Aripiprazole Tablets

830-2016-02

2034677

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ARIPIPRAZOLE TABLETS safely and effectively. See full prescribing information for ARIPIPRAZOLE TABLETS.

ARIPIPRAZOLE tablets, for oral use.

Initial U.S. Approval: 2002

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

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. Aripiprazole tablets are not approved for the treatment of patients with dementia-related psychosis. (5.1)**
- **Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants. Monitor for worsening and emergence of suicidal thoughts and behaviors. (5.3)**

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

Aripiprazole tablets are an atypical antipsychotic. The oral formulations are indicated for:

- Schizophrenia (14.1)

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

	Initial Dose	Recommended Dose	Maximum Dose
Schizophrenia – adults (2.1)	10-15 mg/day	10-15 mg/day	30 mg/day
Schizophrenia – adolescents (2.1)	2 mg/day	10 mg/day	30 mg/day

- Oral formulations: Administer once daily without regard to meals (2)
- Known CYP2D6 poor metabolizers: Half of the usual dose (2.7)

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

- Tablets: 2 mg, 5 mg, 10 mg, 15 mg, 20 mg and 30 mg (3)

----------CONTRAINDICATIONS----------

- Known hypersensititivity to aripiprazole tablets (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:* Atypical antipsychotic drugs have been associated with metabolic changes that include hyperglycemia/ diabetes mellitus, dyslipidemia, and body weight gain (5.6)
  - *Hyperglycemia/Diabetes Mellitus:* Monitor glucose regularly in patients with and at risk for diabetes (5.6)
  - *Dyslipidemia:* Undesirable alterations in lipid levels have been observed in patients treated with atypical antipsychotics (5.6)
  - *Weight Gain:* Weight gain has been observed with atypical antipsychotic use. Monitor weight (5.6)
- *Orthostatic Hypotension:* Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease, and risk of dehydration or syncope (5.7)
- *Leukopenia, Neutropenia, and Agranulocytosis:* have been reported with antipsychotics including aripiprazole tablets. Patients with a history of a clinically significant low white blood cell count (WBC) or a drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of aripiprazole tablets should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors (5.8)
- *Seizures/Convulsions:* Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold (5.9)
- *Potential for Cognitive and Motor Impairment:* Use caution when operating machinery (5.10)
- *Suicide:* The possibility of a suicide attempt is inherent in schizophrenia. Closely supervise high-risk patients (5.12)

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

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

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

To report SUSPECTED ADVERSE REACTIONS, contact Hetero Labs Limited at 866-495-1995 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

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

Dosage adjustment due to drug interactions (7.1) :

Factors	Dosage Adjustment for Aripiprazole tablets
Known CYP2D6 Poor Metabolizers	Administer half of usual dose
Known CYP2D6 Poor Metabolizers and strong CYP3A4 inhibitors	Administer a quarter of usual dose
Strong CYP2D6 **or** CYP3A4 inhibitors	Administer half of usual dose
Strong CYP2D6 **and** CYP3A4 inhibitors	Administer a quarter of usual dose
Strong CYP3A4 inducers	Double usual dose over 1 to 2 weeks

----------USE IN SPECIFIC POPULATIONS----------

- *Pregnancy:* May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure (8.1)
- *Nursing Mothers:* Discontinue drug or nursing, taking into consideration importance of drug to the mother (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Additional pediatric use information is approved for Otsuka America Pharmaceutical, Inc.'s ABILIFY® (aripiprazole) product. However, due to Otsuka America Pharmaceutical, Inc.'s marketing exclusivity rights, this drug product is not labeled with that information.

Revised: February 2016

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FULL PRESCRIBING INFORMATION

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

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Aripiprazole tablets are not approved for the treatment of patients with dementia-related psychosis *[see WARNINGS AND PRECAUTIONS (5.1)]*.

Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a reduction in risk with antidepressant use in patients aged 65 and older *[see WARNINGS AND PRECAUTIONS (5.3)]*.

In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber [*see WARNINGS AND PRECAUTIONS (5.3)*].

1 INDICATIONS AND USAGE

Aripiprazole oral tablets are indicated for the treatment of:

- Schizophrenia *[see CLINICAL STUDIES (14.1)]*

Additional pediatric use information is approved for Otsuka America Pharmaceutical, Inc.'s ABILIFY® (aripiprazole) product. However, due to Otsuka America Pharmaceutical, Inc.'s marketing exclusivity rights, this drug product is not labeled with that information.

2 DOSAGE AND ADMINISTRATION

2.1 Schizophrenia

Adults

The recommended starting and target dose for aripiprazole tablets is 10 or 15 mg/day administered on a once-a-day schedule without regard to meals. Aripiprazole tablets have been systematically evaluated and shown to be effective in a dose range of 10 to 30 mg/day, when administered as the tablet formulation; however, doses higher than 10 or 15 mg/day were not more effective than 10 or 15 mg/day. Dosage increases should generally not be made before 2 weeks, the time needed to achieve steady-state *[see CLINICAL STUDIES (14.1)]*.

Maintenance Treatment: Maintenance of efficacy in schizophrenia was demonstrated in a trial involving patients with schizophrenia who had been symptomatically stable on other antipsychotic medications for periods of 3 months or longer. These patients were discontinued from those medications and randomized to either aripiprazole tablets 15 mg/day or placebo, and observed for relapse *[see CLINICAL STUDIES (14.1)]*. Patients should be periodically reassessed to determine the continued need for maintenance treatment.

Adolescents

The recommended target dose of aripiprazole tablets is 10 mg/day. Aripiprazole was studied in adolescent patients 13 to 17 years of age with schizophrenia at daily doses of 10 mg and 30 mg. The starting daily dose of the tablet formulation 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/day dose was not shown to be more efficacious than the 10 mg/day dose. Aripiprazole tablets can be administered without regard to meals *[see CLINICAL STUDIES (14.1)]*. Patients should be periodically reassessed to determine the need for maintenance treatment.

Switching from Other Antipsychotics

There are no systematically collected data to specifically address switching patients with schizophrenia from other antipsychotics to aripiprazole tablets or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized.

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2.7 Dosage Adjustments for Cytochrome P450 Considerations

Dosage adjustments are recommended in patients who are known CYP2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors or strong CYP3A4 inducers (see Table 1). When the coadministered drug is withdrawn from the combination therapy, aripiprazole tablets dosage should then be adjusted to its original level. When the coadministered CYP3A4 inducer is withdrawn, aripiprazole tablets dosage should be reduced to the original level over 1 to 2 weeks. Patients who may be 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 usual dose initially and then adjusted to achieve a favorable clinical response.

Table 1: Dose Adjustments for aripiprazole tablets in Patients who are known CYP2D6 Poor Metabolizers and Patients Taking Concomitant CYP2D6 Inhibitors, 3A4 Inhibitors, and/or CYP3A4 Inducers

Factors	Dosage Adjustments for Aripiprazole Tablets
Known CYP2D6 Poor Metabolizers	Administer half of usual dose
Known CYP2D6 Poor Metabolizers taking concomitant strong CYP3A4 inhibitors (e.g., itraconazole, clarithromycin)	Administer a quarter of usual dose
Strong CYP2D6 (e.g., quinidine, fluoxetine, paroxetine) **or** CYP3A4 inhibitors (e.g., itraconazole, clarithromycin)	Administer half of usual dose
Strong CYP2D6 **and** CYP3A4 inhibitors	Administer a quarter of usual dose
Strong CYP3A4 inducers (e.g., carbamazepine, rifampin)	Double usual dose over 1 to 2 weeks

2.8 Dosing of Oral Solution

The oral solution can be substituted for tablets on a mg-per-mg basis up to the 25 mg dose level. Patients receiving 30 mg tablets should receive 25 mg of the solution *[see CLINICAL PHARMACOLOGY (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Aripiprazole tablets are available as described in Table 2.

Table 2: Aripiprazole Tablets Presentations

Tablet Strength	Tablet Color/Shape	Tablet Markings
2 mg	Light green to green modified rectangle	"I" and "94"
5 mg	Light blue to blue modified rectangle	"I" and "95"
10 mg	Light pink to pink modified rectangle	"I" and "96"
15 mg	Light yellow to yellow round	"I" and "97"
20 mg	White to off white round	"I" and "98"
30 mg	Light pink to pink round	"I " and "99"

4 CONTRAINDICATIONS

Aripiprazole tablets are contraindicated in patients with a history of a hypersensitivity reaction to aripiprazole. Reactions have ranged from pruritus/urticaria to anaphylaxis *[see ADVERSE REACTIONS (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Increased Mortality

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Aripiprazole tablets are not approved for the treatment of patients with dementia-related psychosis *[see BOXED WARNING]*.

Safety Experience in Elderly Patients with Psychosis Associated with Alzheimer's Disease

In three, 10-week, placebo-controlled studies of aripiprazole tablets in elderly patients with psychosis associated with Alzheimer's disease (n=938; mean age: 82.4 years; range: 56 to 99 years), the adverse reactions that were reported at an incidence of ≥3% and aripiprazole tablets incidence at least twice that for placebo were lethargy [placebo 2%, aripiprazole tablets 5%], somnolence (including sedation) [placebo 3%, aripiprazole tablets 8%], and incontinence (primarily, urinary incontinence) [placebo 1%, aripiprazole tablets 5%], excessive salivation [placebo 0%, aripiprazole tablets 4%], and lightheadedness [placebo 1%, aripiprazole tablets 4%].

The safety and efficacy of aripiprazole tablets in the treatment of patients with psychosis associated with dementia have not been established. If the prescriber elects to treat such patients with aripiprazole tablets, assess for the emergence of difficulty swallowing or excessive somnolence, which could predispose to accidental injury or aspiration *[see BOXED WARNING]*.

5.2 Cerebrovascular Adverse Events, Including Stroke

In placebo-controlled clinical studies (two flexible dose and one fixed dose study) of dementia-related psychosis, there was an increased incidence of cerebrovascular adverse events (eg, 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 events in patients treated with aripiprazole tablets. Aripiprazole tablets are not approved for the treatment of patients with dementia-related psychosis *[see BOXED WARNING]*.

5.3 Suicidal Thoughts and Behaviors in Children, Adolescents and Young Adults

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term, placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18 to 24) with MDD and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

[illegible]

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for aripiprazole tablets should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

It should be noted that aripiprazole tablets are not approved for use in treating depression in the pediatric population.

5.4 Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) may occur with administration of antipsychotic drugs, including aripiprazole tablets. Rare cases of NMS occurred during aripiprazole tablets treatment in the worldwide 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.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (eg, pneumonia, systemic infection) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

5.5 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 rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and, thereby, may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, aripiprazole tablets 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 tarvdive dyskinesia appear in a patient on aripiprazole tablets, drug discontinuation should be considered. However, some patients may require treatment with aripiprazole tablets 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 ketoacidosis or hyperosmolar coma or death, has been reported in patients treated atypical antipsychotics. There have been reports of hyperglycemia in patients treated with aripiprazole tablets *[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. Because aripiprazole tablets were not marketed at the time these studies were performed, it is not known if aripiprazole tablets are associated with this increased risk. Precise risk estimates for hyperglycemia-related adverse reactions in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (eg, 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 suspect 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=1057) was not significantly different than in placebo-treated patients (+2.5 mg/dL; median exposure 22 days; N=799). Table 4 shows the proportion of aripiprazole-treated patients with normal and borderline fasting glucose at baseline (median exposure 25 days) that had treatment-emergent high fasting glucose measurements compared to placebo-treated patients (median exposure 22 days).

Table 4: Changes in Fasting Glucose From Placebo-Controlled Monotherapy Trials in Adult Patients

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

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

Pediatric Patients and Adolescents

In an analysis of two placebo-controlled trials in adolescents with schizophrenia (13 to 17 years) and pediatric patients with another indication (10 to 17 years), the mean change in fasting glucose in aripiprazole tablets-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).

Table 5 shows the proportion of patients with changes in fasting glucose levels from the pooled patients with adolescent schizophrenia and another indication (median exposure of 42 to 43 days).

Table 5: Changes in Fasting Glucose From Placebo-Controlled Trials in Pediatric and Adolescent Patients

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 tablets	2/236	0.8
		Placebo	2/110	1.8
Fasting Glucose Borderline to High (≥100 mg/dL and <126 mg/dL to ≥ 126 mg/dL)	Pooled Schizophrenia and another indication	Aripiprazole tablets	1/22	4.5
		Placebo	0/12	0

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

Dyslipidemia

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

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

Adults

Table 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 tablets	34/1357	2.5
	Placebo	27/973	2.8
Fasting Triglycerides Normal to High	Aripiprazole tablets	40/539	7.4
[illegible]	Placebo	[illegible]	[illegible]

[illegible]

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 tablets-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 tablets-treated patients was –1.5 kg (n=73) compared to –0.2 kg (n=46) in placebo-treated patients.

Table 8 shows the percentage of adult patients with weight gain ≥7% of body weight by indication.

Table 8: Percentage of Patients From Placebo-Controlled Trials in Adult Patients with Weight Gain ≥7% of Body Weight

	Indication	Treatment Arm	N	Patients n (%)
Weight gain ≥ 7% of body weight	Schizophrenia[a]	Aripiprazole tablets	852	69 (8.1)
		Placebo	379	12 (3.2)
	Other indication[b]	Aripiprazole tablets	719	16 (2.2)
		Placebo	598	16 (2.7)

[a]4 to 6 weeks duration. [b]3 weeks duration.

Pediatric Patients and Adolescents

In an analysis of two placebo-controlled trials in adolescents with schizophrenia (13 to 17 years) and pediatric patients with another indication (10 to 17 years) with median exposure of 42 to 43 days, the mean change in body weight in aripiprazole tablets-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 tablets-treated patients was +5.8 kg (n=62) compared to +1.4 kg (n=13) in placebo-treated patients.

Table 9 shows the percentage of pediatric and adolescent patients with weight gain ≥7% of body weight by indication.

Table 9: Percentage of Patients From Placebo-Controlled Monotherapy Trials in Pediatric and Adolescent Patients with Weight Gain ≥7% of Body Weight

	Indication	Treatment Arm	N	Patients n (%)
Weight gain ≥7% of body weight	Pooled Schizophrenia and another Indication[a]	Aripiprazole tablets	381	20 (5.2)
		Placebo	187	3 (1.6)

[a]4 to 6 weeks duration.

In an open-label trial that enrolled patients from the two placebo-controlled trials of adolescents with schizophrenia (13 to 17 years) and pediatric patients with another indication (10 to 17 years), 73.2% of patients (238/325) completed 26 weeks of therapy with aripiprazole tablets. 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.

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

Additional pediatric use information is approved for Otsuka America Pharmaceutical, Inc.'s ABILIFY® (aripiprazole) product. However, due to Otsuka America Pharmaceutical, Inc.'s marketing exclusivity rights, this drug product is not labeled with that information.

5.7 Orthostatic Hypotension

Aripiprazole tablets 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 on oral aripiprazole tablets (n=2467) included (aripiprazole tablets 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 oral aripiprazole tablets 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 aripiprazole tablets was not meaningfully different from placebo (aripiprazole tablets incidence, placebo incidence): in adult oral aripiprazole tablets-treated patients (4%, 2%), in pediatric oral aripiprazole tablets-treated patients aged 6 to 18 years (0.4%, 1%).

Aripiprazole should be used 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)]*.

5.8 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 tablets. 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 aripiprazole tablets 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 treated promptly if such symptoms or signs occur. Discontinue aripiprazole tablets in patients with severe neutropenia (absolute neutrophil count <1000/mm³) and follow their WBC counts until recovery.

5.9 Seizures/Convulsions

In short-term, placebo-controlled trials, patients with a history of seizures excluded seizures/convulsions occurred in 0.1% (3/2467) of undiagnosed adult patients treated with oral aripiprazole tablets, in 0.1% (1/732) of pediatric patients (6 to 18 years).

As with other antipsychotic drugs, aripiprazole tablets should be used 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.

5.10 Potential for Cognitive and Motor Impairment

Aripiprazole tablets, like other antipsychotics, may have the potential to impair judgment, thinking, or motor skills. For example, in short-term, placebo-controlled trials, somnolence (including sedation) was reported as follows (aripiprazole incidence, placebo incidence): in adult patients (n=2467) treated with oral aripiprazole tablets (11%, 6%), in pediatric patients ages 6 to 17 (n=611) (24%, 6%). Somnolence (including sedation) led to discontinuation in 0.3% (8/2467) of adult patients and 3% (20/732) of pediatric patients (6 to 18 years) on oral aripiprazole tablets in short-term, placebo-controlled trials.

Despite the relatively modest increased incidence of these events compared to placebo, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with aripiprazole tablets does not affect them adversely.

5.11 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 aripiprazole tablets 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)]*.

5.12 Suicide

The possibility of a suicide attempt is inherent in psychotic illnesses and close supervision of high-risk patients should accompany drug therapy. Prescriptions for aripiprazole tablets should be written for the smallest quantity consistent with good patient management in order to reduce the risk of overdose *[see ADVERSE REACTIONS (6.1, 6.2)]*.

5.13 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use, including aripiprazole tablets. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. Aripiprazole tablets 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

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

- Increased Mortality in Elderly Patients with Dementia-Related Psychosis *[see BOXED WARNING and WARNINGS AND PRECAUTIONS (5.1)]*
- Cerebrovascular Adverse Events, Including Stroke *[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)]*
- Orthostatic Hypotension *[see WARNINGS AND PRECAUTIONS (5.7)]*
- Leukopenia, Neutropenia, and Agranulocytosis *[see WARNINGS AND PRECAUTIONS (5.8)]*
- Seizures/Convulsions *[see WARNINGS AND PRECAUTIONS (5.9)]*
- Potential for Cognitive and Motor Impairment *[see WARNINGS AND PRECAUTIONS (5.10)]*
- Body Temperature Regulation *[see WARNINGS AND PRECAUTIONS (5.11)]*
- Suicide *[see WARNINGS AND PRECAUTIONS (5.12)]*
- Dysphagia *[see WARNINGS AND PRECAUTIONS (5.13)]*

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

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

Aripiprazole has been evaluated for safety in 13,543 adult patients who participated in multiple-dose, clinical trials in schizophrenia, other indications, Dementia of the Alzheimer's type, Parkinson's disease, and alcoholism, and who had approximately 7619 patient-years of exposure to oral aripiprazole tablets . A total of 3390 patients were treated with oral aripiprazole tablets for at least 180 days and 1933 patients treated with oral aripiprazole tablets had at least 1 year of exposure.

Aripiprazole has been evaluated for safety in 1,686 patients (6 to 18 years) who participated in multiple-dose, clinical trials in schizophrenia, or other indications and 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 1 year of exposure.

The conditions and duration of treatment with aripiprazole tablets 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.

Additional pediatric use information is approved for Otsuka America Pharmaceutical, Inc.'s ABILIFY® (aripiprazole) product. However, due to Otsuka America Pharmaceutical, Inc.'s marketing exclusivity rights, this drug product is not labeled with that information.

6.1 Clinical Trials Experience

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 tablets were administered in doses ranging from 2 to 30 mg/day.

Commonly Observed Adverse Reactions

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

Less Common Adverse Reactions in Adults

Table 10 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 tablets (doses =2 mg/day) and for which the incidence in patients treated with aripiprazole tablets was greater than the incidence in patients treated with placebo in the combined dataset.

Table 10: Adverse Reactions in Short-Term, Placebo-Controlled Trials in Adult Patients Treated with Oral Aripiprazole Tablets

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

[illegible]

Table 11: Adverse Reactions in Short-Term, Placebo-Controlled Trials of Pediatric Patients (6 to 18 years) Treated with Oral Aripiprazole Tablets

System Organ Class Preferred Term	Percentage of Patients Reporting Reaction[a] Aripiprazole tablets (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

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

Dose-Related Adverse Reactions

Schizophrenia

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

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

Extrapyramidal Symptoms

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 tablets-treated patients was 13% vs. 12% for placebo; and the incidence of akathisia-related events for aripiprazole tablets-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 tablets-treated patients was 25% vs. 7% for placebo; and the incidence of akathisia-related events for aripiprazole tablets-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 tablets 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 tablets and placebo, with the exception of the Simpson Angus Rating Scale (aripiprazole tablets, 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 tablets 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 tablets 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 infrequently led to discontinuation (<1%) of aripiprazole tablets. In addition, in a long-term (52-week), active-controlled study, the incidence of tremor was 5% (40/859) for aripiprazole tablets.

Other Adverse Reactions Observed During the Premarketing Evaluation of Aripiprazole Tablets

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

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

Adults - Oral Administration

Blood and Lymphatic System Disorders:

rare - thrombocytopenia

Cardiac Disorders:

infrequent – bradycardia, palpitations, *rare* – atrial flutter, 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

[illegible]

Pregnant rats were treated with oral doses of 3, 10, and 30 mg/kg/day (1, 3, and 10 times the maximum recommended human dose [MRHD] on a mg/m[2] basis) of aripiprazole during the period of organogenesis. Gestation was slightly prolonged at 30 mg/kg/day. Treatment at the high dose of 30 mg/kg/day caused a slight delay in fetal development (decreased fetal weight), undescended testes, and delayed skeletal ossification (also seen at 10 mg/kg/day). There were no adverse effects on embryofetal or pup survival. Delivered offspring had decreased body weights (10 and 30 mg/kg/day), and increased incidences of hepatodiaphragmatic nodules and diaphragmatic hernia at 30 mg/kg (the other dose groups were not examined for these findings). Postnatally, delayed vaginal opening was seen at 10 and 30 mg/kg/day and impaired reproductive performance (decreased fertility rate, corpora lutea, implants, live fetuses, and increased post-implantation loss, likely mediated through effects on female offspring) was seen at 30 mg/kg/day. Some maternal toxicity was seen at 30 mg/kg/day however, there was no evidence to suggest that these developmental effects were secondary to maternal toxicity.

Pregnant rabbits were treated with oral doses of 10, 30, and 100 mg/kg/day (2, 3, and 11 times human exposure at MRHD based on AUC and 6, 19, and 65 times the MRHD based on mg/m[2]) of aripiprazole during the period of organogenesis. At the high dose of 100 mg/kg/day decreased maternal food consumption, and increased abortions were seen as well as increased fetal mortality, decreased fetal weight (also seen at 30 mg/kg/day), increased incidence of a skeletal abnormality (fused sternebrae) (also seen at 30 mg/kg/day).

In a study in which rats were treated peri- and post-natally with oral doses of 3, 10, and 30 mg/kg/day (1, 3, and 10 times the MRHD on a mg/m[2] basis) of aripiprazole from day 17 through day 21 postpartum, slight maternal toxicity, slightly prolonged gestation an increase in stillbirths and, decreases in pup weight (persisting into adulthood) and survival were seen at 30 mg/kg/day.

8.2 Labor and Delivery

The effect of aripiprazole tablets on labor and delivery in humans is unknown.

8.3 Nursing Mothers

Aripiprazole is present in human breast milk. Because of the potential for serious adverse reactions in nursing infants from aripiprazole tablets, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

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 in 202 pediatric patients aged 13 to 17 years *[see DOSAGE AND ADMINISTRATION (2.1), ADVERSE REACTIONS (6.1), and CLINICAL STUDIES (14.1)]*. 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.

Information describing a clinical study in which efficacy was not demonstrated in patients ages 6 to 17 years is approved for Otsuka America Pharmaceutical, Inc.'s ABILIFY® (aripiprazole). Additional pediatric use information in patients ages 6 to 18 years is approved for Otsuka America Pharmaceutical, Inc.'s ABILIFY® (aripiprazole) product. However, due to Otsuka America Pharmaceutical, Inc.'s marketing exclusivity rights, this drug product is not labeled with that pediatric information.

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, 40mg/kg/day from weaning (21 days old) through maturity (80 days old). At 40mg/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 10mg/kg/day, there is no safety margin relative to the systemic exposures ($AUC_{0\ to\ 24}$) 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_{0to24}) for aripiprazole or its major active metabolite in adolescents at the maximum recommended pediatric dose of 15 mg/day. All drug-related effects were reversible after a 2-month recovery period.

8.5 Geriatric Use

No dosage adjustment is recommended for elderly patients *[see BOXED WARNING, WARNINGS AND PRECAUTIONS (5.1), and CLINICAL PHARMACOLOGY (12.3)]*.

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

Aripiprazole tablets are not approved for the treatment of patients with psychosis associated with Alzheimer's disease *[see also BOXED WARNING and WARNINGS AND PRECAUTIONS (5.1)]*.

8.6 CYP2D6 Poor Metabolizers

Dosage adjustment is recommended in known CYP2D6 poor metabolizers due to high aripiprazole concentrations. Approximately 8% of Caucasians and 3 to 8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers (PM) [*see DOSAGE AND ADMINISTRATION (2.7) and CLINICAL PHARMACOLOGY (12.3)*].

8.7 Hepatic and Renal Impairment

No dosage adjustment for aripiprazole tablets is required on the basis of a patient's hepatic function (mild to severe hepatic impairment, Child-Pugh score between 5 and 15), or renal function (mild to severe renal impairment, glomerular filtration rate between 15 and 90 mL/minute) *[see CLINICAL PHARMACOLOGY (12.3)]*.

8.8 Other Specific Populations

No dosage adjustment for aripiprazole tablets are required on the basis of a patient's sex, race, or smoking status *[see CLINICAL PHARMACOLOGY (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Aripiprazole tablet is not a controlled substance.

9.2 Abuse

Aripiprazole tablet 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 tablets 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

MedDRA terminology has been used to classify the adverse reactions.

10.1 Human Experience

In clinical trials and in postmarketing experience, adverse reactions of deliberate or accidental overdosage with oral aripiprazole tablets have been reported worldwide. These include overdoses with oral aripiprazole tablets alone and in combination with other substances. No fatality was reported with aripiprazole tablets alone. The largest known dose with a known outcome involved acute ingestion of 1260 mg of oral aripiprazole tablets (42 times the maximum recommended daily dose) by a patient who fully recovered. Deliberate or accidental overdosage was also reported in children (age 12 and younger) involving oral aripiprazole tablet ingestions up to 195 mg with no fatalities

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

10.2 Management of Overdosage

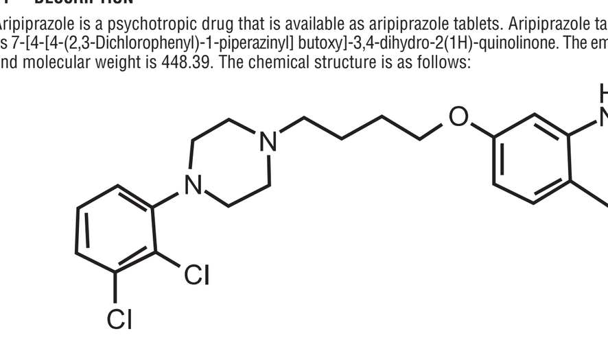
No specific information is available on the treatment of overdose with aripiprazole tablets. An electrocardiogram should be obtained in case of overdosage and if QT interval prolongation is present, cardiac monitoring should be instituted. Otherwise, management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. Close medical supervision and monitoring should continue until the patient recovers.

Charcoal: In the event of an overdose of aripiprazole tablets , 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 tablets, decreased the mean AUC and C_{max} of aripiprazole by 50%.

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

11 DESCRIPTION

Aripiprazole is a psychotropic drug that is available as aripiprazole tablets. Aripiprazole tablets are chemically designated as 7-[4-[4-(2,3-Dichlorophenyl)-1-piperazinyl] butoxy]-3,4-dihydro-2(1H)-quinolinone. The empirical formula is $C_{23}H_{27}Cl_2N_3O_2$, and molecular weight is 448.39. The chemical structure is as follows:



Aripiprazole tablets are available in 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg strengths. Inactive ingredients include corn starch, FD&C Blue #2/Indigo Carmine Al, ferric oxide red, ferric oxide yellow, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate and microcrystalline cellulose.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of aripiprazole in schizophrenia is unknown. However, the efficacy of aripiprazole could be mediated through a combination of partial agonist activity at D_2 and $5\text{-}HT_{1A}$ receptors and antagonist activity at $5\text{-}HT_{2A}$ receptors. Actions at receptors other than D_2, $5\text{-}HT_{1A}$, and $5\text{-}HT_{2A}$ may explain some of the other clinical effects of aripiprazole (e.g., the orthostatic hypotension observed with aripiprazole may be explained by its antagonist activity at adrenergic $alpha_1$ receptors).

12.2 Pharmacodynamics

Aripiprazole exhibits high affinity for dopamine D_2 and D_3, serotonin $5\text{-}HT_{1A}$ and $5\text{-}HT_{2A}$ receptors (K_i values of 0.34 nM, 0.8 nM, 1.7 nM, and 3.4 nM, respectively), moderate affinity for dopamine D_4, serotonin $5\text{-}HT_{2C}$ and $5\text{-}HT_7$, $alpha_1$-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 (K_i=98 nM). Aripiprazole has no appreciable affinity for cholinergic muscarinic receptors (IC_{50}>1000 nM). [Aripiprazole functions as a partial agonist at the dopamine D_2 and the serotonin $5\text{-}HT_{1A}$ receptors, and as an antagonist at serotonin $5\text{-}HT_{2A}$ receptor.]

12.3 Pharmacokinetics

Aripiprazole tablets 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. The mean elimination half-lives are about 75 hours and 94 hours for aripiprazole and dehydro-aripiprazole, 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. Elimination of aripiprazole is mainly through hepatic metabolism involving two P450 isozymes, CYP2D6 and CYP3A4. For CYP2D6 poor metabolizers, the mean elimination half-life for aripiprazole is about 146 hours.

ORAL ADMINISTRATION

Absorption

Tablet: Aripiprazole is well absorbed after administration of the tablet, with peak plasma concentrations occurring within 3 hours to 5 hours; the absolute oral bioavailability of the tablet formulation is 87%. Aripiprazole tablets can be administered with or without food. Administration of a 15 mg aripiprazole tablet with a standard high-fat meal did not significantly affect the C_{max} or AUC of aripiprazole or its active metabolite, dehydro-aripiprazole, but delayed T_{max} by 3 hours for aripiprazole and 12 hours for dehydro-aripiprazole.

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 D2 receptor occupancy indicating brain penetration of aripiprazole in humans.

Metabolism and Elimination

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.

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

Effects 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 effects of other drugs on aripiprazole pharmacokinetics

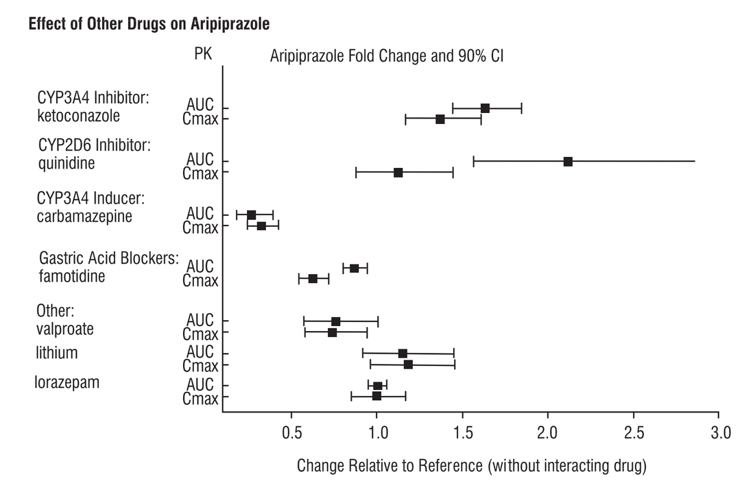
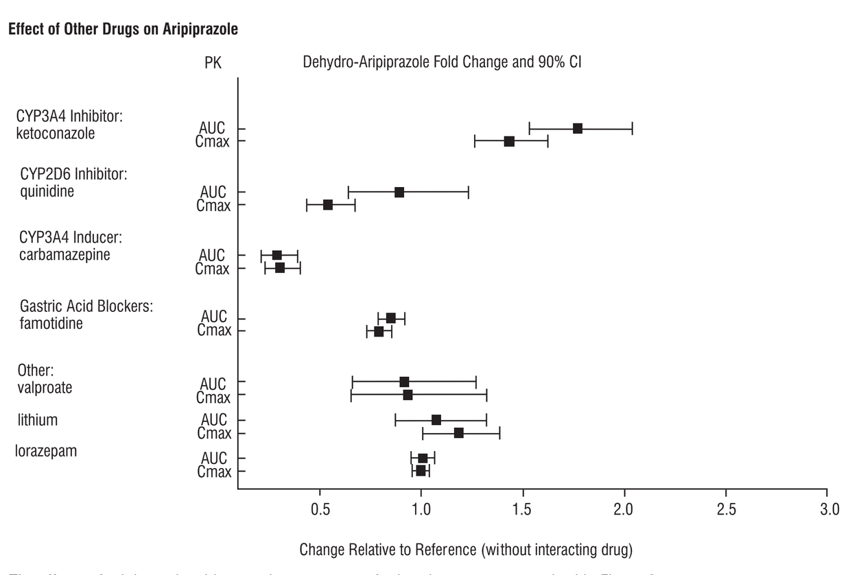
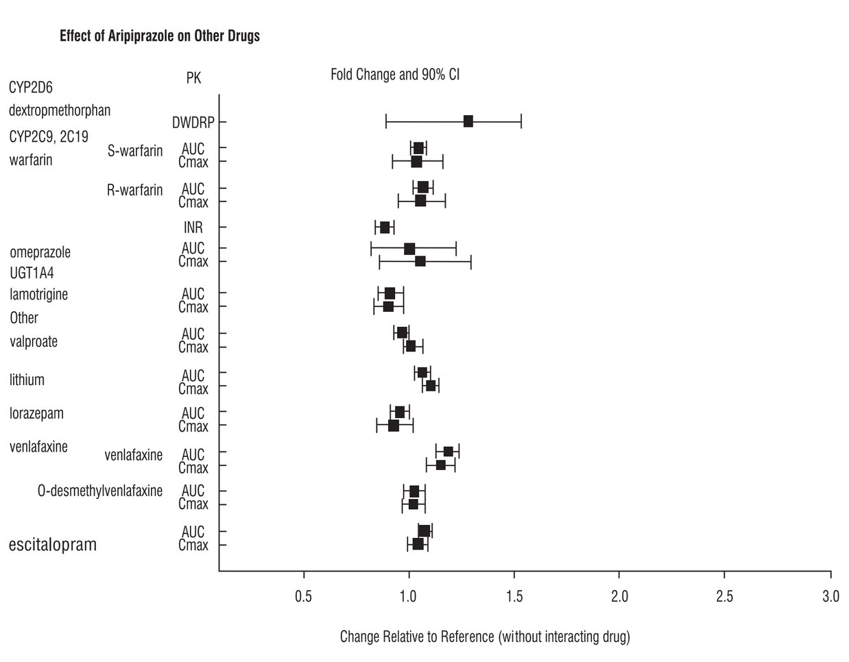


Figure 2: The effects of other drugs on dehydro-aripiprazole pharmacokinetics



The effects of aripiprazole tablets on the exposures of other drugs are summarized in Figure 3.

Figure 3: The effects of aripiprazole on pharmacokinetics of other drugs



Studies in Specific Populations

Exposures of aripiprazole and dehydro-aripiprazole in specific populations are summarized in Figure 4 and Figure 5, respectively. In addition, in pediatric patients (10 to 17 years of age) administered with aripiprazole tablets (20 mg to 30 mg), the body weight corrected aripiprazole clearance was similar to the adults.

Figure 4: Effects of intrinsic factors on aripiprazole pharmacokinetics

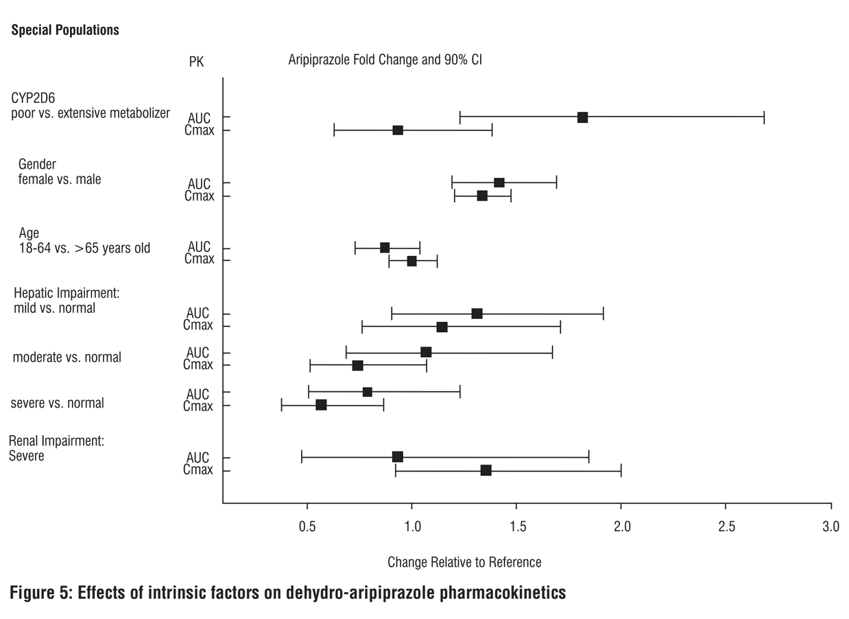
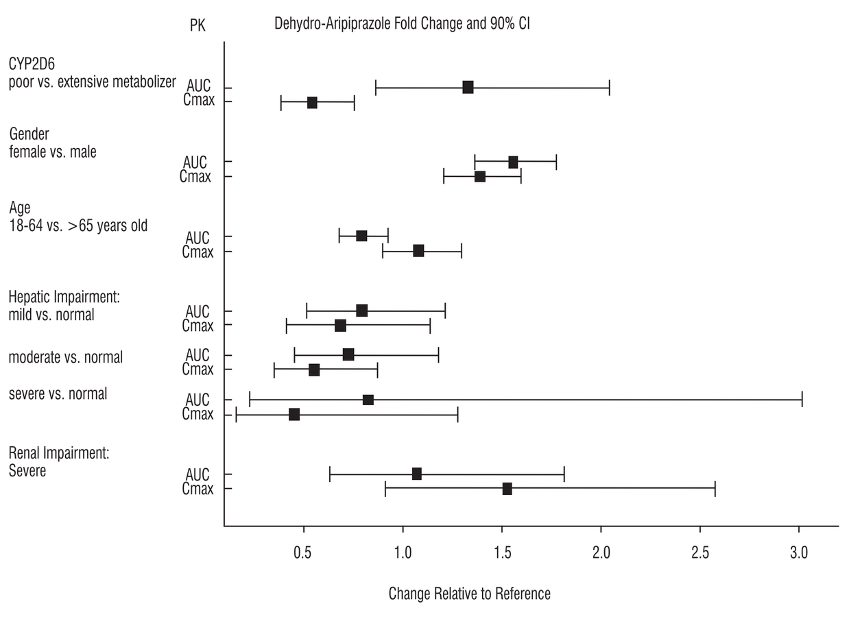


Figure 5: Effects of intrinsic factors on dehydro-aripiprazole pharmacokinetics



13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Lifetime carcinogenicity studies were conducted in ICR mice and in Sprague-Dawley (SD) rats, and F344 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 to 5 times and 0.3 to 3 times the maximum recommended human dose [MRHD] based on mg/m[2], respectively). In addition, SD rats were dosed orally for 2 years at 10, 20, 40, and 60 mg/kg/day (3 to 19 times the MRHD based on mg/m[2]). 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 (0.1 to 0.9 times human exposure at MRHD based on AUC and 0.5 to 5 times the MRHD based on mg/m[2]). In female rats, the incidence of mammary gland fibroadenomas was increased at a dietary dose of 10 mg/kg/day (0.1 times human exposure at MRHD based on AUC and 3 times the MRHD based on mg/m[2]); and the incidences of adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas were increased at an oral dose of 60 mg/kg/day (14 times human exposure at MRHD based on AUC and 19 times the MRHD based on mg/m[2]).

Proliferative changes in the pituitary and mammary gland of rodents have been observed following chronic administration of other antipsychotic agents and are considered prolactin-mediated. 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 unknown.

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, produced increases in 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 with oral doses of 2, 6, and 20 mg/kg/day (0.6, 2 , and 6 times the maximum recommended human dose [MRHD] on a mg/m[2]basis) of aripiprazole from 2 weeks prior to mating through day 7 of gestation. 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 6 and 20 mg/kg/day and decreased fetal weight was seen at 20 mg/kg/day.

Male rats were treated with oral doses of 20 , 40 , and 60 mg/kg/day (6, 13, and 19 times the MRHD on a mg/m[2] basis) of aripiprazole from 9 weeks prior to mating through mating. Disturbances in spermatogenesis were seen at 60 mg/kg and prostate atrophy was seen at 40 and 60 mg/kg, but no impairment of fertility was seen.

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 and in a 2-year carcinogenicity study at doses of 40 and 60 mg/kg. The 40 and 60 mg/kg/day doses are 13 and 19 times the maximum recommended human dose (MRHD) based on mg/m[2] and 7 to 14 times human exposure at MRHD based on AUC. 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

Efficacy of the oral formulations of aripiprazole tablet was established in the following adequate and well-controlled trials:

- Four short-term trials and one maintenance trial in adult patients and one short-term trial in adolescents (ages 13 to 17) with schizophrenia [*see CLINICAL STUDIES (14.1)*]

Additional pediatric use information is approved for Otsuka America Pharmaceutical, Inc.'s ABILIFY® (aripiprazole) product. However, due to Otsuka America Pharmaceutical, Inc.'s marketing exclusivity rights, this drug product is not labeled with that information.

14.1 Schizophrenia

Adults

The efficacy of aripiprazole tablets 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 tablets 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 tablets and the active comparators.

In the four positive trials for aripiprazole tablets, 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 tablets (15 or 30 mg/day) to placebo, both doses of aripiprazole tablets were superior to placebo in the PANSS total score (Study 1 in Table 16), 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 tablets (20 or 30 mg/day) to placebo, both doses of aripiprazole tablets were superior to placebo in the PANSS total score (Study 2 in Table 13), PANSS positive subscale, PANSS negative subscale, and CGI-severity score.

In a 6-week trial (n=420) comparing three fixed doses of aripiprazole tablets (10, 15, or 20 mg/day) to placebo, all three doses of aripiprazole tablets were superior to placebo in the PANSS total score (Study 3 in Table 13), PANSS positive subscale, and the PANSS negative subscale.

In a 6-week trial (n=367) comparing three fixed doses of aripiprazole tablets (2, 5, or 10 mg/day) to placebo, the 10 mg dose of aripiprazole tablets was superior to placebo in the PANSS total score (Study 4 in Table 13), 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 tablets 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 tablets 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

The efficacy of aripiprazole tablets 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 tablets (10 mg/day or 30 mg/day) to placebo, aripiprazole tablets were 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 tablets were superior to placebo in the PANSS total score (Study 6 in Table 13), 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 13: Schizophrenia Studies

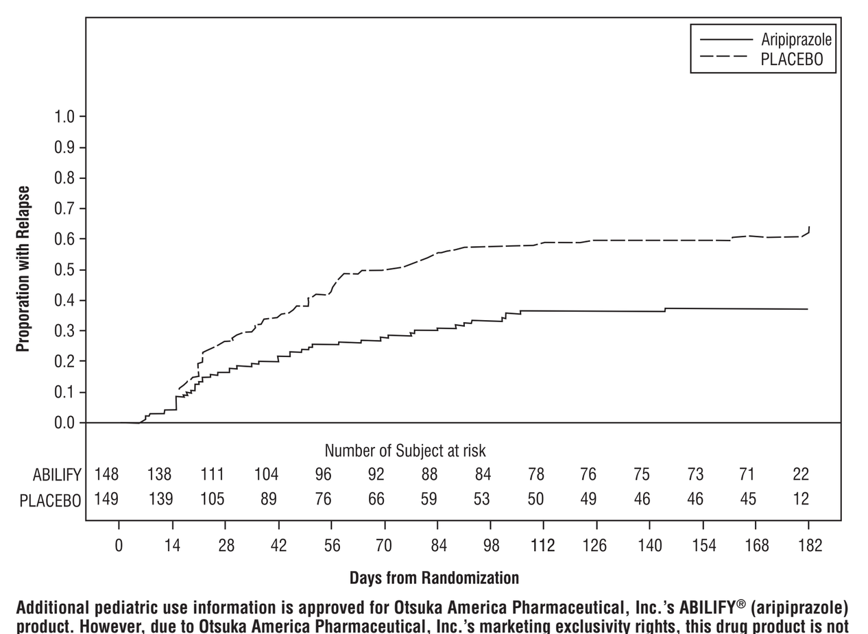
Study Number	Treatment Group	Primary Efficacy Measure: PANSS		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo subtracted Difference[a] (95% CI)
Study 1	Aripiprazole tablets (15 mg/day)*	98.5 (17.2)	-15.5 (2.40)	-12.6 (-18.9, -6.2)
	Aripiprazole tablets (30 mg/day)*	99 (19.2)	-11.4 (2.39)	-8.5 (-14.8, -2.1)
	Placebo	100.2 (16.5)	-2.9 (2.36)	--
Study 2	Aripiprazole tablets (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 (-14.8, -3.1)
	Placebo	94.3 (18.5)	-5 (2.17)	--
Study 3	Aripiprazole (10 mg/day)*	92.7(19.5)	-15 (2.38)	-12.7 (-19, -6.41)
	Aripiprazole tablets (15 mg/day)*	93.2 (21.6)	-11.7 (2.38)	-9.4 (-15.71, 3.08)
	Aripiprazole tablets (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 tablets (2 mg/day)	90.7(14.5)	-8.2 (1.90)	-2.9 (-8.29, 2.47)
	Aripiprazole tablets (5 mg/day)	92 (12.6)	-10.6 (1.93)	-5.2 (-10.7, 0.19)
	Aripiprazole tablets (10 mg/day)*	90 (11.9)	-11.3 (1.88)	-5.9 (-11.3, -0.58)
	Placebo	90.8 (13.3)	-5.3 (1.97)	--
Study 6	Aripiprazole tablets (10 mg/day)*	93.6 (15.7)	-26.7 (1.91)	-5.5 (-10.7, -0.21)
(Pediatric	Aripiprazole tablets (30 mg/day)*	94 (16.1)	-28.6 (1.92)	-7.4 (-12.7, -2.13)
13-17 Years)	Placebo	94.6 (15.6)	-21.2 (1.93)	--

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

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

* Doses statistically significantly superior to placebo.

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



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16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Aripiprazole tablets, 2 mg are light green to green, modified rectangular, bevel edged biconvex tablets debossed with 'I' on one side and '94' on other side.

Bottles of 30 Tablets	NDC 31722-819-30
Bottles of 100 Tablets	NDC 31722-819-01
Blister card of 10 Unit dose tablets	NDC 31722-819-31
Blister pack of 250 (25 x 10) Unit dose tablets	NDC 31722-819-32

Aripiprazole tablets, 5 mg are light blue to blue, modified rectangular, bevel edged biconvex tablets debossed with 'I' on one side and '95' on other side.

Bottles of 30 Tablets	NDC 31722-820-30
Bottles of 100 Tablets	NDC 31722-820-01
Blister card of 10 Unit dose tablets	NDC 31722-820-31
Blister pack of 250 (25 x 10) Unit dose tablets	NDC 31722-820-32

Aripiprazole tablets, 10 mg are light pink to pink, modified rectangular, bevel edged biconvex tablets debossed with 'I' on one side and '96' on other side.

Bottles of 30 Tablets	NDC 31722-827-30
Bottles of 100 Tablets	NDC 31722-827-01
Blister card of 10 Unit dose tablets	NDC 31722-827-31
Blister pack of 250 (25 x 10) Unit dose tablets	NDC 31722-827-32

Aripiprazole tablets, 15 mg are light yellow to yellow, round, bevel edged biconvex tablets debossed with 'I' on one side and '97' on other side.

Bottles of 30 Tablets	NDC 31722-828-30
Bottles of 100 Tablets	NDC 31722-828-01
Blister card of 10 Unit dose tablets	NDC 31722-828-31
Blister pack of 250 (25 x 10) Unit dose tablets	NDC 31722-828-32

Aripiprazole tablets, 20 mg are white to off-white, round, bevel edged biconvex tablets debossed with 'I' on one side and '98' on other side.

Bottles of 30 Tablets	NDC 31722-829-30
Bottles of 100 Tablets	NDC 31722-829-01
Blister card of 10 Unit dose tablets	NDC 31722-829-31
Blister pack of 250 (25 x 10) Unit dose tablets	NDC 31722-829-32

Aripiprazole tablets, 30 mg are light pink to pink, round, bevel edged biconvex tablets debossed with 'I' on one side and '99' on other side.

Bottles of 30 Tablets	NDC 31722-830-30
Bottles of 100 Tablets	NDC 31722-830-01
Blister card of 10 Unit dose tablets	NDC 31722-830-31
Blister pack of 250 (25 x 10) Unit dose tablets	NDC 31722-830-32

16.2 Storage

Store at 20º to 25º C (68º to 77ºF) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See Medication Guide

Discuss the following issues with patients prescribed aripiprazole tablets:

Clinical Worsening of Depression and Suicide Risk

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior **and indicate a need for very close monitoring and possibly changes in the medication** *[see WARNINGS AND PRECAUTIONS (5.3)]*.

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with aripiprazole tablets and should counsel them in its appropriate use. A patient Medication Guide including information about "Antidepressant Medicines, Depression and other Serious Mental Illness, and Suicidal Thoughts or Actions" is available for aripiprazole tablets. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. It should be noted that aripiprazole tablets are not approved as a single agent for treatment of depression and has not been evaluated in pediatric major depressive disorder.

Interference with Cognitive and Motor Performance

Because aripiprazole tablets may have the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that aripiprazole tablets therapy does not affect them adversely *[see WARNINGS AND PRECAUTIONS (5.10)]*.

Nursing

Advise patients that breastfeeding is not recommended with aripiprazole treatment because of the potential for serious adverse reactions in a nursing infant *[see USE IN SPECIFIC POPULATIONS (8.3)]*.

Concomitant Medication

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions *[see DRUG INTERACTIONS (7)]*.

Heat Exposure and Dehydration

Patients should be advised regarding appropriate care in avoiding overheating and dehydration *[see WARNINGS AND PRECAUTIONS (5.11)]*.

CAMBER™ PHARMACEUTICALS, INC.

2034677

Manufactured for:
Camber Pharmaceuticals, Inc.
Piscataway, NJ 08854

By: HETERO™
Hetero Labs Limited, Unit V, Polepally, Jadcherla,
Mahaboob Nagar - 509 301, India.

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Revised: February 2016

What should I avoid while taking aripiprazole tablets?

- Do not drive, operate heavy machinery, or do other dangerous activities until you know how aripiprazole tablets affects you. Aripiprazole tablets may make you drowsy.
- Avoid getting over-heated or dehydrated.
  - Do not over-exercise.
  - In hot weather, stay inside in a cool place if possible.
  - Stay out of the sun. Do not wear too much or heavy clothing.
  - Drink plenty of water.

What are the possible side effects of aripiprazole tablets?

Aripiprazole tablets may cause serious side effects, including:

- **See "What is the most important information I should know about aripiprazole tablets?"**
- **Stroke in elderly people (cerebrovascular problems) that can lead to death**
- **Neuroleptic malignant syndrome (NMS):** Tell your healthcare provider right away if you have some or all of the following symptoms: high fever, stiff muscles, confusion, sweating, changes in pulse, heart rate, and blood pressure. These may be symptoms of a rare and serious condition that can lead to death. Call your healthcare provider right away if you have any of these symptoms.
- **Uncontrolled body movements (tardive dyskinesia).** Aripiprazole tablets 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 receiving aripiprazole tablets. Tardive dyskinesia may also start after you stop receiving aripiprazole tablets.
- **Problems with your metabolism such as:**
- **high blood sugar (hyperglycemia) and diabetes:** Increases in blood sugar can happen in some people who take aripiprazole tablets. 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 aripiprazole tablets and during your treatment.

  Call your healthcare provider if you have any of these symptoms of high blood sugar while receiving aripiprazole tablets:
  - feel very thirsty
  - need to urinate more than usual
  - feel very hungry
  - feel weak or tired
  - feel sick to your stomach
  - feel confused, or your breath smells fruity.
- **increased fat levels (cholesterol and triglycerides) in your blood.**
- **weight gain.** You and your healthcare provider should check your weight regularly.
- **Orthostatic hypotension (decreased blood pressure):** Lightheadedness or fainting may happen when rising too quickly from a sitting or lying position.
- **Low white blood cell count**
- **Seizures (convulsions)**
- **problems with control of your body temperature especially when you exercise a lot or are in an area that is very hot. It is important for you to drink water to avoid dehydration.** See "What should I avoid while receiving aripiprazole tablets?"
- **difficulty swallowing that can cause food or liquid to get into your lungs.**

The most common side effects with aripiprazole tablets in adults include:

• nausea	• dizziness
• vomiting	• anxiety
• constipation	• insomnia
• headache	• restlessness
• blurred vision	• inner sense of restlessness/need to move (akathisia)
• upper respiratory illness	

The most common side effects with aripiprazole tablets in children include:

• feeling sleepy	• insomnia
• headache	• nausea
• vomiting	• stuffy nose
• fatigue	• weight gain
• increased or decreased appetite	• uncontrolled movement such as restlessness, tremor, muscle stiffness
• increased saliva or drooling	

These are not all the possible side effects of aripiprazole tablets. For more information, ask your healthcare provider or pharmacist.

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 aripiprazole tablets?

- Store aripiprazole tablets at 20° to 25° C (68° to 77°F) [see USP Controlled Room Temperature].

Keep aripiprazole tablets and all medicines out of the reach of children.

General information about the safe and effective use of aripiprazole tablets

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use aripiprazole tablets for a condition for which it was not prescribed. Do not give aripiprazole tablets to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about aripiprazole tablets. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about aripiprazole tablets that was written for healthcare professionals.

What are the ingredients in aripiprazole tablets?

Active ingredient: aripiprazole USP

Inactive ingredients: corn starch, FD&C Blue #2/Indigo Carmine Al, ferric oxide red, ferric oxide yellow, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate and microcrystalline cellulose.

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This Medication Guide has been approved by the U.S. Food and Drug Administration.

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