients ages 6 to 17 years for the treatment of irritability associated with autistic disorder *[see Clinical Studies (14.4)]*
- Two short-term trials in pediatric patients ages 6 to 18 years with Tourette's disorder *[see Clinical Studies (14.5)]*

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 26), 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 26), 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 26), 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 26), 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 19), 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 19: Schizophrenia Studies (Adults and Pediatric Patients 13 to 17 years)

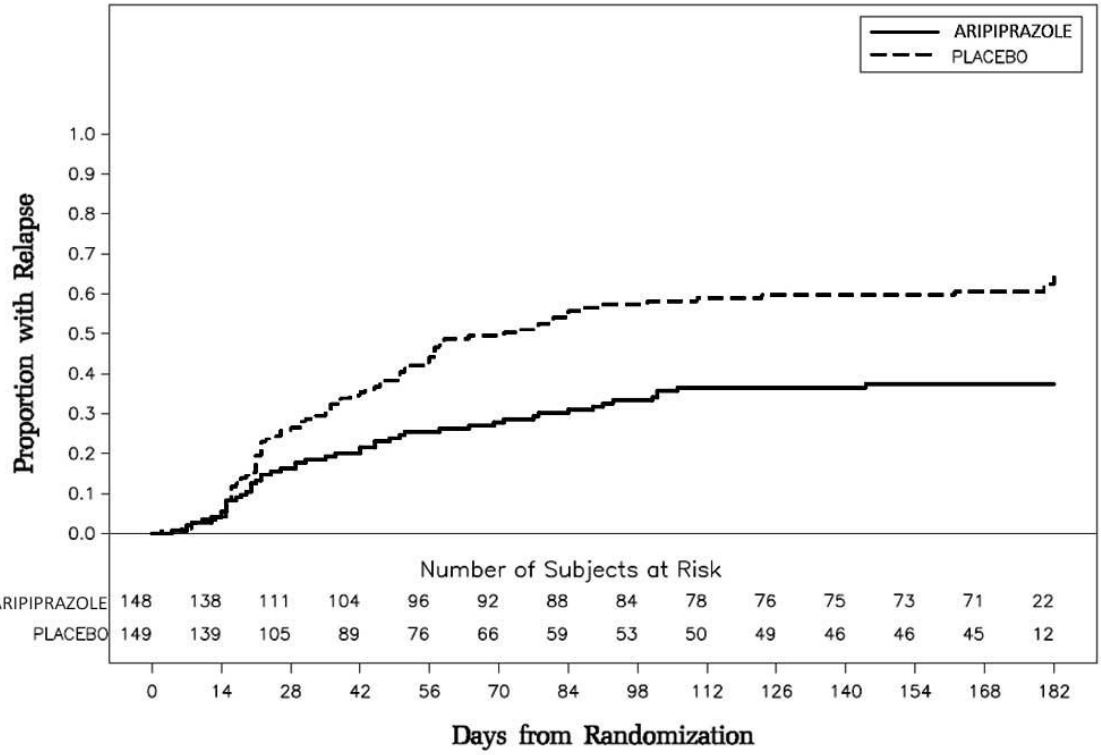
Study Number	Treatment Group	Primary Efficacy Measure: PANSS		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference* (95% CI)
Study 1	Aripiprazole (15 mg/day) †	98.5 (17.2)	-15.5 (2.40)	-12.6 (-18.9, -6.2)
	Aripiprazole (30 mg/day) †	99.0 (19.2)	-11.4 (2.39)	-8.5 (-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 patients (13 to 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.

* 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)



14.3 Adjunctive Treatment of Adults with Major Depressive Disorder

The efficacy of aripiprazole in the adjunctive treatment of major depressive disorder (MDD) was demonstrated in two short-term (6-week), placebo-controlled trials of adult patients meeting DSM-IV criteria for MDD who had had an inadequate response to prior antidepressant therapy (1 to 3 courses) in the current episode and who had also demonstrated an inadequate response to 8 weeks of prospective antidepressant therapy (paroxetine controlled-release, venlafaxine extended-release, fluoxetine, escitalopram, or sertraline). Inadequate response for prospective treatment was defined as less than 50% improvement on the 17 item version of the Hamilton Depression Rating Scale (HAMD17), minimal HAMD17 score of 14, and a Clinical Global Impressions Improvement rating of no better than minimal improvement. Inadequate response to prior treatment was defined as less than 50% improvement as perceived by the patient after a minimum of 6 weeks of antidepressant therapy at or above the minimal effective dose.

The primary instrument used for assessing depressive symptoms was the Montgomery-Asberg Depression Rating Scale (MADRS), a 10 item clinician-rated scale used to assess the degree of depressive symptomatology. The key secondary instrument was the Sheehan Disability Scale (SDS), a 3 item self-rated instrument used to assess the impact of depression on three domains of functioning with each item scored from 0 (not at all) to 10 (extreme).

In the two trials (n=381, n=362), aripiprazole was superior to placebo in reducing mean MADRS total scores (Studies 1, 2 in Table 28). In one study, aripiprazole was also superior to placebo in reducing the mean SDS score.

In both trials, patients received aripiprazole adjunctive to antidepressants at a dose of 5 mg/day. Based on tolerability and efficacy, doses could be adjusted by 5 mg increments, one week apart. Allowable doses were: 2, 5, 10, 15 mg/day, and for patients who were not on potent CYP2D6 inhibitors fluoxetine and paroxetine, 20 mg/day. The mean final dose at the end point for the two trials was 10.7 and 11.4 mg/day.

An examination of population subgroups did not reveal evidence of differential response based on age, choice of prospective antidepressant, or race. With regard to gender, a smaller mean reduction on the MADRS total score was seen in males than in females.

Table 20: Adjunctive Treatment of Major Depressive Disorder Studies (Adults)

		Primary Efficacy Measure: MADRS		
Study Number	**Treatment Group**	**Mean Baseline Score (SD)**	**LS Mean Change from Baseline (SE)**	**Placebo-subtracted Difference* (95% CI)**
Study 1	Aripiprazole (5 to 20 mg/day) †+ Antidepressant	25.2 (6.2)	-8.49 (0.66)	-2.84 (-4.53, -1.15)
	Placebo + Antidepressant	27.0 (5.5)	-5.65 (0.64)	--
Study 2	Aripiprazole (5 to 20 mg/day) †+ Antidepressant	26.0 (6.0)	-8.78 (0.63)	-3.01 (-4.66, -1.37)
	Placebo + Antidepressant	26.0 (6.5)	-5.77 (0.67)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.

* Difference (drug minus placebo) in least-squares mean change from baseline.

† Doses statistically significantly superior to placebo.

14.4 Irritability Associated with Autistic Disorder

Pediatric Patients (6 to 17 years)

The efficacy of aripiprazole in the treatment of irritability associated with autistic disorder was established in two 8 week, placebo-controlled trials in pediatric patients (6 to 17 years) who met the DSM-IV criteria for autistic disorder and demonstrated behaviors such as tantrums, aggression, self-injurious behavior, or a combination of these problems. Over 75% of these patients were under 13 years of age.

Efficacy was evaluated using two assessment scales: The Aberrant Behavior Checklist (ABC) and the Clinical Global Impression-Improvement (CGI-I) scale. The primary outcome measure in both trials was the change from baseline to endpoint in the Irritability subscale of the ABC (ABC-I). The ABC-I subscale measured symptoms of irritability in autistic disorder.

The results of these trials are as follows:

In one of the 8 week, placebo-controlled trials, pediatric patients 6 to 17 years with autistic disorder (n=98), received daily doses of placebo or aripiprazole 2 to 15 mg/day. Aripiprazole, starting at 2 mg/day with increases allowed up to 15 mg/day based on clinical response, significantly improved scores on the ABC-I subscale and on the CGI-I scale compared with placebo. The mean daily dose of aripiprazole at the end of 8 week treatment was 8.6 mg/day (Study 1 in Table 29).

In the other 8 week, placebo-controlled trial in pediatric patients 6 to 17 years with autistic disorder (n=218), three fixed doses of aripiprazole (5 mg/day, 10 mg/day, or 15 mg/day) were compared to placebo. aripiprazole dosing started at 2 mg/day and was increased to 5 mg/day after one week. After a second week, it was increased to 10 mg/day for patients in the 10 and 15 mg dose arms, and after a third week, it was increased to 15 mg/day in the 15 mg/day treatment arm (Study 2 in Table 21). All three doses of aripiprazole significantly improved scores on the ABC-I subscale compared with placebo.

Table 21: Irritability Associated with Autistic Disorder Studies (Pediatric Patients 6 to 17 years)

Study Number	Treatment Group	Primary Efficacy Measure: ABC-I		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference* (95% CI)
Study 1	Aripiprazole (2 to 15 mg/day) †	29.6 (6.37)	-12.9 (1.44)	-7.9 (-11.7, -4.1)
	Placebo	30.2 (6.52)	-5.0 (1.43)	--
Study 2	Aripiprazole (5 mg/day) †	28.6 (7.56)	-12.4 (1.36)	-4.0 (-7.7, -0.4)
	Aripiprazole (10 mg/day) †	28.2 (7.36)	-13.2 (1.25)	-4.8 (-8.4, -1.3)
	Aripiprazole (15 mg/day) †	28.9 (6.41)	-14.4 (1.31)	-6.0 (-9.6, -2.3)
	Placebo	28.0 (6.89)	-8.4 (1.39)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.
* Difference (drug minus placebo) in least-squares mean change from baseline.
† Doses statistically significantly superior to placebo.

14.5 Tourette's Disorder

Pediatric Patients (6 to 18 years)

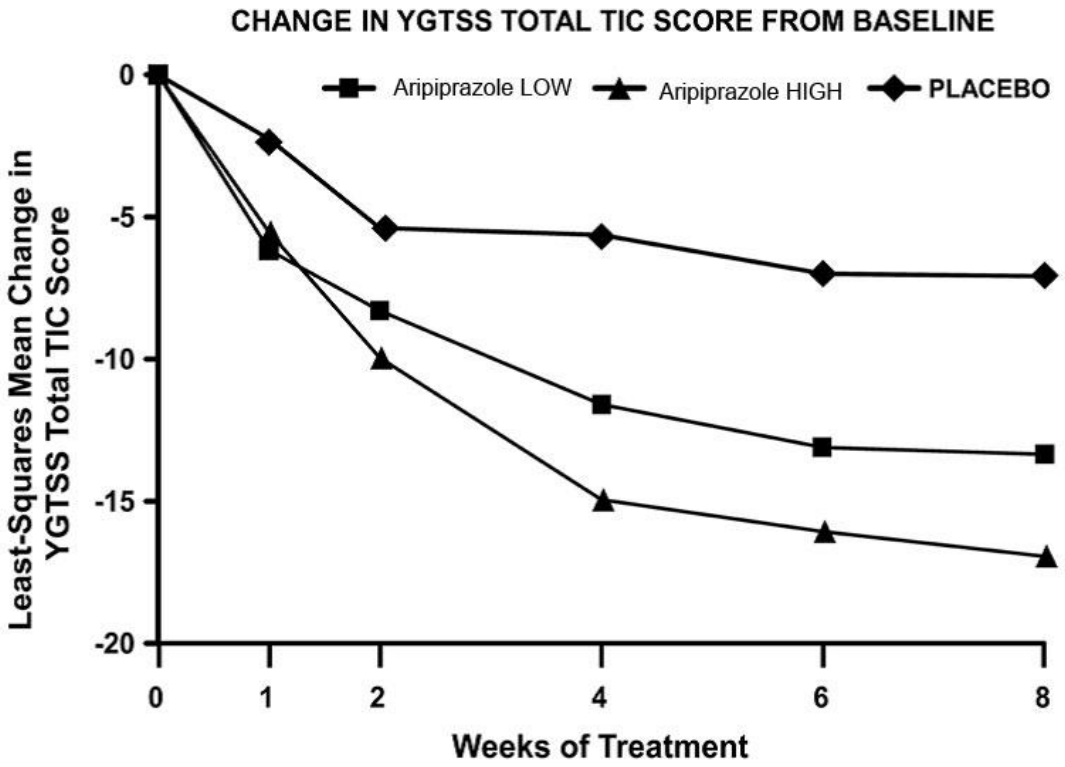
The efficacy of aripiprazole in the treatment of Tourette's disorder was established in one 8 week (7 to 17 years of age) and one 10 week (6 to 18 years of age), placebo-controlled trials in pediatric patients (6 to 18 years of age) who met the DSM-IV criteria for Tourette's disorder and had a Total Tic score (TTS) ≥ 20 to 22 on the Yale Global Tic Severity Scale (YGTSS). The YGTSS is a fully validated scale designed to measure current tic severity. Efficacy was evaluated using two assessment scales: 1) the Total Tic score (TTS) of the YGTSS and 2) the Clinical Global Impressions Scale for Tourette's Syndrome (CGI-TS), a clinician-determined summary measure that takes into account all available patient information. Over 65% of these patients were under 13 years of age.

The primary outcome measure in both trials was the change from baseline to endpoint in the TTS of the YGTSS. Ratings for the TTS are made along 5 different dimensions on a scale of 0 to 5 for motor and vocal tics each. Summation of these 10 scores provides a TTS (i.e., 0 to 50).

The results of these trials are as follows:

In the 8 week, placebo-controlled, fixed-dose trial, pediatric patients 7 to 17 years with Tourette's disorder (n=133), were randomized 1:1:1 to low dose aripiprazole, high dose aripiprazole, or placebo. The target doses for the low and high dose aripiprazole groups were based on weight. Patients < 50 kg in the low dose aripiprazole group started at 2 mg per day with a target dose of 5 mg per day after 2 days. Patients ≥ 50 kg in the low dose aripiprazole group, started at 2 mg per day increased to 5 mg per day after 2 days, with a subsequent increase to a target dose of 10 mg per day at Day 7. Patients <50 kg in the high dose aripiprazole group started at 2 mg per day increased to 5 mg per day after 2 days, with a subsequent increase to a target dose of 10 mg per day at Day 7. Patients ≥ 50 kg in the high dose aripiprazole group, started at 2 mg per day increased to 5 mg per day after 2 days, with a subsequent increase to a dose of 10 mg per day at Day 7 and were allowed weekly increases of 5 mg per day up to a target dose 20 mg per day at Day 21. Aripiprazole (both high and low dose groups) demonstrated statistically significantly improved scores on the YGTSS TTS (Study 1 in Table 22) and on the CGI-TS scale compared with placebo. The estimated improvements on the YGTSS TTS over the course of the study are displayed in Figure 7.

Figure 7: Least Square Means of Change from Baseline in YGTSS TTS by Week in Pediatric Patients 7 to 17 years (Tourette's Disorder Study 1)



In the 10 week, placebo-controlled, flexible-dose trial in pediatric patients 6 to 18 years with Tourette's disorder (n=61), patients received daily doses of placebo or aripiprazole, starting at 2 mg/day with increases allowed up to 20 mg/day based on clinical response. Aripiprazole demonstrated statistically significantly improved scores on the YGTSS TTS scale compared with placebo (Study 2 in Table 22). The mean daily dose of aripiprazole at the end of 10-week treatment was 6.54 mg/day.

Table 22: Tourette's Disorder Studies (Pediatric Patients)

Study Number Population (Age Range)	Treatment Group	Primary Efficacy Measure: YGTSS TTS		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference* (95% CI)
Study 1 Pediatric patients (7 to 17 years)	Aripiprazole (low dose) †	29.2 (5.63)	-13.4 (1.59)	-6.3 (-10.2, -2.3)
	Aripiprazole (high dose) †	31.2 (6.40)	-16.9 (1.61)	-9.9 (-13.8, -5.9)
	Placebo	30.7 (5.95)	-7.1 (1.55)	--
Study 2 Pediatric patients (6 to 18 years)	Aripiprazole (2 to 20 mg/day)†	28.3 (5.51)	-15.0 (1.51)	-5.3 (-9.8, -0.9)
	Placebo	29.5 (5.60)	-9.6 (1.64)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.
* Difference (drug minus placebo) in least-squares mean change from baseline.
† Doses statistically significantly superior to placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

OPIPZA is available in the strengths and packages listed in Table 23.

Table 23: OPIPZA Presentations

Strength	Color/Shape	Markings	Pack Size	NDC Code
2 mg	1 cm × 1.2 cm Rectangular white film	A2	30 Pouches of 1	15370-401-30
5 mg	2 cm × 1.5 cm Rectangular white film	A5	30 Pouches of 1	15370-402-30
10 mg	2 cm × 3 cm Rectangular white film	A10	30 Pouches of 1	15370-403-30

Storage

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling *(Medication Guide and Instructions for Use)*.

Suicidal Thoughts and Behaviors

Advise patients and caregivers to look for the emergence of suicidal ideation and behavior, especially early during treatment and when the dose is adjusted up or down, and instruct them to report such symptoms to the healthcare provider *[see Boxed Warning, and Warnings and Precautions (5.1)]*.

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, family members, or caregivers to contact a health care provider or report to the emergency room if they experience signs and symptoms of NMS *[see Warnings and Precautions (5.4)]*.

Tardive Dyskinesia

Counsel patients on the signs and symptoms of tardive dyskinesia and to contact their health care provider if these abnormal movements occur *[see Warnings and Precautions (5.5)]*.

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 (5.6)]*.

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 OPIPZA . In some cases, but not all, the urges were reported to have stopped when the

dose was reduced or stopped *[see Warnings and Precautions (5.7)]*.

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 or increases in dosage *[see Warnings and Precautions (5.8)]*.

Leukopenia/Neutropenia

Advise patients with a pre-existing low WBC count or a history of drug-induced leukopenia/neutropenia that they should have their CBC monitored while receiving OPIPZA *[see Warnings and Precautions (5.10)]*.

Potential for Cognitive and Motor Impairment

Inform patients that OPIPZA has the potential to impair judgment, thinking, or motor skills. Caution patients about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle until they are reasonably certain that OPIPZA therapy does not affect them adversely *[see Warnings and Precautions (5.12)]*.

Concomitant Medication

Advise patients to inform their healthcare providers of any changes to their current prescription or over-the-counter medications because there is a potential for clinically significant interactions *[see Drug Interactions (7.1)]*.

Heat Exposure and Dehydration

Educate patients regarding appropriate care in avoiding overheating and dehydration *[see Warnings and Precautions (5.13)]*.

Pregnancy

Advise patients that OPIPZA may cause extrapyramidal and/or withdrawal symptoms (agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder) in a neonate. Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with OPIPZA. Advise patients that there is a pregnancy registry that monitors pregnancy outcomes in women exposed to OPIPZA during pregnancy *[see Use in Specific Populations (8.1)]*.

Administration Information

Advise the patient of the following *[see Dosage and Administration (2.5)]*:

- Administer OPIPZA with or without food.
- Apply OPIPZA on top of the tongue where it dissolves in saliva and can be swallowed in a normal manner without the need for water or other liquids.
- Refrain from chewing the film or swallowing an undissolved film. Do not cut or split OPIPZA.
- Administer only one oral film at a time. If an additional film is needed to complete the dosage, administer after the previous film has completely dissolved.

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Manufactured by
Xiamen LP Pharmaceutical Co., Ltd.
2010 Wengjiao West Road, Xiamen, Fujian 361027, China

MEDICATION GUIDE
OPIPZA™ (o-PIP-sah)
(aripiprazole) oral film

What is the most important information I should know about OPIPZA?

OPIPZA may cause serious side effects, including:

- **Increased risk of death in elderly people with dementia-related psychosis:** Medicines like OPIPZA can increase the risk of death in elderly people who have lost touch with reality (psychosis) due to confusion and memory loss (dementia). OPIPZA is not for the treatment of people with dementia-related psychosis.
- **Increased risk of suicidal thoughts and actions:** OPIPZA and antidepressant medicines increase the risk of suicidal thoughts and actions in people 24 years of age and younger, **especially within the first few months of treatment or when the dose is changed**.
  - **Depression and other mental illnesses are the most important causes of suicidal thoughts and actions.**

How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?

- Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings or if you develop suicidal thoughts or actions. This is very important when OPIPZA or the antidepressant medicine is started or when the dose is changed.
- Call your healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings of if you develop suicidal thoughts or actions.
- Keep all follow-up visits with your healthcare provider as scheduled. Call your healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worsening depression
- new or worsening anxiety
- feeling very agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worsening irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

See **"What are the possible side effects of OPIPZA?"** for more information about side effects.

What is OPIPZA?

OPIPZA is a prescription medicine used to treat:

- schizophrenia in people ages 13 years and older
- major depressive disorder (MDD) in adults when OPIPZA is used along with antidepressant medicines
- irritability associated with autistic disorder in children ages 6 years and older
- Tourette's disorder in children ages 6 years and older

It is not known if OPIPZA is safe and effective for treatment in children:

- under 13 years of age with schizophrenia
- with MDD
- under 6 years of age with irritability associated with autistic disorder
- under 6 years of age with Tourette's disorder

Who should not take OPIPZA?

Do not take OPIPZA if you are allergic to aripiprazole or any of the ingredients in OPIPZA. See the end of this Medication Guide for a complete list of ingredients in OPIPZA.

Before taking OPIPZA, tell your healthcare provider about all your medical conditions, including if you:

- have or had diabetes or high blood sugar in you or your family. Your healthcare provider should check your blood sugar before you start OPIPZA and during your treatment with OPIPZA.
- have or had high levels of total cholesterol, LDL cholesterol, or triglycerides, or low levels of HDL cholesterol
- have or had low or high blood pressure
- have or had heart problems or stroke
- have or had low white blood cell counts
- have or had seizures (convulsions)
- are pregnant or plan to become pregnant. OPIPZA may harm your unborn baby. Taking OPIPZA during your third trimester of pregnancy may cause your baby to have abnormal muscle movements or withdrawal symptoms after birth. Talk to your healthcare provider about the risk to your unborn baby if you take OPIPZA during pregnancy.
  - Tell your healthcare provider right away if you become pregnant during treatment with OPIPZA.

- If you become pregnant during treatment with OPIPZA, talk to your healthcare provider about registering with the National Pregnancy Registry for Atypical Antipsychotics. You can register by calling 1-866-961-2388 or go to http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/
- are breastfeeding or plan to breastfeed. OPIPZA passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby during treatment with OPIPZA.

Tell your healthcare provider about all the medicines that you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

OPIPZA and other medicines may affect each other causing possible serious side effects. OPIPZA may affect the way other medicines work, and other medicines may affect how OPIPZA works.

Your healthcare provider can tell you if it is safe to take OPIPZA with your other medicines. Do not start or stop any medicines during treatment with OPIPZA without first talking to your healthcare provider.

Know the medicines you take. Keep a list of your medicines to show your healthcare provider and pharmacist when you get a new medicine.

How should I take OPIPZA?

- Take OPIPZA exactly as your healthcare provider tells you to take it. Do not change the dose or stop taking OPIPZA unless your healthcare provider tells you to.
- Take OPIPZA with or without food.
- Each OPIPZA film comes in a sealed child-resistant pouch. Do not open the pouch until you are ready to take your dose of OPIPZA.
- Let the film dissolve on your tongue before swallowing it.
- Do not chew the film or swallow it whole.
- Do not cut or split the film.
- See the detailed **Instructions for Use** for information on how to take a dose of OPIPZA.
- If you take too much OPIPZA, call your healthcare provider or Poison Help line at 1-800-222-1222, or go to the nearest hospital emergency room right away.

What should I avoid while taking OPIPZA?

- **Do not** drive, operate heavy machinery, or do other dangerous activities until you know how OPIPZA affects you. OPIPZA may make you drowsy or may affect your judgement, thinking, or motor skills.
- **Do not** become too hot or dehydrated during treatment with OPIPZA.
  - Do not exercise too much.
  - In hot weather, stay inside in a cool place if possible.
  - Stay out of the sun.
  - Do not wear too much clothing or heavy clothing.
  - Drink plenty of water.

What are the possible side effects of OPIPZA?

OPIPZA may cause serious side effects, including:

- See **"What is the most important information I should know about OPIPZA?"**
- **Stroke (cerebrovascular problems) in elderly people with dementia-related psychosis that can lead to death**
- **Neuroleptic malignant syndrome (NMS), a serious condition that can lead to death.** Call your healthcare provider right away or go to the nearest emergency room if you have some or all of the following signs and symptoms of NMS:
  - high fever
  - confusion
  - changes in pulse, heart rate, and blood pressure
  - stiff muscles
  - sweating
- **Uncontrolled body movements (tardive dyskinesia).** OPIPZA may cause movements that you cannot control in your face, tongue, or other body parts. Tardive dyskinesia may not go away, even if you stop taking OPIPZA. Tardive dyskinesia may also start after you stop taking OPIPZA.
- **Problems with your metabolism such as:**
  - **High blood sugar (hyperglycemia) and diabetes.** Increases in blood sugar can happen in some people who are treated with OPIPZA. Extremely high blood sugar can lead to coma or death. If you have diabetes or risk factors for diabetes such as being overweight, or a family history of diabetes, your healthcare provider should check your blood sugar before you start treatment and during your treatment with OPIPZA.

    Call your healthcare provider if you have any of these symptoms of high blood sugar while receiving OPIPZA:
    - feel very thirsty
    - feel very hungry
    - feel sick to your stomach
    - need to urinate more than usual
    - feel weak or tired
    - feel confused, or your breath smells fruity

- **Increased fat levels (cholesterol and triglycerides) in your blood.** You healthcare provider may check your cholesterol and triglyceride levels during treatment with OPIPZA.
- **Weight gain.** You and your healthcare provider should check your weight regularly during treatment with OPIPZA.

- **Unusual and uncontrollable (compulsive) urges.** Some people taking OPIPZA have had unusual strong urges to gamble and gambling that cannot be controlled (compulsive gambling). Other compulsive urges can happen including sexual urges, shopping, and binge eating or eating that you cannot control. If you or your family members notice that you are having unusual urges or behaviors, talk to your healthcare provider.
- **Decreased blood pressure (orthostatic hypotension) and fainting.** You may feel lightheaded or faint when you rise too quickly from a sitting or lying position.
- **Falls.** OPIPZA may make you sleepy or dizzy, may cause a decrease in your blood pressure when changing position (orthostatic hypotension), and can slow your thinking and motor skills which may lead to falls that can cause fractures or other injuries.
- **Low white blood cell count.** Your healthcare provider may do blood cell count tests during your first few months of treatment with OPIPZA.
- **Seizures (convulsions).**
- **Sleepiness, drowsiness, feeling tired, difficulty thinking and doing normal activities.** See **"What should I avoid while taking OPIPZA?"**
- **Problems controlling your body temperature so that you feel too warm.** See "**What should I avoid while taking OPIPZA?**"
- **Difficulty swallowing that can cause food or liquid to get into your lungs.**

The most common side effects of OPIPZA in adults include:

- feeling like you need to move (akathisia)
- trouble sleeping (insomnia)
- restlessness
- constipation
- feeling tired
- blurred vision

The most common side effects of OPIPZA in children include:

- feeling sleepy or tired
- headache
- vomiting
- nausea
- increased or decreased appetite
- increased saliva or drooling
- uncontrolled movements, muscle stiffness, or tremors
- fever
- cold symptoms
- having no energy

These are not all of the possible side effects of OPIPZA.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store OPIPZA?

- Store OPIPZA at room temperature between 68°F to 77°F (20°C to 25°C).

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

General information about the safe and effective use of OPIPZA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use OPIPZA for a condition for which it was not prescribed. Do not give OPIPZA to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for information about OPIPZA that is written for health professionals.

What are the ingredients in OPIPZA?

Active ingredient: aripiprazole.
Inactive ingredients: hydroxypropyl cellulose, sodium lauryl sulfate, and sucralose. Imprinting ink contains glycerin, FD&C Blue No.1, polysorbate 20, and propylene glycol.

Distributed by
Carwin Pharmaceutical Associates, LLC
Hazlet, NJ 07730

Manufactured by
Xiamen LP Pharmaceutical Co., Ltd.
2010 Wengjiao West Road, Xiamen, Fujian 361027, China

For more information about OPIPZA go to https://carwinpharma.com/opipza/ or call 1-877-676-0778.

INSTRUCTIONS FOR USE

OPIPZA™ (o-PIP-sah)
(aripiprazole) oral film

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

Figure A

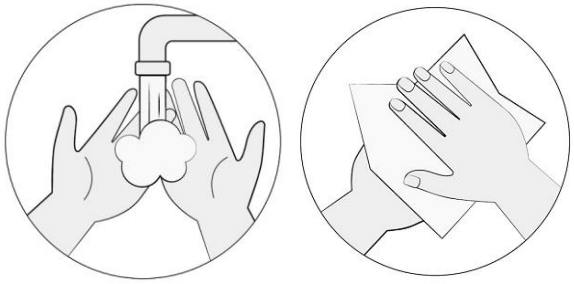
Important Information You Need to Know Before Taking OPIPZA.

- **Do not take** OPIPZA until:
  - you have read and understand these instructions.
  - you have reviewed the steps with your healthcare provider on how to take it.
  - you know the right time, how often, and the dose to take.
  - you feel comfortable with how to use OPIPZA.
  - If you are not sure about how or when to take OPIPZA, **call your healthcare provider.**
- OPIPZA is for oral use only (taken by mouth).
- Take OPIPZA with or without food.
- Each OPIPZA film comes in a sealed child-resistant pouch. Do not open the pouch until you are ready to take your dose of OPIPZA.
- **Do not** chew the film or swallow it whole.
- **Do not** cut or split the film.
- Check the expiration date printed on the pouch. **Do not** take OPIPZA if it is expired or if the pouch has been previously cut or pierced. Instead, throw away OPIPZA in your household trash and get a new pouch that is not expired or damaged.

Step 1. Preparing to Take OPIPZA

- Wash and dry your hands before handling and taking OPIPZA (see **Figure B**).

Figure B

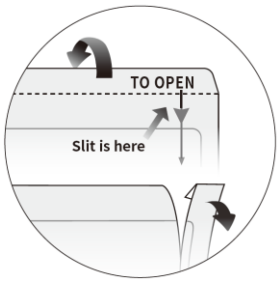


- Remove the number of pouches that you need for your prescribed dose from the OPIPZA carton.
- If you need to take more than 1 OPIPZA film for your dose, open only 1 pouch and take only 1 film at a time.

Step 2. Opening the OPIPZA Pouch

- Fold the pouch along the dashed line.
- Find the slit, the arrow, and the words “TO OPEN” on the OPIPZA pouch. Carefully tear the pouch in the direction of the arrow starting at the slit to open the pouch (see **Figure C**).

Figure C



Step 3. Taking OPIPZA

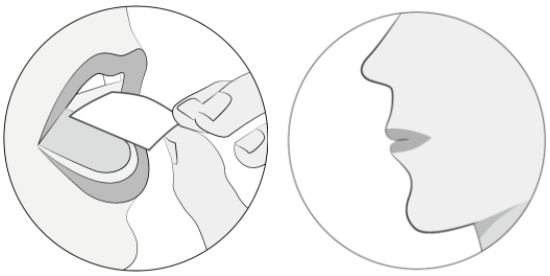
- Carefully remove the film from the OPIPZA pouch (see **Figure D**).
  If the film tears or dissolves in your hands (hands were not dry enough) when it is removed from the pouch, throw away (dispose of) the film as described below (see **“Disposing of OPIPZA”)** and get a new film. Repeat steps 1 to 3 with the new film.

Figure D

- Take the OPIPZA film right away after opening the pouch and removing the film.
- **Do not** split or cut the OPIPZA film.
- Place the entire OPIPZA film on the top of your tongue and close your mouth. Let the film dissolve on your tongue before swallowing it. The film will dissolve quickly (see **Figure E**).
- **Do not** chew the film or swallow the film whole.

- **Do not** rinse your mouth with liquid.

Figure E



If you need more than 1 film for your prescribed dose wait until the previous film has completely dissolved before taking another OPIPZA film. Repeat steps 1 to 3 with each additional film that you need to take for your prescribed dose.

When you are finished taking OPIPZA, wash and dry your hands.

Disposing of OPIPZA

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

Storing OPIPZA

- Store OPIPZA at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep OPIPZA in the unopened pouch until you are ready to take your dose.
- **Keep OPIPZA and all medicines out of the reach of children.**

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For more information or support regarding OPIPZA: Call 1-877-676-0778

The Instructions for Use has been approved by the U.S. Food and Drug Administration. Approved: 8/2024