ARIPIPRAZOLE - aripiprazole tablet, orally disintegrating
Alembic Pharmaceuticals Limited

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

ARIPIPRAZOLE orally disintegrating 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 is 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. (5.2)

RECENT MAJOR CHANGES

Warnings and Precautions, Metabolic Changes (5.6) 12/2014

INDICATIONS AND USAGE

Aripiprazole is an atypical antipsychotic indicated as oral formulations for the: (1)
- Schizophrenia (14.1)

DOSAGE AND ADMINISTRATION

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

DOSAGE FORMS AND STRENGTHS

- Orally Disintegrating Tablets: 10 mg and 15 mg (3)

CONTRAINDICATIONS

- Known hypersensitivity to aripiprazole (4)

WARNINGS AND PRECAUTIONS

- *Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis:* Increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack, including fatalities) (5.2)
- *Neuroleptic Malignant Syndrome:* Manage with immediate discontinuation and close monitoring (5.3)
- *Tardive Dyskinesia:* Discontinue if clinically appropriate (5.4)
- *Metabolic Changes:* Atypical antipsychotic drugs have been associated with metabolic changes that include hyperglycemia/diabetes mellitus, dyslipidemia, and body weight gain (5.5)
  - *Hyperglycemia/Diabetes Mellitus:* Monitor glucose regularly in patients with and at risk for diabetes (5.5)
  - *Dyslipidemia:* Undesirable alterations in lipid levels have been observed in patients treated with atypical antipsychotics (5.5)
  - *Weight Gain:* Weight gain has been observed with atypical antipsychotic use. Monitor weight (5.5)
- *Orthostatic Hypotension:* Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease, and risk of dehydration or syncope (5.6)

- *Leukopenia, Neutropenia, and Agranulocytosis:* have been reported with antipsychotics including aripiprazole. 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 should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors (5.7)
- *Seizures/Convulsions:* Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold (5.8)
- *Potential for Cognitive and Motor Impairment:* Use caution when operating machinery (5.9)
- *Suicide:* The possibility of a suicide attempt is inherent in schizophrenia . Closely supervise high-risk patients (5.11)

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 FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

Dosage adjustment due to drug interactions (7.1):
(7)

Factors	**Dosage Adjustments for Aripiprazole**
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)
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. (8)
See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 9/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

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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 is 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 (5.2)].*
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 (5.2)].*

1 INDICATIONS AND USAGE

Aripiprazole Orally Disintegrating 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 is 10 or 15 mg/day administered on a once-a-day schedule without regard to meals. Aripiprazole has 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 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 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 can be administered without regard to meals *[see CLINICAL STUDIES (14.1)]*. Patients should be periodically reassessed to determine the continued 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 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.
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.

2.7 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 dosage should then be adjusted to its original level. When the coadministered CYP3A4 inducer is withdrawn, aripiprazole 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 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**
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	

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)].*

2.9 Dosing of Orally Disintegrating Tablets

The dosing for Aripiprazole Orally Disintegrating Tablets is the same as for the oral tablets *[see DOSAGE AND ADMINISTRATION (2.1 and 2.2)].*

3 DOSAGE FORMS AND STRENGTHS

Aripiprazole Orally Disintegrating Tablets are available as described in Table 2.

Table 2: Aripiprazole Orally Disintegrating Tablet Presentations

Tablet Strength	**Tablet Color/Shape**	**Tablet Markings**
10 mg	light pink (mottled) round	“256”
15 mg	light pink (mottled) round	“L257”

4 CONTRAINDICATIONS

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

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

The safety and efficacy of aripiprazole in the treatment of patients with psychosis associated with dementia have not been established. If the prescriber elects to treat such patients with aripiprazole, assess for the emergence of difficulty swallowing or excessive somnolence, which could predispose to accidental injury or aspiration *[see also 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 (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 events in patients treated with aripiprazole. Aripiprazole is not approved for the treatment of patients with dementia-related psychosis *[see also 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 18to 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.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, Obsessive Compulsive Disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These

risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 3.

Table 3:

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18 to 24	5 additional cases
	Decreases Compared to Placebo
25 to 64	1 fewer case
≥65	6 fewer case

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, ie, beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for MDD as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

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 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 is 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. Rare cases of NMS occurred during aripiprazole 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 (e.g., 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.

Ifa 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 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 on aripiprazole, drug discontinuation should be considered. However, some patients may require treatment with aripiprazole 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 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. Because aripiprazole was not marketed at the time these studies were performed, it is not known if aripiprazole is associated with this increased risk. Precise risk estimates for hyperglycemia-related adverse events 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 (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 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 6 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 6: Changes in Fasting Glucose From Placebo-Controlled Monotherapy Trials in Adult Patients

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

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

Pediatric Patients 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-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 8 shows the proportion of patients with changes in fasting glucose levels from the pooled adolescent schizophrenia and another indication (median exposure of 42 to 43 days).

Table 8: 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	Pooled Schizophrenia and Another Indication	Aripiprazole	2/236	0.8
Normal to High (<100 mg/dL to ≥126 mg/dL)		Placebo	2/110	1.8
Fasting Glucose	Pooled Schizophrenia and Another Indication	Aripiprazole	1/22	4.5
Borderline to High (≥100 mg/dL and <126 mg/dL to ≥126 mg/dL)		Placebo	0/12	0

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

Dyslipidemia

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

There were no significant differences between aripiprazole- and placebo-treated patients in the proportion with changes from normal to clinically significant levels for fasting/nonfasting total cholesterol, fasting triglycerides, fasting LDLs, and

fasting/nonfasting HDLs. Analyses of patients with at least 12 or 24 weeks of exposure were limited by small numbers of patients.

Adults

Table 9 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 9: Changes in Blood Lipid Parameters From Placebo-Controlled Monotherapy Trials in Adults

	Treatment Arm	n/N	%
Total Cholesterol	Aripiprazole	34/1357	2.5
Normal to High(<200 mg/dL to ≥240 mg/dL)	Placebo	27/973	2.8
Fasting Triglycerides	Aripiprazole	40/539	7.4
Normal to High (<150 mg/dL to ≥200 mg/dL)	Placebo	30/431	7
Fasting LDL Cholesterol	Aripiprazole	2/332	0.6
Normal to High (<100 mg/dL to ≥160 mg/dL)	Placebo	2/268	0.7
HDL Cholesterol	Aripiprazole	121/1066	11.4
Normal to Low (≥40 mg/dL to <40 mg/dL)	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%), respectively; and at 24 weeks, Total Cholesterol (fasting/nonfasting), 1/42 (2.4%) vs. 3/37 (8.1%); Fasting Triglycerides, 5/34 (14.7%) vs. 5/20 (25%); Fasting LDL Cholesterol, 0/22 (0%) vs. 1/18 (5.6%), respectively.

Pediatric Patients and Adolescents

Table 11 shows the proportion of adolescents with schizophrenia (13 to 17 years) and pediatric patients with another indication (10 to 17 years) 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 11: Changes in Blood Lipid Parameters From Placebo-Controlled Monotherapy Trials in Pediatric and Adolescent Patients Schizophrenia and Another Indication

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

In monotherapy trials of adolescents 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%), respectively.

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

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

Table 14 shows the percentage of adult patients with weight gain ≥7% of body weight by indication.

Table 14: Percentage of Patients From Placebo-Controlled Trials in Adult Patients with Weight Gain ≥7% of Body Weight

	Indication	**Treatment Arm**	**N**	**Patients n (%)**
	Schizophrenia[a]	Aripiprazole	852	69 (8.1)
Weight gain ≥7% of body weight		Placebo	379	12 (3.2)
	Other Indication[b]	Aripiprazole	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-treated patients was +1.6 kg (N=381) compared to +0.3 kg (N=187) in placebo-treated patients. At 24 weeks, the mean change from baseline in body weight in aripiprazole-treated patients was +5.8 kg (n=62) compared to +1.4 kg (n=13) in placebo-treated patients.
Table 15 shows the percentage of pediatric and adolescent patients with weight gain ≥7% of body weight by indication.
Table 15: Percentage of Patients From Placebo-Controlled Monotherapy Trials in Pediatric and Adolescent Patients with Weight Gain ≥7% of Body Weight

	Indication	**Treatment**	**N**	**Patients**

	Indication	Arm	N	n (%)
Weight gain ≥7% of body weight	Pooled Schizophrenia and Another Indication[a]	Aripiprazole	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. 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 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 (n=2467) included (aripiprazole incidence, placebo incidence) orthostatic hypotension (1%, 0.3%), postural dizziness (0.5%, 0.3%), and syncope (0.5%, 0.4%,); of pediatric patients 6 to 18 years of age (n=732) on oral aripiprazole 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 when comparing standing to supine values) for aripiprazole was not meaningfully different from placebo (aripiprazole incidence, placebo incidence): in adult oral aripiprazole-treated patients (4%, 2%), in pediatric oral aripiprazole-treated patients aged 6 to 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 trial and/or postmarketing experience, events of leukopenia/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. Patients with a history of a clinically significant low WBC/ANC or drug-induced leukopenia/neutropenia, perform a complete blood count (CBC) monitored frequently during the first few months of therapy. In such patients, consider discontinuation of aripiprazole 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 aripiprazole 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, in 0.1% (1/732) of pediatric patients (6 to 18 years).

As with other antipsychotic drugs, aripiprazole 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, 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 (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 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 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 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 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. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. Aripiprazole 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, another indication, Dementia of the Alzheimer's type, Parkinson's disease, and alcoholism, and who had approximately 7619 patient-years of exposure to oral aripiprazole and 749 patients with exposure to aripiprazole injection. A total of 3390 patients were treated with oral aripiprazole for at least 180 days and 1933 patients treated with oral aripiprazole had at least 1 year of exposure.

Aripiprazole has been evaluated for safety in 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 was 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 in patients with schizophrenia (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) was akathisia (aripiprazole 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 (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 10: Adverse Reactions in Short-Term, Placebo-Controlled Trials in Adult Patients Treated with Oral Aripiprazole

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

Headache	27	23
Dizziness	10	7
Akathisia	10	4
Sedation	7	4
Extrapyramidal Disorder	5	3
Tremor	5	3
Somnolence	5	3
Psychiatric Disorders		
Agitation	19	17
Insomnia	18	13
Anxiety	17	13
Restlessness	5	3
Respiratory, Thoracic, and Mediastinal Disorders		
Pharyngolaryngeal Pain	3	2
Cough	3	2
[a] Adverse reactions reported by at least 2% of patients treated with oral aripiprazole, except adverse reactions 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.

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.

Adverse Reactions Associated with Discontinuation of Treatment

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

Commonly observed adverse reactions associated with the use of aripiprazole in adolescent patients with schizophrenia (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) were extrapyramidal disorder, somnolence, and tremor.

Less Common Adverse Reactions in Pediatric Patients (6 to 18 years) with Schizophrenia or Other Indications

Table 11 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 one indication, up to 8 weeks in another indication, and up to 10 weeks in another indication), 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 11: Adverse Reactions in Short-Term, Placebo-Controlled Trials of Pediatric Patients (6 to 18 years) Treated with Oral Aripiprazole		
	Percentage of Patients Reporting Reaction [a]	
System Organ Class	**Aripiprazole**	**Placebo**

Preferred Term	(n=732)	(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 Disorders		
Rash	2	1

[a]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.

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

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

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

Dystonia

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

Additional Findings Observed in Clinical Trials

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

The adverse reactions reported in a 26-week, double-blind trial comparing oral aripiprazole and placebo in patients with schizophrenia were generally consistent with those reported in the short-term, placebo-controlled trials, except for a higher incidence of tremor [8% (12/153) for aripiprazole vs. 2% (3/153) for placebo]. In this study, the majority of the cases of tremor were of mild intensity (8/12 mild and 4/12 moderate),

occurred early in therapy (9/12 ≤49 days), and were of limited duration (7/12 ≤10 days). Tremor infrequently led to discontinuation (<1%) of aripiprazole. In addition, in a long-term (52-week), active-controlled study, the incidence of tremor was 5% (40/859) for aripiprazole.

Other Adverse Reactions Observed During the Premarketing Evaluation of Aripiprazole

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:

in*frequent* – 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 - weight decreased,*infrequent* - hepatic enzyme increased, blood glucose

increased, blood lactate dehydrogenase increased, gamma glutamyl transferase

increased; *rare* – blood prolactin increased, blood urea inceased, blood creatinine increased, blood bilirubin increased, electrocardiogram QT prolonged, glycosylated hemoglobin increased

Metabolism and Nutrition Disorders:

frequent –anorexia; *infrequent* -rare -hypokalemia, hyponatremia, hypoglycemia

Musculoskeletal and Connective Tissue Disorders:

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

Nervous System Disorders:

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

Psychiatric Disorders:

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

Renal and Urinary Disorders:

rare - urinary retention, nocturia

Reproductive System and Breast Disorders:

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

Respiratory, Thoracic, and Mediastinal Disorders:

infrequent -nasal congestion, dyspnea

Skin and Subcutaneous Tissue Disorders:

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

Vascular Disorders:

infrequent – hypotension, hypertension;

Pediatric Patients - Oral Administration

Most adverse events observed in the pooled database of 1,686 pediatric patients, 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

Additional pediatric use information is approved for Otsuka America

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6.2 Postmarketing Experience

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

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with Aripiprazole

Table 12: Clinically Important Drug Interactions with Aripiprazole:

Concomitant Drug Name or Drug Class	**Clinical Rationale**	**Clinical Recommendation**
Strong CYP3A4 Inhibitors (e.g., itraconazole, clarithromycin) or strong CYP2D6 inhibitors (e.g., quinidine, fluoxetine, paroxetine)	The concomitant use of aripiprazole with strong CYP 3A4 or CYP2D6 inhibitors increased the exposure of aripiprazole compared to the use of aripiprazole alone *[see CLINICAL PHARMACOLOGY (12.3)].*	With concomitant use of aripiprazole with a strong CYP3A4 inhibitor or CYP2D6 inhibitor, reduce the aripiprazole dosage *[see DOSAGE AND ADMINISTRATION (2.7)].*
Strong CYP3A4 Inducers (e.g., carbamazepine, rifampin)	The concomitant use of aripiprazole and carbamazepine decreased the exposure of aripiprazole compared to the use of aripiprazole alone *[see CLINICAL PHARMACOLOGY (12.3)].*	With concomitant use of aripiprazole with a strong CYP3A4 inducer, consider increasing the aripiprazole dosage *[see DOSAGE AND ADMINISTRATION (2.7)].*
Antihypertensive Drugs	Due to its alpha adrenergic antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.	Monitor blood pressure and adjust dose accordingly *[see WARNINGS AND PRECAUTIONS (5.7)].*
Benzodiazepines (e.g., lorazepam)	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*	Monitor sedation and blood pressure. Adjust dose accordingly.

	PRECAUTIONS (5.7)]	

7.2 Drugs Having No Clinically Important Interactions with Aripiprazole

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 (e.g., dextromethorphan, fluoxetine, paroxetine, or venlafaxine), CYP2C9 (e.g., warfarin), CYP2C19 (e.g., omeprazole, warfarin, escitolopram) or CYP3A4 (e.g., dextromethorphan) when co-administered with aripiprazole. Additionally, no dosage adjustment is necessary for valproate, lithium, lamotrigine, lorazepam, or sertraline when co-administered with aripiprazole. *[see CLINICAL PHARMACOLOGY (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects
Pregnancy Category C:

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to aripiprazole during pregnancy. For more information contact the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or visit http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/.

Risk Summary

Neonates exposed to antipsychotic drugs (including aripiprazole) during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms. Adequate and well controlled studies with aripiprazole have not been conducted in pregnant women. Animal reproduction studies were conducted with aripiprazole in rats and rabbits during organogenesis, and in rats during the pre-and post-natal period. Oral and intravenous aripiprazole administration during organogenesis in rats and/or rabbits at doses higher than the maximum recommended human dose (MRHD) 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 higher than the maximum recommended human dose (MRHD) produced prolonged gestation, stillbirths, decreased pup weight, and decreased pup survival. Administer aripiprazole during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

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. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization. Monitor neonates for extrapyramidal and/or withdrawal symptoms.

Data

Animal Data

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

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 30mg/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 100mg/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 gestation 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 30mg/kg/day.

8.3 Nursing Mothers

Aripiprazole is present in human breast milk. Because of the potential for serious adverse reactions in nursing infants from aripiprazole, 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, 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 (AUC0 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 (AUC0 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.

8.5 Geriatric Use

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

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

Aripiprazole is 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 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 is 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 is not a controlled substance.

9.2 Abuse and Dependance

Aripiprazole has not been systematically studied in humans for its potential for abuse, tolerance, or physical 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. 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).

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 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 1260 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 children (age 12 and younger) involving oral aripiprazole ingestions up to 195 mg 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.

10.2 Management of Overdosage

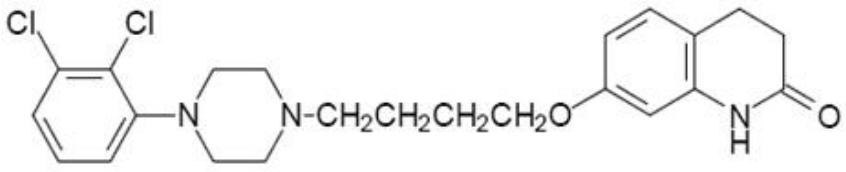
No specific information is available on the treatment of overdose with aripiprazole. An electrocardiogram should be obtained in case of overdosage and if QT interval prolongation is present, cardiac monitoring should be instituted. Otherwise, management of overdose should concentrate on supportive therapy,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

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

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

11 DESCRIPTION

Aripiprazole is a psychotropic drug that is available as Aripiprazole Orally Disintegrating Tablets. Aripiprazole is 7-[4-[4-(2,3-dichlorophenyl)-1piperazinyl]butoxy]-3,4-dihydrocarbostyril. The empirical formula is $C_{23}H_{27}Cl_2N_3O_2$ and its molecular weight is 448.39. The chemical structure is:



Aripiprazole Orally Disintegrating Tablets are available in 10 mg and 15 mg strengths. Inactive ingredients include mannitol, aspartame, calcium stearate, crospovidone, vanilla, silicified microcrystalline cellulose, and lactose monohydrate. Colorants include iron oxide red.

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-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors. Actions at receptors other than D_2, 5-HT_{1A}, and 5-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-HT_{1A} and 5-HT_{2A} receptors (K_i values of 0.34 nM, 0.8 nM, 1.7 nM, and 3.4 nM, respectively), moderate affinity for dopamine D_4, serotonin 5-HT_{2C} and 5-HT_7, 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-HT_{1A} receptors, and as an antagonist at serotonin 5-HT_{2A} receptor.]

12.3 Pharmacokinetics

Aripiprazole 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 are 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.
Pharmacokinetic studies showed that aripiprazole orally disintegrating tablets are bioequivalent to aripiprazole tablets.

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 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 D_2 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 [14C]-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

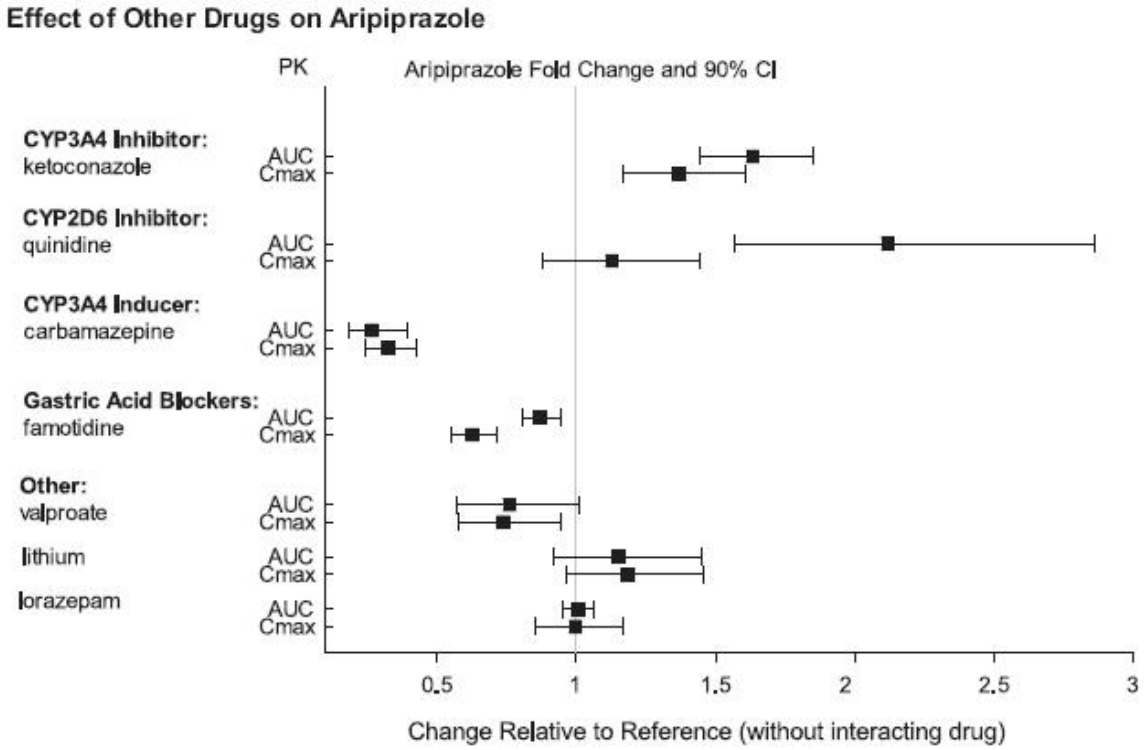
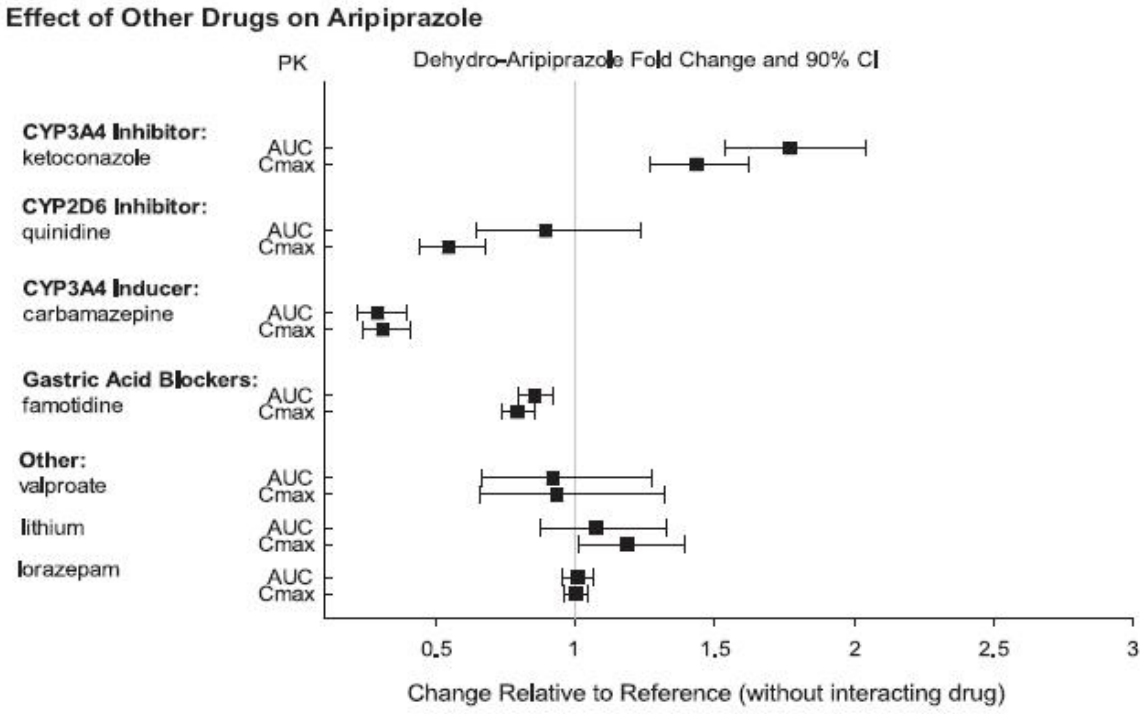


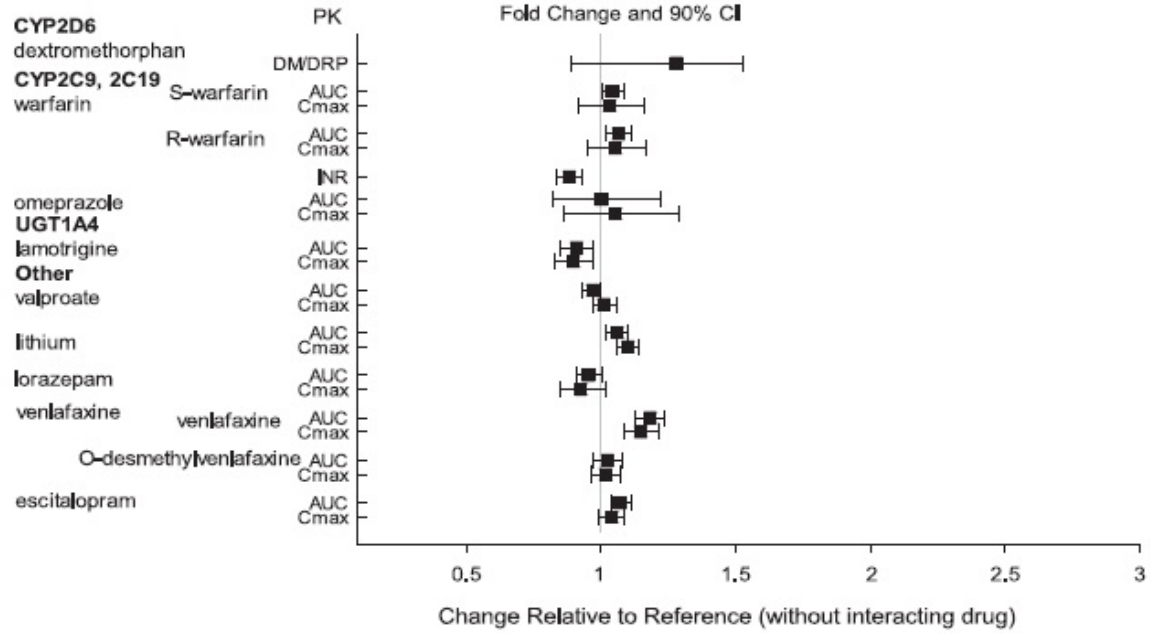
Figure 2: The effects of other drugs on dehydro-aripiprazole pharmacokinetics



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

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

Effect of Aripiprazole on 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 (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

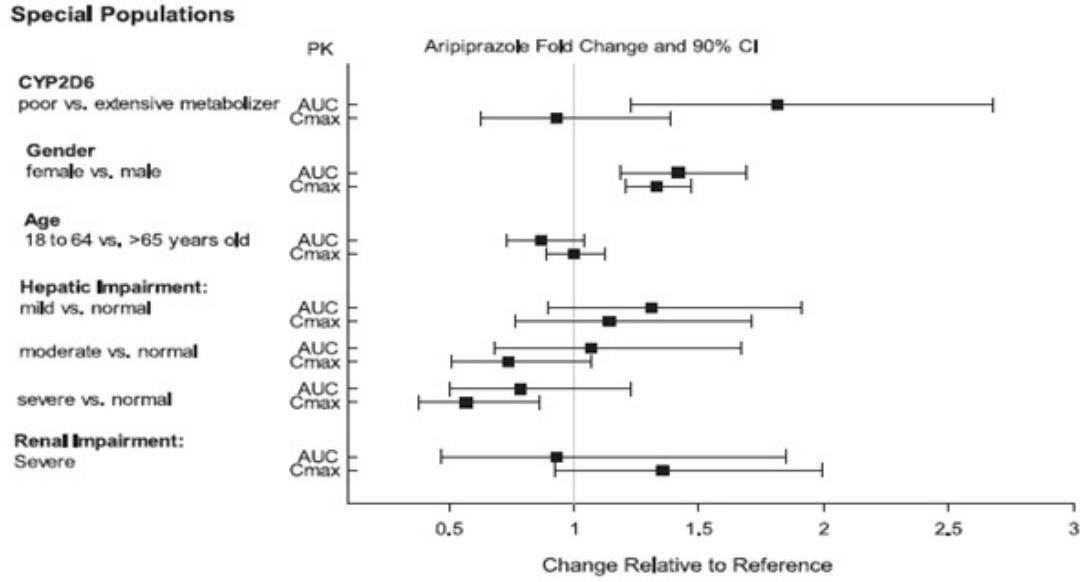
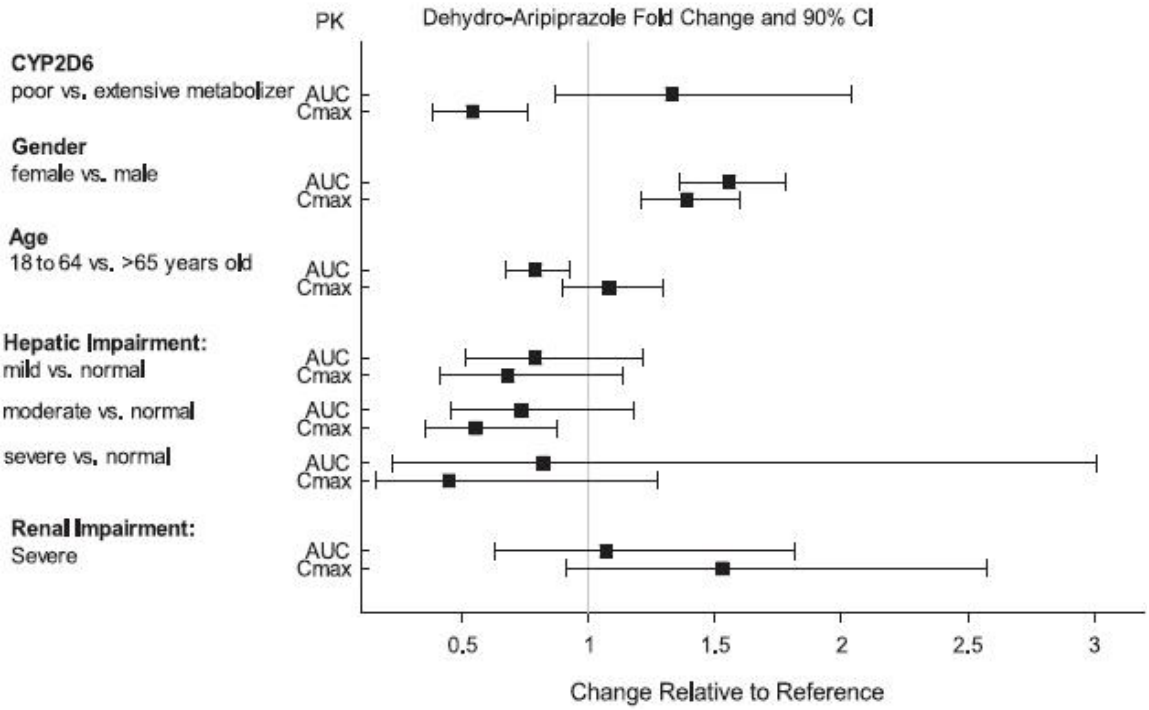


Figure 5: Effects of intrinsic factors on dehydro-aripiprazole pharmacokinetics:



13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Lifetime carcinogenicity studies were conducted in ICR mice and in Sprague-Dawley (SD) 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 times to 19 times the MRHD based on mg/m^2). Aripiprazole did not induce tumors in male mice or 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 doses are 13 times 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 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 (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 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 13), 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 13), 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 13), 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 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 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

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 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 (15 mg/day)*	98.5 (17.2)	-15.5 (2.4)	-12.6 (-18.9, -6.2)
	Aripiprazole (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 (20 mg/day)*	92.6 (19.5)	-14.5 (2.23)	-9.6 (-15.4, -3.8)

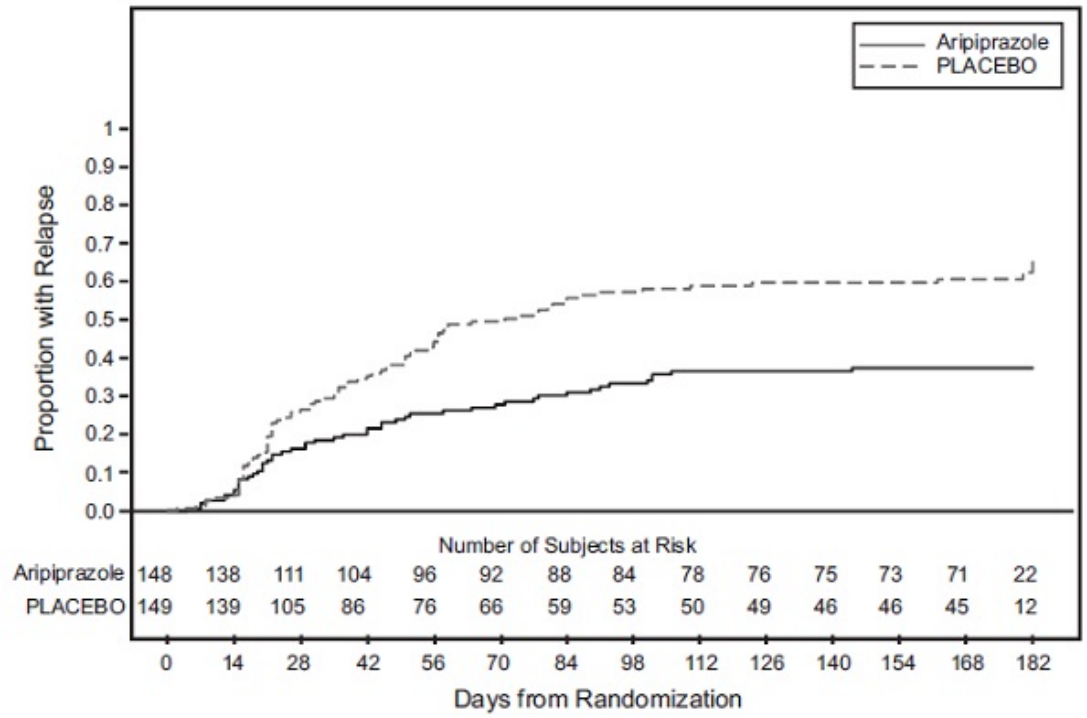
	Aripiprazole (30 mg/day)*	94.2 (18.5)	-13.9 (2.24)	-9 (-14.8, -3.1)
	Placebo	94.3 (18.5)	-5 (2.17)	---
Study 3	Aripiprazole (10 mg/day)*	92.7 (19.5)	-15 (2.38)	-12.7 (-19, -6.41)
	Aripiprazole (15 mg/day)*	93.2 (21.6)	-11.7 (2.38)	-9.4 (-15.71, -3.08)
	Aripiprazole (20 mg/day)*	92.5 (20.9)	-14.4 (2.45)	-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 (1.9)	-2.9 (-8.29, 2.47)
	Aripiprazole (5 mg/day)	92 (12.6)	-10.6 (1.93)	-5.2 (-10.7, 0.19)
	Aripiprazole (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 (Pediatric, 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 (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.

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

* Doses statistically significantly superior to placebo.

Figure6 : Kaplan-Meier Estimation of Cumulative Proportion of Patients with Relapse (Schizophrenia Study 5)



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.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Aripiprazole Orally Disintegrating Tablets are round tablets with markings on one side and plain on other side. Aripiprazole Orally Disintegrating Tablet is available in the strengths and packages listed in Table 14.

Table 14: Aripiprazole Orally Disintegrating Tablets Presentations

Tablet Strength	Tablet Color	Tablet Markings	Pack Size	NDC Code
10 mg	light pink (mottled)	"256"	Cartons of 30 (3 x10) blisters	46708-260-10
15 mg	light pink(mottled)	"L257"	Cartons of 30 (3 x10) blisters	46708-261-10

16.2 Storage

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

17 PATIENT COUNSELING INFORMATION

See Medication Guide

Discuss the following issues with patients prescribed aripiprazole:

Clinical Worsening of Depression and Suicide Risk

Patients, their families, and 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 (5.2)].*

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with aripiprazole 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. 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.

Use of Orally Disintegrating Tablet

Do not open the blister until ready to administer. For single tablet removal, open the package and peel back the foil on the blister to expose the tablet. Do not push the tablet through the foil because this could damage the tablet. Immediately upon opening the blister, using dry hands, remove the tablet and place the entire Aripiprazole Orally Disintegrating Tablet on the tongue. Tablet disintegration occurs rapidly in saliva. It is recommended that Aripiprazole Orally Disintegrating Tablet be taken without liquid. However, if needed, it can be taken with liquid. Do not attempt to split the tablet.

Interference with Cognitive and Motor Performance

Because aripiprazole 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 therapy does not affect them adversely *[see WARNINGS AND PRECAUTIONS (5.9)]*.

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 (5.10)]*.

Phenylketonurics

Phenylalanine is a component of aspartame. Each Aripiprazole Orally Disintegrating Tablet contains the following amounts: 10 mg - 1.12 mg phenylalanine and 15 mg - 1.68 mg phenylalanine.

ABILIFY® is a trademark of Otsuka Pharmaceutical Company.

Manufactured by:

Alembic Pharmaceuticals Limited(Formulation Division),

Village Panelav, P. O. Tajpura, Near Baska,

Taluka-Halol, Panchmahal 389350, Gujarat, India.

Revision: 10/2015

MEDICATION GUIDE

Aripiprazole (AR-i-PIP-ra-zole)
Orally Disintegrating Tablets

Read this Medication Guide before you start taking aripiprazole and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about aripiprazole?
(For other side effects, also see "**What are the possible side effects of aripiprazole**?").

Serious side effects may happen when you take aripiprazole, including:

• **Increased risk of death in elderly patients with dementia-related psychosis:** Medicines like aripiprazole can raise the risk of death in elderly people who have lost touch with reality (psychosis) due to confusion and memory loss (dementia). Aripiprazole is not approved for the treatment of patients with dementia-related psychosis.

• **Risk of suicidal thoughts or actions:** Antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions:

1. Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.

2. Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions. These include people who have (or have a family history of) suicidal thoughts or actions.

3. 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. This is very important when an antidepressant medicine is started or when the dose is changed.
• Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
• Keep all follow-up visits with the healthcare provider as scheduled. Call the 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 worse depression
• new or worse anxiety
• feeling very agitated or restless
• panic attacks
• trouble sleeping (insomnia)
• new or worse 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
What else do I need to know about antidepressant medicines?
• **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
• **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.
• **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
• **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
• **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information.
What is aripiprazole?
Aripiprazole is a prescription medicine used to treat:
• schizophrenia

It is not known if aripiprazole is safe or effective in children:
• under 13 years of age with schizophrenia

Who should not take aripiprazole?
Do not take aripiprazole if you are allergic to aripiprazole or any of the ingredients in aripiprazole. See the end of this Medication Guide for a complete list of ingredients in aripiprazole.
What should I tell my healthcare provider before taking aripiprazole?
Before taking aripiprazole, tell your healthcare provider 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 aripiprazole and also during therapy.
• seizures (convulsions).
• low or high blood pressure.
• heart problems or stroke.

• pregnancy or plans to become pregnant. It is not known if aripiprazole will harm your unborn baby.
• breast-feeding or plans to breast-feed. Aripiprazole can pass into your breast milk and may harm your baby. Talk to your healthcare provider about the best way to feed your baby if you receive aripiprazole.
• low white blood cell count.
•phenylketonuria. Aripiprazole Orally Disintegrating Tablets contain phenylalanine.
• any other medical conditions.

Tell your healthcare provider about all the medicines that you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. Aripiprazole and other medicines may affect each other causing possible serious side effects. Aripiprazole may affect the way other medicines work, and other medicines may affect how aripiprazole works.

Your healthcare provider can tell you if it is safe to take aripiprazole with your other medicines. Do not start or stop any medicines while taking aripiprazole without talking to your healthcare provider first. 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 aripiprazole?

• Take aripiprazole exactly as your healthcare provider tells you to take it. Do not change the dose or stop taking aripiprazole yourself.
• Aripiprazole can be taken with or without food.
• Aripiprazole tablets should be swallowed whole.
• If you miss a dose of aripiprazole, take the missed dose as soon as you remember. If it is almost time for the next dose, just skip the missed dose and take your next dose at the regular time. Do not take two doses of aripiprazole at the same time.
•If you have been prescribed Aripiprazole Orally Disintegrating Tablet, take it as follows:
oDo not open the blister until ready to take the orally disintegrating tablet.
oTo remove one orally disintegrating tablet, open the package and peel back the foil on the blister to expose the tablet.
oDo not push the tablet through the foil because this could damage the tablet.
oImmediately upon opening the blister, using dry hands, remove the tablet and place the entire Aripiprazole Orally Disintegrating Tablet on the tongue.
oTablet disintegration occurs rapidly in saliva. It is recommended that Aripiprazole Orally Disintegrating Tablet be taken without liquid. However, if needed, it can be taken with liquid.
oDo not attempt to split the Aripiprazole Orally Disintegrating Tablet.

• If you take too much aripiprazole, call your healthcare provider or poison control center at 1-800-222-1222 right away, or go to the nearest hospital emergency room.

What should I avoid while taking aripiprazole?

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

What are the possible side effects of aripiprazole?

Aripiprazole may cause serious side effects, including:

• See "<u>What is the most important information I should know about aripiprazole</u>?"
• 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 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. Tardive dyskinesia may also start after you stop receiving aripiprazole.
• **Problems with your metabolism such as:**
• **High blood sugar (hyperglycemia) and diabetes.** Increases in blood sugar can happen in some people who take aripiprazole. 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 and during your treatment.
Call your healthcare provider if you have any of these symptoms of high blood sugar while taking aripiprazole:
.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 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?"
• **difficulty swallowing that can cause food or liquid to get into your lungs.**
The most common side effects of aripiprazole 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 of aripiprazole 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. 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?
• Store aripiprazole at 20° to 25°C (68° to 77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature].
Keep aripiprazole and all medicines out of the reach of children.
General information about the safe and effective use of aripiprazole
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use aripiprazole for a condition for which it was not prescribed. Do not give aripiprazole to other people, even if they have the same condition. It may harm them.
This Medication Guide summarizes the most important information about aripiprazole. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about aripiprazole that was written for healthcare professionals.
What are the ingredients in Aripiprazole Orally Disintegrating Tablets?
Active ingredient: aripiprazole
Inactive ingredients: mannitol, aspartame, calcium stearate, crospovidone, vanilla, silicified microcrystalline cellulose, and lactose monohydrate. Colorants include iron oxide red.
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.
This Medication Guide has been approved by the U.S. Food and Drug Administration.
ABILIFY® is a trademark of Otsuka Pharmaceutical Company.
Manufactured by:
Alembic Pharmaceuticals Limited (Formulation Division),
Village Panelav, P. O. Tajpura, Near Baska,
Taluka-Halol, Panchmahal 389350, Gujarat, India.

Issued: 10/2015

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL -10 mg

Aripiprazole Orally Disintegrating Tablets 10 mg (30 Tablets in 1 Carton)

Each orally disintegrating tablet contains 10 mg aripiprazole USP
46708-260-10

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL -15 mg

Aripiprazole Orally Disintegrating Tablets 15 mg (30 Tablets in 1 Carton)
Each orally disintegrating tablet contains 15 mg aripiprazole USP
46708-261-10

ARIPIPRAZOLE

aripiprazole tablet, orally disintegrating

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:46708-260
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ARIPIPRAZOLE (UNII: 82VFR53I78) (ARIPIPRAZOLE - UNII:82VFR53I78)	ARIPIPRAZOLE	10 mg

Inactive Ingredients	
Ingredient Name	**Strength**
MANNITOL (UNII: 3OWL53L36A)	
CROSPOVIDONE (UNII: 68401960MK)	
ASPARTAME (UNII: Z0H242BBR1)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	

FERRIC OXIDE RED (UNII: 1K09F3G675)	
CALCIUM STEARATE (UNII: 776XM7047L)	

Product Characteristics

Color	PINK (light pink)	**Score**	no score
Shape	ROUND (round, flat, beveled edge)	**Size**	7mm
Flavor		**Imprint Code**	256
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:46708-260-10	30 in 1 CARTON; Type 0: Not a Combination Product	05/21/2015	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA202102	05/21/2015	

ARIPIPRAZOLE

aripiprazole tablet, orally disintegrating

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:46708-261
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ARIPIPRAZOLE (UNII: 82VFR53I78) (ARIPIPRAZOLE - UNII:82VFR53I78)	ARIPIPRAZOLE	15 mg

Inactive Ingredients

Ingredient Name	Strength
MANNITOL (UNII: 3OWL53L36A)	
CROSPOVIDONE (UNII: 68401960MK)	
ASPARTAME (UNII: Z0H242BBR1)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
CALCIUM STEARATE (UNII: 776XM7047L)	

Product Characteristics

Color	PINK (light pink)	**Score**	no score
Shape	ROUND (round, flat, beveled edge)	**Size**	8mm
Flavor		**Imprint Code**	L257
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:46708-261-10	30 in 1 CARTON; Type 0: Not a Combination Product	05/21/2015	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA202102	05/21/2015	

Labeler - Alembic Pharmaceuticals Limited (650574663)

Establishment

Name	Address	ID/FEI	Business Operations
Alembic Pharmaceuticals Limited		650574671	MANUFACTURE(46708-260, 46708-261)

Revised: 1/2023 Alembic Pharmaceuticals Limited