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

ABILIFY MYCITE® (aripiprazole tablets with sensor), for oral use
Initial U.S. Approval: 2002

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS and SUICIDAL THOUGHTS AND BEHAVIORS
See full prescribing information for complete boxed warning.

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ABILIFY MYCITE is not approved for the treatment of patients with dementia-related psychosis. (5.1)**
- **Increased risk of suicidal thoughts and behaviors in pediatric and young adult patients taking antidepressants. Closely monitor for worsening and emergence of suicidal thoughts and behaviors. (5.2)**
- **The safety and effectiveness of ABILIFY MYCITE have not been established in pediatric patients. (8.4)**

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

ABILIFY MYCITE, a drug-device combination product comprised of aripiprazole tablets embedded with an Ingestible Event Marker (IEM) sensor intended to track drug ingestion, is indicated for the:

- Treatment of adults with schizophrenia (1)
- Treatment of bipolar I disorder (1)
  - Acute treatment of adults with manic and mixed episodes as monotherapy and as adjunct to lithium or valproate
  - Maintenance treatment of adults as monotherapy and as adjunct to lithium or valproate
- Adjunctive treatment of adults with major depressive disorder (MDD) (1)

Limitations of Use:

- The ability of ABILIFY MYCITE to improve patient compliance or modify aripiprazole dosage has not been established. (1)
- The use of ABILIFY MYCITE to track drug ingestion in "real-time" or during an emergency is not recommended because detection may be delayed or not occur. (1)

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

	Initial Dose	Recommended Dose	Maximum Dose
Schizophrenia – adults (2.3)	10 to 15 mg/day	10 to 15 mg/day	30 mg/day
Bipolar mania – adults: monotherapy (2.4)	15 mg/day	15 mg/day	30 mg/day
Bipolar mania – adults: adjunct to lithium or valproate (2.4)	10 to 15 mg/day	15 mg/day	30 mg/day
Major Depressive Disorder – adults: adjunct to antidepressants (2.5)	2 to 5 mg/day	5 to 10 mg/day	15 mg/day

- Administer once daily without regard to meals (2.2)
- Swallow whole; do not divide, crush, or chew (2.2)
- Known CYP2D6 poor metabolizers: Administer half of the usual dose (2.6)

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

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

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

Known hypersensitivity to aripiprazole tablets (4)

----------WARNINGS AND PRECAUTIONS----------

- *Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis:* Increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack, including fatalities) (5.3)
- *Neuroleptic Malignant Syndrome:* Manage with immediate discontinuation and close monitoring (5.4)
- *Tardive Dyskinesia:* Discontinue if clinically appropriate (5.5)
- *Metabolic Changes:* Monitor for hyperglycemia/diabetes mellitus, dyslipidemia, and weight gain (5.6)
- *Pathological Gambling and other Compulsive Behaviors:* Consider dose reduction or discontinuation (5.7)
- *Orthostatic Hypotension:* Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease, and risk of dehydration or syncope (5.8)
- *Leukopenia, Neutropenia, and Agranulocytosis:* Perform complete blood cell counts in patients with a history of a clinically significant low white blood cell count (WBC)/absolute neutrophil count (ANC). Consider discontinuation if clinically significant decline in WBC/ANC in the absence of other causative factors (5.10)
- *Seizures:* Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold (5.11)
- *Potential for Cognitive and Motor Impairment:* Use caution when operating machinery (5.12)

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

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

- Schizophrenia: akathisia
- Bipolar mania (monotherapy): akathisia, sedation, restlessness, tremor, and extrapyramidal disorder
- Bipolar mania (adjunctive therapy with lithium or valproate): akathisia, insomnia, and extrapyramidal disorder
- MDD (adjunctive treatment to antidepressant therapy): akathisia, restlessness, insomnia, constipation, fatigue, and blurred vision

To report SUSPECTED ADVERSE REACTIONS, contact Otsuka America Pharmaceutical, Inc. at 1-800-438-9927 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

Dosage adjustment due to drug interactions and CYP2D6 poor metabolizers (7.1):

Factors	**Dosage Adjustments for ABILIFY MYCITE**
Known CYP2D6 Poor Metabolizers	Administer half recommended dose
Known CYP2D6 Poor Metabolizers and strong CYP3A4 inhibitors	Administer a quarter of recommended dose
Strong CYP2D6 **or** CYP3A4 inhibitors	Administer half recommended dose
Strong CYP2D6 **and** CYP3A4 inhibitors	Administer a quarter of recommended dose
Strong CYP3A4 inducers	Double recommended 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)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 02/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

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

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

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

Suicidal Thoughts and Behaviors

Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric and young adult patients in short-term studies. Closely monitor all antidepressant-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors *[see Warnings and Precautions (5.2)]*. The safety and efficacy of ABILIFY MYCITE have not been established in pediatric patients *[see Use in Specific Populations (8.4)]*.

1 INDICATIONS AND USAGE

ABILIFY MYCITE, a drug-device combination product comprised of aripiprazole tablets embedded with an Ingestible Event Marker (IEM) sensor intended to track drug ingestion, is indicated for the:

- Treatment of adults with schizophrenia.
- Treatment of bipolar I disorder
  - Acute treatment of adults with manic and mixed episodes as monotherapy and as adjunct to lithium or valproate.
  - Maintenance treatment of adults as monotherapy and as adjunct to lithium or valproate.
- Adjunctive treatment of adults with Major Depressive Disorder.

Limitations of Use:

- The ability of the ABILIFY MYCITE to improve patient compliance or modify aripiprazole dosage has not been established *[see Dosage and Administration (2.1)]*.
- The use of ABILIFY MYCITE to track drug ingestion in “real-time” or during an emergency is not recommended because detection may be delayed or not occur *[see Dosage and Administration (2.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Overview of the ABILIFY MYCITE System

The ABILIFY MYCITE System is composed of the following:

- Aripiprazole tablet embedded with an IEM sensor (ABILIFY MYCITE);
- MYCITE® Patch (wearable sensor) that detects the signal from the IEM sensor after ingestion and transmits data to a smartphone (referred to as the *patch*);

- MYCITE App - a smartphone application which is used with a compatible smartphone to display information for the patient (referred to as the *app*);
- Web-based *portal* for healthcare professionals and caregivers

Prior to initial patient use of the ABILIFY MYCITE System, facilitate use of ABILIFY MYCITE and the *patch*, *app*, and *portal*; ensure the patient is capable and willing to use a smartphone and the *app*; and instruct patients to *[see How Supplied/Storage and Handling (16.1)]*:

- Download the *app*,
- Follow all the instructions in the Instructions for Use within the *app* and the Quick Start Guide within the carton, and
- Ensure that the *app* is compatible with their specific smartphone and is paired with the *patch* prior to use.

Prior to prescribing the ABILIFY MYCITE *Maintenance Kit* ensure the patient has access to the appropriate components of the patch *[see How Supplied/Storage and Handling (16.1)]*.

Although most ingestions will be detected within 30 minutes, it may take up to two hours for the *app* and *portal* to detect the ingestion of ABILIFY MYCITE; in some cases, the ingestion of the tablet with sensor may not be detected. If the tablet with sensor is not detected after ingestion, do not repeat the dose *[see Adverse Reactions (6)]*.

2.2 Administration Instructions

ABILIFY MYCITE

Administer ABILIFY MYCITE orally with or without food *[see Clinical Pharmacology (12.3)]*. Swallow tablets with sensor whole; do not divide, crush, or chew.

MYCITE Patch

Refer to the Instructions for Use (IFU) within the *app [see How Supplied/Storage and Handling (16.1)]:*

- Apply only when instructed by the app to the *right or left side* of the body just above the lower edge of the rib cage.

Additional *patch* instructions:

- Do not place the *patch* in areas where the skin is scraped, cracked, inflamed, or irritated, or in a location that overlaps the area of the most recently removed *patch* (if there is skin irritation, instruct patients to remove the *patch*).
- The *app* will prompt the patient to change the *patch* (at least weekly or sooner), and to apply and remove the *patch* correctly.
- Keep the *patch* on when showering, swimming, or exercising.
- For those undergoing an MRI, remove the *patch* and replace with a new *patch* as soon as possible.

2.3 Dosage in Schizophrenia

The recommended starting and target dosage for ABILIFY MYCITE in adults with schizophrenia is 10 or 15 mg daily. Dosage increases should generally not be made before 2 weeks *[see*

Clinical Pharmacology (12.3)]. The maximum recommended dosage is 30 mg daily; however, doses above 15 mg daily have shown no additional clinically meaningful benefit.

2.4 Dosage in Bipolar I Disorder

The recommended starting dosage in adults with acute and mixed episodes associated with bipolar I disorder is 15 mg given once daily as monotherapy and 10 mg to 15 mg given once daily as adjunctive treatment with lithium or valproate. The recommended target dose of ABILIFY MYCITE is 15 mg daily, as monotherapy or as adjunctive treatment with lithium or valproate. The dosage may be increased to 30 mg daily based on clinical response. The maximum recommended daily dosage is 30 mg.

2.5 Dosage in Adjunctive Treatment of Major Depressive Disorder

The recommended starting dose for ABILIFY MYCITE as adjunctive treatment of adults with MDD taking an antidepressant is 2 to 5 mg daily. The recommended dosage range is 2 to 15 mg daily. Dosage adjustments of up to 5 mg daily should occur gradually, at intervals of no less than one week. The maximum recommended daily dosage is 15 mg. Periodically reassess to determine the continued need for maintenance treatment.

2.6 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, ABILIFY MYCITE dosage should then be adjusted to its original level. When the coadministered CYP3A4 inducer is withdrawn, ABILIFY MYCITE 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 based on clinical response.

Table 1: Dose Adjustments for ABILIFY MYCITE in Patients Who Are Known CYP2D6 Poor Metabolizers and Patients Taking Concomitant CYP2D6 Inhibitors, 3A4 Inhibitors, and/or CYP3A4 Inducers

Factors	Dosage Adjustments for ABILIFY MYCITE
Known CYP2D6 Poor Metabolizers	Administer half of recommended dose
Known CYP2D6 Poor Metabolizers taking concomitant strong CYP3A4 inhibitors (e.g., itraconazole, clarithromycin)	Administer a quarter of recommended dose
Strong CYP2D6 (e.g., quinidine, fluoxetine, paroxetine) **or** CYP3A4 inhibitors (e.g., itraconazole, clarithromycin)	Administer half of recommended dose
Strong CYP2D6 **and** CYP3A4 inhibitors	Administer a quarter of recommended dose

Strong CYP3A4 inducers (e.g., carbamazepine, rifampin)	Double recommended dose over 1 to 2 weeks

When adjunctive ABILIFY MYCITE is administered to patients with major depressive disorder, ABILIFY MYCITE should be administered without dosage adjustment as specified in *[Dosage and Administration (2.5)].*

3 DOSAGE FORMS AND STRENGTHS

ABILIFY MYCITE (aripiprazole tablets with sensor) is available as described in Table 2.

Table 2: ABILIFY MYCITE Presentations

Strength	Color/Shape	Markings
2 mg	pale green modified rectangle	"DA-029" and "2"
5 mg	pale blue modified rectangle	"DA-030" and "5"
10 mg	off-white to pale pink modified rectangle	"DA-031" and "10"
15 mg	pale yellow round	"DA-032" and "15"
20 mg	white to pale yellowish white round	"DA-033" and "20"
30 mg	off-white to pale pink round	"DA-034" and "30"

4 CONTRAINDICATIONS

ABILIFY MYCITE 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

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group.

Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. ABILIFY MYCITE is not approved

for the treatment of patients with dementia-related psychosis *[see Boxed Warning, and Warnings and Precautions (5.3)]*.

5.2 Suicidal Thoughts and Behaviors in Pediatric and Young Adult Patients

In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients and over 4,400 pediatric patients, the incidence of suicidal thoughts and behaviors in pediatric and young adult patients was greater in antidepressant-treated patients than in placebo-treated patients. The safety and efficacy of ABILIFY MYCITE have not been established in pediatric patients *[see Use in Specific Populations (8.4)]*. The drug-placebo differences in the number of cases of suicidal thoughts and behaviors per 1000 patients treated are provided in Table 3.

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

Table 3: Risk Differences of the Number of Cases of Suicidal Thoughts or Behaviors in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric and Adult Patients

Age Range (years)	Drug-Placebo Difference in Number of Patients with Suicidal Thoughts or Behaviors per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional patients
18 to 24	5 additional patients
	Decreases Compared to Placebo
25 to 64	1 fewer patient
≥65	6 fewer patients

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

Monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing ABILIFY MYCITE, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

5.3 Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis

In placebo-controlled clinical studies (two flexible-dose and one fixed-dose study) of dementia-related psychosis, there was an increased incidence of cerebrovascular adverse 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. ABILIFY MYCITE is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning]*.

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 ABILIFY MYCITE. 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.

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

5.5 Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs, including ABILIFY MYCITE. 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.

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, ABILIFY MYCITE 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 ABILIFY MYCITE, drug discontinuation should be considered. However, some patients may require treatment with ABILIFY MYCITE despite the presence of the syndrome.

5.6 Metabolic Changes

Atypical antipsychotic drugs have caused metabolic changes that include hyperglycemia, diabetes mellitus, dyslipidemia, and body weight gain. While all of the 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.

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 atypical antipsychotic drug.

In an analysis of 13 placebo-controlled monotherapy trials in adults, primarily with schizophrenia or bipolar disorder, the mean change in fasting glucose in aripiprazole -treated patients (+4.4 mg/dL; median exposure 25 days; N=1057) was not significantly different than in placebo-treated patients (+2.5 mg/dL; median exposure 22 days; N=799). Table 4 shows the proportion of aripiprazole-treated patients with normal and borderline fasting glucose at baseline (median exposure 25 days) that had treatment-emergent high fasting glucose measurements compared to placebo-treated patients (median exposure 22 days).

Table 4: Changes in Fasting Glucose in Placebo-Controlled Monotherapy Trials in Adult Patients (Primarily Schizophrenia and Bipolar Disorder)

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

	Borderline to High (≥100 mg/dL and <126 mg/dL to ≥126 mg/dL)	Aripiprazole	31/176	17.6
		Placebo	13/142	9.2

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

The mean change in fasting glucose in adjunctive aripiprazole-treated patients with major depressive disorder (+0.7 mg/dL; median exposure 42 days; N=241) was not significantly different than in placebo-treated patients (+0.8 mg/dL; median exposure 42 days; N=246). Table 5 shows the proportion of adult patients with changes in fasting glucose levels from two placebo-controlled, adjunctive trials (median exposure 42 days) in patients with major depressive disorder.

Table 5: Changes in Fasting Glucose from Placebo-Controlled Adjunctive Trials in Adult Patients with Major Depressive Disorder

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

Dyslipidemia

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

Analyses of patients with at least 12 or 24 weeks of exposure were limited by small numbers of patients. Table 6 shows the proportion of adult patients, primarily from pooled schizophrenia and bipolar disorder monotherapy placebo-controlled trials, with changes in total cholesterol (pooled from 17 trials; median exposure 21 to 25 days), fasting triglycerides (pooled from eight trials; median exposure 42 days), fasting LDL cholesterol (pooled from eight trials; median exposure 39 to 45 days, except for placebo-treated patients with baseline normal fasting LDL measurements, who had median treatment exposure of 24 days) and HDL cholesterol (pooled from nine trials; median exposure 40 to 42 days).

Table 6: Changes in Blood Lipid Parameters from Placebo-Controlled Monotherapy Trials in Adults (Primarily Schizophrenia and Bipolar Disorder)

	Treatment Arm	n/N	%
Total Cholesterol Normal to High (<200 mg/dL to ≥240 mg/dL)	Aripiprazole	34/1357	2.5
	Placebo	27/973	2.8
Fasting Triglycerides Normal to High (<150 mg/dL to ≥200 mg/dL)	Aripiprazole	40/539	7.4
	Placebo	30/431	7.0
Fasting LDL Cholesterol	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 (4.0%), respectively; and at 24 weeks, total cholesterol (fasting/nonfasting), 1/42 (2.4%) vs. 3/37 (8.1%); fasting triglycerides, 5/34 (14.7%) vs. 5/20 (25%); fasting LDL cholesterol, 0/22 (0%) vs. 1/18 (5.6%), respectively.

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

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

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

Weight Gain

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

In an analysis of 13 placebo-controlled monotherapy trials, primarily from pooled schizophrenia and bipolar disorder, with a median exposure of 21 to 25 days, the mean change in body weight in aripiprazole-treated patients was +0.3 kg (N=1,673) compared to –0.1 kg (N=1,100) in placebo-controlled patients. At 24 weeks, the mean change from baseline in body weight in aripiprazole-treated patients was –1.5 kg (n=73) compared to –0.2 kg (n=46) in placebo-treated patients.

In the trials adding aripiprazole to antidepressants, patients first received 8 weeks of antidepressant treatment followed by 6 weeks of adjunctive aripiprazole or placebo in addition to their ongoing antidepressant treatment. The mean change in body weight in patients receiving

adjunctive aripiprazole was +1.7 kg (N=347) compared to +0.4 kg (N=330) in patients receiving adjunctive placebo.

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

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

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

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

5.7 Pathological Gambling and Other Compulsive Behaviors

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

5.8 Orthostatic Hypotension

ABILIFY MYCITE 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%) *[see Adverse Reactions (6.1)]*.

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

ABILIFY MYCITE 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)]*.

5.9 Falls

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

5.10 Leukopenia, Neutropenia, and Agranulocytosis

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

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

5.11 Seizures

In short-term, placebo-controlled trials, patients with a history of seizures excluded seizures/convulsions occurred in 0.1% (3/2,467) of undiagnosed adult patients treated with oral aripiprazole.

As with other antipsychotic drugs, ABILIFY MYCITE 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.

5.12 Potential for Cognitive and Motor Impairment

ABILIFY MYCITE, like other antipsychotics, has the potential to impair judgment, thinking, or motor skills. In short-term, placebo-controlled trials, somnolence (including sedation) was reported in 11% of aripiprazole-treated patients compared with 6% of placebo-treated patients. Somnolence (including sedation) led to discontinuation in 0.3% (8/2,467) of adult patients on oral aripiprazole in short-term, placebo-controlled trials.

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

5.13 Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing ABILIFY MYCITE 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).

5.14 Dysphagia

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

6 ADVERSE REACTIONS

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

- Increased Mortality in Elderly Patients with Dementia-Related Psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Suicidal Thoughts and Behaviors in Pediatric and Young Adult Patients *[see Boxed Warning and Warnings and Precautions (5.2)]*
- Cerebrovascular Adverse Events, Including Stroke *[see Warnings and Precautions (5.3)]*
- Neuroleptic Malignant Syndrome (NMS) *[see Warnings and Precautions (5.4)]*
- Tardive Dyskinesia *[see Warnings and Precautions (5.5)]*
- Metabolic Changes *[see Warnings and Precautions (5.6)]*
- Pathological Gambling and Other Compulsive Behaviors *[see Warnings and Precautions (5.7)]*
- Orthostatic Hypotension *[see Warnings and Precautions (5.8)]*
- Falls *[see Warnings and Precautions (5.9)]*
- Leukopenia, Neutropenia, and Agranulocytosis *[see Warnings and Precautions (5.10)]*
- Seizures *[see Warnings and Precautions (5.11)]*
- Potential for Cognitive and Motor Impairment *[see Warnings and Precautions (5.12)]*
- Body Temperature Regulation *[see Warnings and Precautions (5.13)]*
- Dysphagia *[see Warnings and Precautions (5.14)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of ABILIFY MYCITE for the treatment of adults with schizophrenia, treatment of adults with manic and mixed episodes associated with bipolar I disorder, and adjunctive treatment of adults with major depressive disorder (MDD) has been established and is based on trials of aripiprazole including 13,543 adult patients who participated in multiple-dose clinical trials in schizophrenia, bipolar disorder, major depressive disorder, and other disorders, and who had approximately 7,619 patient-years of exposure to oral aripiprazole. A total of 3,390 patients were treated with oral aripiprazole for at least 180 days and 1,933 patients treated with oral aripiprazole had at least one year of exposure.

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

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

Adverse Reactions in Adult Patients with Schizophrenia

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

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

Adverse Reactions in Adult Patients with Bipolar Mania

Adult Patients Who Received Monotherapy

The following findings are based on a pool of 3-week, placebo-controlled bipolar mania trials in which oral aripiprazole was administered at doses of 15 or 30 mg/day.

Commonly observed adverse reactions associated with the use of aripiprazole tablets in patients with bipolar mania (incidence of 5% or greater and aripiprazole tablets incidence at least twice that for placebo) are shown in Table 9.

Table 9: Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials of Adult Patients with Bipolar Mania Treated with Oral Aripiprazole Monotherapy

	Percentage of Patients Reporting Reaction	
Preferred Term	**Aripiprazole tablets (n=917)**	**Placebo (n=753)**
Akathisia	13	4
Sedation	8	3
Restlessness	6	3
Tremor	6	3
Extrapyramidal Disorder	5	2

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 bipolar mania), including only those reactions that occurred in 2% or more of patients treated with aripiprazole tablets (doses ≥2 mg/day) and for which the incidence in patients treated with aripiprazole tablets was greater than the incidence in patients treated with placebo in the combined dataset.

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

	Percentage of Patients Reporting Reaction*	
System Organ Class Preferred Term	**Aripiprazole tablets (n=1843)**	**Placebo (n=1166)**
Eye Disorders		
Blurred Vision	3	1
Gastrointestinal Disorders		
Nausea	15	11
Constipation	11	7
Vomiting	11	6
Dyspepsia	9	7
Dry Mouth	5	4
Toothache	4	3
Abdominal Discomfort	3	2
Stomach Discomfort	3	2
General Disorders and Administration Site Conditions		
Fatigue	6	4
Pain	3	2
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal Stiffness	4	3
Pain in Extremity	4	2
Myalgia	2	1
Muscle Spasms	2	1
Nervous System Disorders		
Headache	27	23
Dizziness	10	7
Akathisia	10	4
Sedation	7	4
Extrapyramidal Disorder	5	3
Tremor	5	3
Somnolence	5	3
Psychiatric Disorders		
Agitation	19	17
Insomnia	18	13
Anxiety	17	13
Restlessness	5	3
Respiratory, Thoracic, and Mediastinal Disorders		
Pharyngolaryngeal Pain	3	2
Cough	3	2

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

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

Adult Patients with Adjunctive Therapy with Bipolar Mania

The following findings are based on a placebo-controlled trial of adult patients with bipolar disorder in which aripiprazole tablets was administered at doses of 15 or 30 mg/day as adjunctive therapy with lithium or valproate.

In a study of patients who were already tolerating either lithium or valproate as monotherapy, discontinuation rates due to adverse reactions were 12% for patients treated with adjunctive aripiprazole tablets compared to 6% for patients treated with adjunctive placebo. The most common adverse drug reactions associated with discontinuation in the adjunctive aripiprazole-treated compared to placebo-treated patients were akathisia (5% and 1%, respectively) and tremor (2% and 1%, respectively).

The commonly observed adverse reactions associated with adjunctive aripiprazole tablets and lithium or valproate in patients with bipolar mania (incidence of 5% or greater and incidence at least twice that for adjunctive placebo) were: akathisia, insomnia, and extrapyramidal disorder.

Table 11 enumerates the incidence, rounded to the nearest percent, of adverse reactions that occurred during acute treatment (up to 6 weeks), including only those reactions that occurred in 2% or more of patients treated with adjunctive aripiprazole tablets (doses of 15 or 30 mg/day) and lithium or valproate and for which the incidence in patients treated with this combination was greater than the incidence in patients treated with placebo plus lithium or valproate.

Table 11: Adverse Reactions in a Short-Term, Placebo-Controlled Trial of Adjunctive Therapy in Patients with Bipolar Disorder

	Percentage of Patients Reporting Reaction*	
System Organ Class Preferred Term	**Aripiprazole tablets + Li or Val† (n=253)**	**Placebo + Li or Val† (n=130)**
Gastrointestinal Disorders		
Nausea	8	5
Vomiting	4	0
Salivary Hypersecretion	4	2
Dry Mouth	2	1
Infections and Infestations		
Nasopharyngitis	3	2
Investigations		
Weight Increased	2	1
Nervous System Disorders		
Akathisia	19	5
Tremor	9	6
Extrapyramidal Disorder	5	1
Dizziness	4	1
Sedation	4	2
Psychiatric Disorders		
Insomnia	8	4
Anxiety	4	1

Restlessness	2	1

*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
†Lithium or Valproate

Adult Patients Receiving Aripiprazole Tablets as Adjunctive Treatment of Major Depressive Disorder

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

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

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

Table 12 enumerates the pooled incidence, rounded to the nearest percent, of adverse reactions that occurred during acute therapy (up to 6 weeks), including only those adverse reactions that occurred in 2% or more of patients treated with adjunctive aripiprazole tablets (doses ≥2 mg/day) and for which the incidence in patients treated with adjunctive aripiprazole tablets was greater than the incidence in patients treated with adjunctive placebo in the combined dataset.

Table 12: Adverse Reactions in Short-Term, Placebo-Controlled Adjunctive Trials in Patients with Major Depressive Disorder

	Percentage of Patients Reporting Reaction*	
System Organ Class Preferred Term	**Aripiprazole tablets + ADT† (n=371)**	**Placebo + ADT† (n=366)**
Eye Disorders		
Blurred Vision	6	1
Gastrointestinal Disorders		
Constipation	5	2
General Disorders and Administration Site Conditions		
Fatigue	8	4
Feeling Jittery	3	1
Infections and Infestations		
Upper Respiratory Tract Infection	6	4
Investigations		
Weight Increased	3	2
Metabolism and Nutrition Disorders		
Increased Appetite	3	2
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	4	3
Myalgia	3	1
Nervous System Disorders		

Akathisia	25	4
Somnolence	6	4
Tremor	5	4
Sedation	4	2
Dizziness	4	2
Disturbance in Attention	3	1
Extrapyramidal Disorder	2	0
Psychiatric Disorders		
Restlessness	12	2
Insomnia	8	2

*Adverse reactions reported by at least 2% of patients treated with adjunctive aripiprazole tablets, except adverse reactions which had an incidence equal to or less than placebo
†Antidepressant Therapy

Dose-Related Adverse Reactions in Patients with 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%).

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.

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

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

Bipolar Mania

In the short-term, placebo-controlled trials in bipolar mania in adults, the incidence of reported EPS-related events, excluding events related to akathisia, for monotherapy aripiprazole-treated patients was 16% vs. 8% for placebo and the incidence of akathisia-related events for monotherapy aripiprazole-treated patients was 13% vs. 4% for placebo. In the 6-week placebo-controlled trial in bipolar mania for adjunctive therapy with lithium or valproate, the incidence of reported EPS-related events, excluding events related to akathisia for adjunctive aripiprazole-treated patients was 15% vs. 8% for adjunctive placebo and the incidence of akathisia-related events for adjunctive aripiprazole-treated patients was 19% vs. 5% for adjunctive placebo.

In the adult bipolar mania trials with monotherapy aripiprazole tablets, the Simpson Angus Rating Scale and the Barnes Akathisia Scale showed a significant difference between aripiprazole tablets and placebo (aripiprazole tablets, 0.50; placebo, –0.01 and aripiprazole tablets, 0.21; placebo, –0.05). Changes in the Assessments of Involuntary Movement Scales were similar for the aripiprazole tablets and placebo groups. In the bipolar mania trials with aripiprazole tablets as adjunctive therapy with either lithium or valproate, the Simpson Angus Rating Scale and the Barnes Akathisia Scale showed a significant difference between adjunctive aripiprazole tablets and adjunctive placebo (aripiprazole tablets, 0.73; placebo, 0.07 and aripiprazole tablets, 0.30; placebo, 0.11). Changes in the Assessments of Involuntary Movement Scales were similar for adjunctive aripiprazole tablets and adjunctive placebo.

Major Depressive Disorder

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

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

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.

Skin Irritation for MYCITE Patch

Symptoms of skin irritation localized at the site of the MYCITE Patch may occur in some patients. In clinical studies with the 1-component patch, sixty-one patients (12.4%) experienced skin rashes localized at the site of patch placement.

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

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

Other Adverse Reactions Observed during Clinical Trial Evaluation of Aripiprazole

Other adverse reactions associated with aripiprazole are presented below. The 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:

- *Blood and Lymphatic System Disorders: rare* - thrombocytopenia
- *Cardiac Disorders: infrequent* – bradycardia, palpitations, *rare* – atrial flutter, cardio-respiratory arrest, atrioventricular block, atrial fibrillation, angina pectoris, myocardial ischemia, myocardial infarction, cardiopulmonary failure
- *Eye Disorders: infrequent* – photophobia; *rare* - diplopia
- *Gastrointestinal Disorders: infrequent* - gastroesophageal reflux disease
- *General Disorders and Administration Site Conditions: frequent* - asthenia; *infrequent* – peripheral edema, chest pain; *rare* – face edema
- *Hepatobiliary Disorders: rare* - hepatitis, jaundice
- *Immune System Disorders: rare*- hypersensitivity
- *Injury, Poisoning, and Procedural Complications: infrequent* – fall; *rare* – heatstroke
- *Investigations: frequent* - blood prolactin decreased, weight decreased; *infrequent* - hepatic enzyme increased, blood glucose increased, blood lactate dehydrogenase increased, gamma glutamyl transferase increased; *rare* – blood prolactin increased, blood urea increased, blood creatinine increased, blood bilirubin increased, electrocardiogram QT prolonged, glycosylated hemoglobin increased
- *Metabolism and Nutrition Disorders: frequent* – anorexia; *rare* - hypokalemia, hyponatremia, hypoglycemia
- *Musculoskeletal and Connective Tissue Disorders: infrequent* - muscular weakness, muscle tightness; *rare* – rhabdomyolysis, mobility decreased
- *Nervous System Disorders: infrequent* - parkinsonism, memory impairment, cogwheel rigidity, hypokinesia, bradykinesia; *rare* – akinesia, myoclonus, coordination abnormal, speech disorder, grand mal convulsion; *<1/10,000* patients - choreoathetosis
- *Psychiatric Disorders: infrequent* – aggression, loss of libido, delirium; *rare* – libido increased, anorgasmia, tic, homicidal ideation, catatonia, sleep walking
- *Renal and Urinary Disorders: rare* - urinary retention, nocturia
- *Reproductive System and Breast Disorders: infrequent* - erectile dysfunction; *rare* – gynaecomastia, menstruation irregular, amenorrhea, breast pain, priapism
- *Respiratory, Thoracic, and Mediastinal Disorders: infrequent* - nasal congestion, dyspnea
- *Skin and Subcutaneous Tissue Disorders: infrequent* - rash, hyperhidrosis, pruritus, photosensitivity reaction, alopecia; *rare* - urticaria
- *Vascular Disorders: infrequent* – hypotension, hypertension

6.2 Postmarketing Experience

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

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with ABILIFY MYCITE

Table 13 below includes clinically important drug interactions with ABILIFY MYCITE.

Table 13: Clinically Important Drug Interactions with ABILIFY MYCITE

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 CYP3A4 or CYP2D6 inhibitors increased the exposure of aripiprazole compared to the use of aripiprazole alone *[see Clinical Pharmacology (12.3)]*.	With concomitant use of ABILIFY MYCITE with a strong CYP3A4 inhibitor or CYP2D6 inhibitor, reduce the ABILIFY MYCITE dosage *[see Dosage and Administration (2.6)]*.
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 ABILIFY MYCITE with a strong CYP3A4 inducer, consider increasing the ABILIFY MYCITE dosage *[see Dosage and Administration (2.6)]*.
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 (5.8)]*.
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 Precautions (5.8)]*	Monitor sedation and blood pressure. Adjust dose accordingly.

7.2 Drugs Having No Clinically Important Interactions with ABILIFY MYCITE

Based on pharmacokinetic studies, no dosage adjustment of ABILIFY MYCITE 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, escitalopram), or CYP3A4 (e.g., dextromethorphan) when co-

administered with ABILIFY MYCITE. Additionally, no dosage adjustment is necessary for valproate, lithium, lamotrigine, lorazepam, or sertraline when co-administered with ABILIFY MYCITE *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ABILIFY MYCITE 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 ABILIFY MYCITE, during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms *[see Clinical Considerations].* There are no available data on aripiprazole use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. 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 MRHD produced prolonged gestation, stillbirths, decreased pup weight, and decreased pup survival. Consider the benefits and risks of ABILIFY MYCITE and possible risks to the fetus when prescribing ABILIFY MYCITE to a pregnant woman. Advise pregnant women of potential fetal risk.

The background risk of major birth defects and miscarriage for the indicated population are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

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

In pregnant rats receiving aripiprazole injection intravenously (3, 9, and 27 mg/kg/day) during the period of organogenesis, decreased fetal weight and delayed skeletal ossification were seen at the highest dose where it also caused maternal toxicity.

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

In pregnant rabbits receiving aripiprazole injection intravenously (3, 10, and 30 mg/kg/day) during the period of organogenesis, the highest dose, which caused pronounced maternal toxicity, resulted in decreased fetal weight, increased fetal abnormalities (primarily skeletal), and decreased fetal skeletal ossification. The fetal no-effect dose was 10 mg/kg/day, which is 5 times the human exposure at the MRHD based on AUC and is 6 times the MRHD based on mg/m^2.

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 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 30 mg/kg/day.

In rats receiving aripiprazole injection intravenously (3, 8, and 20 mg/kg/day) from gestation Day 6 through Day 20 postpartum, an increase in stillbirths was seen at 8 and 20 mg/kg/day, and decreases in early postnatal pup weights and survival were seen at 20 mg/kg/day; these effects were seen in presence of maternal toxicity. There were no effects on postnatal behavioral and reproductive development.

The effect of ABILIFY MYCITE on labor and delivery in humans is unknown.

8.2 Lactation

Risk Summary

Aripiprazole is present in human breast milk; however, there are insufficient data to assess the amount in human milk, the effects on the breastfed infant, or the effects on milk production.

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

8.4 Pediatric Use

Safety and effectiveness of ABILIFY MYCITE in pediatric patients have not been established.

Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric patients *[see Boxed Warning,and Warnings and Precautions (5.2)].*

8.5 Geriatric Use

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

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

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Elderly patients treated with antipsychotic drugs with dementia-related psychosis had a greater incidence of stroke and transient ischemic attack. ABILIFY MYCITE is not approved for the treatment of elderly patients with dementia-related psychosis *[see Boxed Warning and Warnings and Precautions (5.1, 5.3)]*.

8.6 CYP2D6 Poor Metabolizers

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

8.7 Hepatic and Renal Impairment

No dosage adjustment for ABILIFY MYCITE 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 ABILIFY MYCITE 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

ABILIFY MYCITE is not a controlled substance.

9.2 Abuse

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

9.3 Dependence

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

10 OVERDOSAGE

10.1 Human Experience

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

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

10.2 Management of Overdosage

No specific information is available on the treatment of overdose with ABILIFY MYCITE. If over-exposure occurs call your poison control center at 1-800-222-1222. 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.

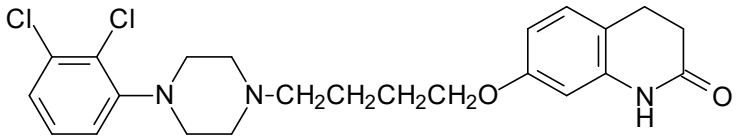
Charcoal: In the event of an overdose of ABILIFY MYCITE, an early charcoal administration may be useful in partially preventing the absorption of aripiprazole. Administration of 50 g of activated charcoal, one hour after a single 15 mg oral dose of aripiprazole, decreased the mean AUC and C_{max} of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

ABILIFY MYCITE (aripiprazole tablets with sensor) is a drug-device combination product containing aripiprazole, an atypical antipsychotic, embedded with an Ingestible Event Marker (IEM) sensor.

Aripiprazole is 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyril. The empirical formula is $C_{23}H_{27}Cl_2N_3O_2$ and its molecular weight is 448.38. The chemical structure is:



ABILIFY MYCITE is available in 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg strength tablets with sensor. Inactive ingredients of the tablets with sensor include cornstarch, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. Colorants include ferric oxide (yellow or red) and FD&C Blue No. 2 Aluminum Lake. Ingredients of the IEM include aluminum, cuprous chloride, ethyl cellulose, gold, hydroxypropyl cellulose, magnesium, silicon, silicon dioxide, silicon nitride, titanium-tungsten, titanium and triethyl citrate.

The ABILIFY MYCITE System is a drug-device combination product composed of the following components:

- An aripiprazole tablet with an embedded Ingestible Event Marker (IEM) sensor. The IEM is a 1 mm sized sensor embedded in the ABILIFY MYCITE tablets with sensor. Upon contact with gastric fluid, magnesium and cuprous chloride within the IEM react to activate and power the device. The IEM then communicates to the MYCITE Patch, to track aripiprazole ingestion.
- A MYCITE Patch (wearable sensor) is designed to detect the ingestion of the ABILIFY MYCITE tablets with sensor, record the ingestion of the IEM, and transmit ingestion data to the mobile patient application (app).
- A compatible app displays this data to allow patients to review their medication ingestion. These data can be shared with healthcare providers and caregivers.
- Web-based portal or dashboard for healthcare professionals and caregivers.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of aripiprazole in the treatment of schizophrenia, bipolar I disorder, or adjunctive treatment of major depressive disorder 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.

12.2 Pharmacodynamics

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

muscarinic receptors (IC_{50}>1,000 nM). Actions at receptors other than D_2, 5-HT_{1A}, and 5-HT_{2A} may explain some of the adverse reactions of aripiprazole (e.g., the orthostatic hypotension observed with aripiprazole may be explained by its antagonist activity at adrenergic alpha1 receptors).

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 is dose-proportional. Elimination of aripiprazole is mainly through hepatic metabolism involving two P450 isozymes, CYP2D6 and CYP3A4. For CYP2D6 poor metabolizers, the mean elimination half-life for aripiprazole is about 146 hours.

Absorption

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%. ABILIFY MYCITE 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.

Elimination

Metabolism

Aripiprazole is metabolized primarily by three biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation. Based on in vitro studies, CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalyzed by CYP3A4. Aripiprazole is the predominant drug moiety in the systemic circulation. At steady-state, dehydro-aripiprazole, the active metabolite, represents about 40% of aripiprazole AUC in plasma.

Excretion

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

Drug Interaction Studies

Effect of other drugs on the exposures of aripiprazole and dehydro-aripiprazole are summarized in Figure 1 and Figure 2, respectively. Based on simulation, a 4.5-fold increase in mean C_{max} and AUC values at steady-state is expected when extensive metabolizers of CYP2D6 are administered with both strong CYP2D6 and CYP3A4 inhibitors. A 3-fold increase in mean C_{max} and AUC values at steady-state is expected in poor metabolizers of CYP2D6 administered with strong CYP3A4 inhibitors.

Figure 1: The Effect of Other Drugs on Aripiprazole Pharmacokinetics

Effect of Other Drugs on Aripiprazole Tablets

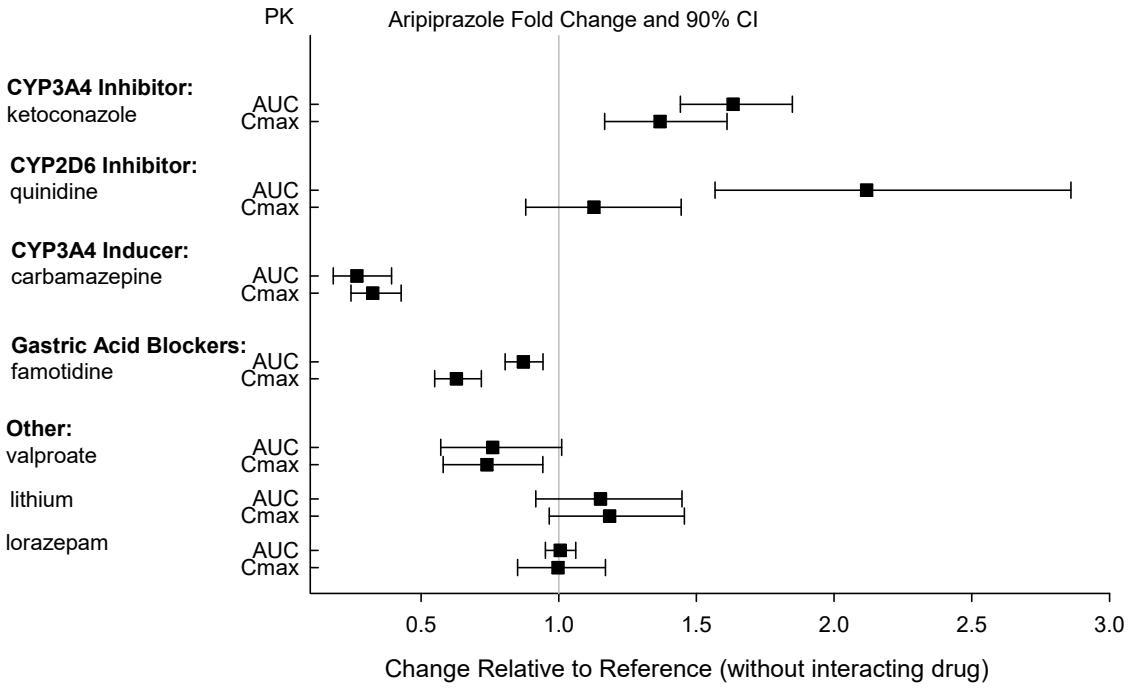
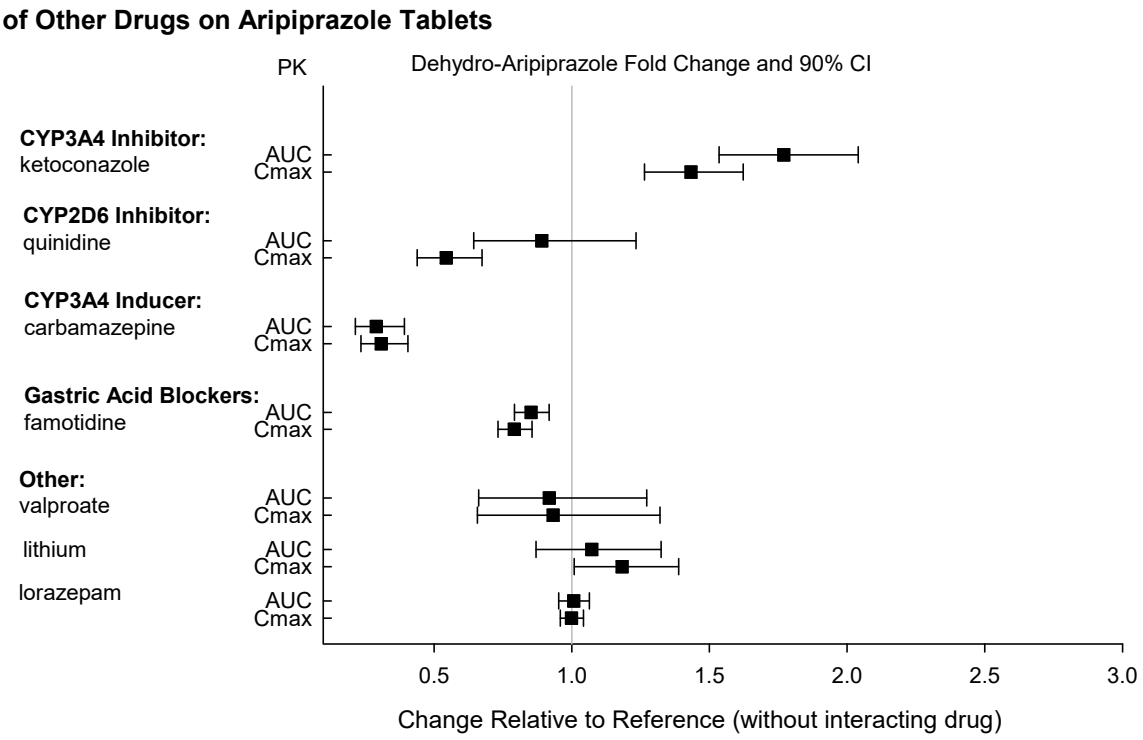
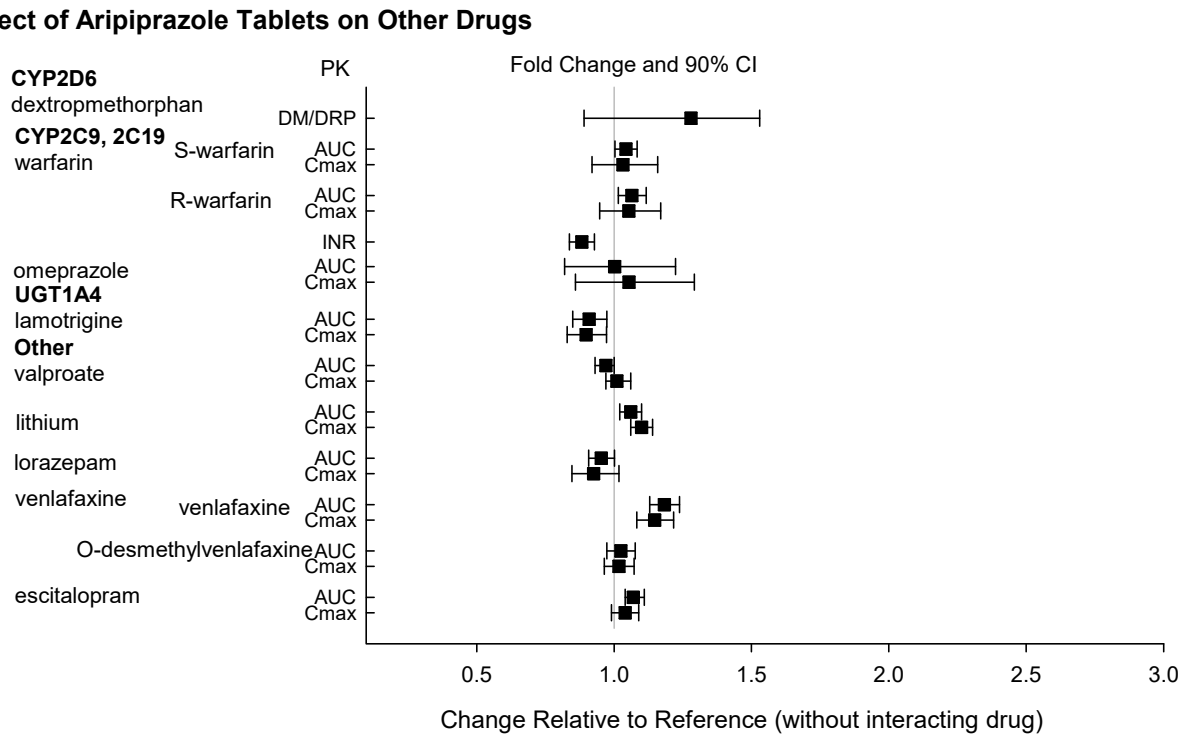


Figure 2: The Effect of Other Drugs on Dehydro-Aripiprazole Pharmacokinetics



The effect of aripiprazole on the exposures of other drugs are summarized in Figure 3. A population PK analysis in patients with major depressive disorder showed no substantial change in plasma concentrations of fluoxetine (20 or 40 mg/day), paroxetine CR (37.5 or 50 mg/day), or sertraline (100 or 150 mg/day) dosed to steady-state. The steady-state plasma concentrations of fluoxetine and norfluoxetine increased by about 18% and 36%, respectively, and concentrations of paroxetine decreased by about 27%. The steady-state plasma concentrations of sertraline and desmethylsertraline were not substantially changed when these antidepressant therapies were coadministered with aripiprazole.

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



Specific Populations

Exposure of aripiprazole and dehydro-aripiprazole in specific populations are summarized in Figure 4 and Figure 5, respectively.

Figure 4: Effect of Intrinsic Factors on Aripiprazole Pharmacokinetics

Special Populations

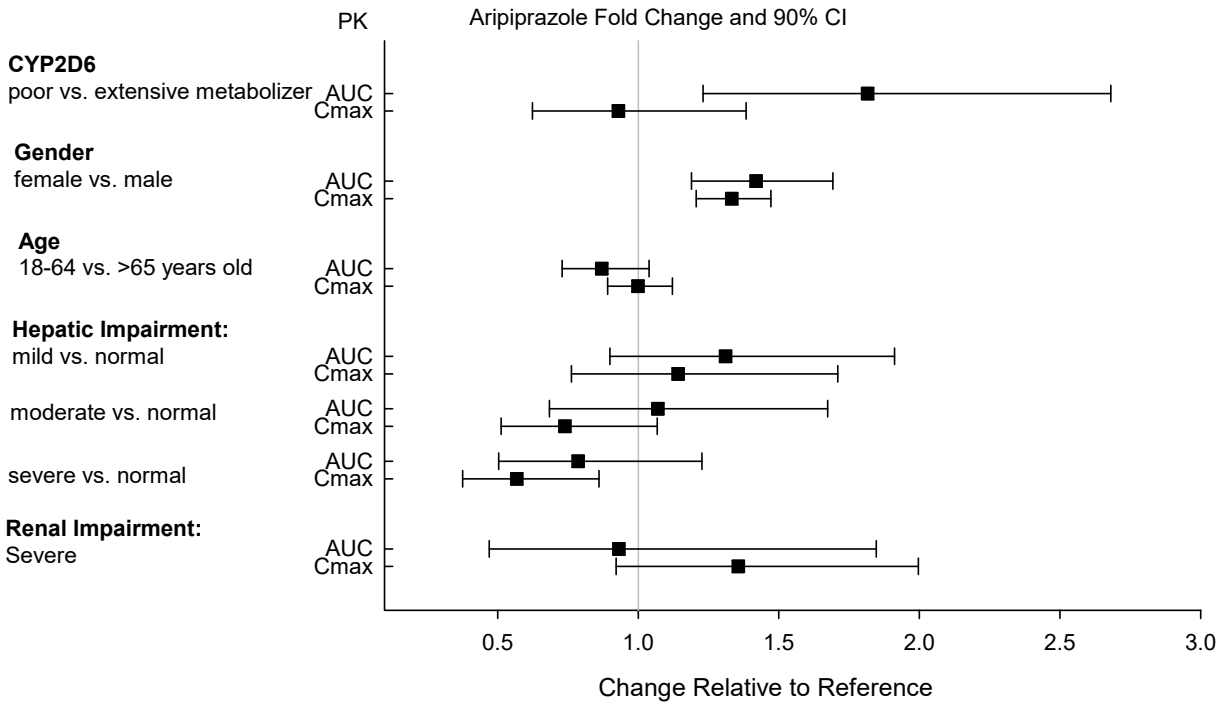
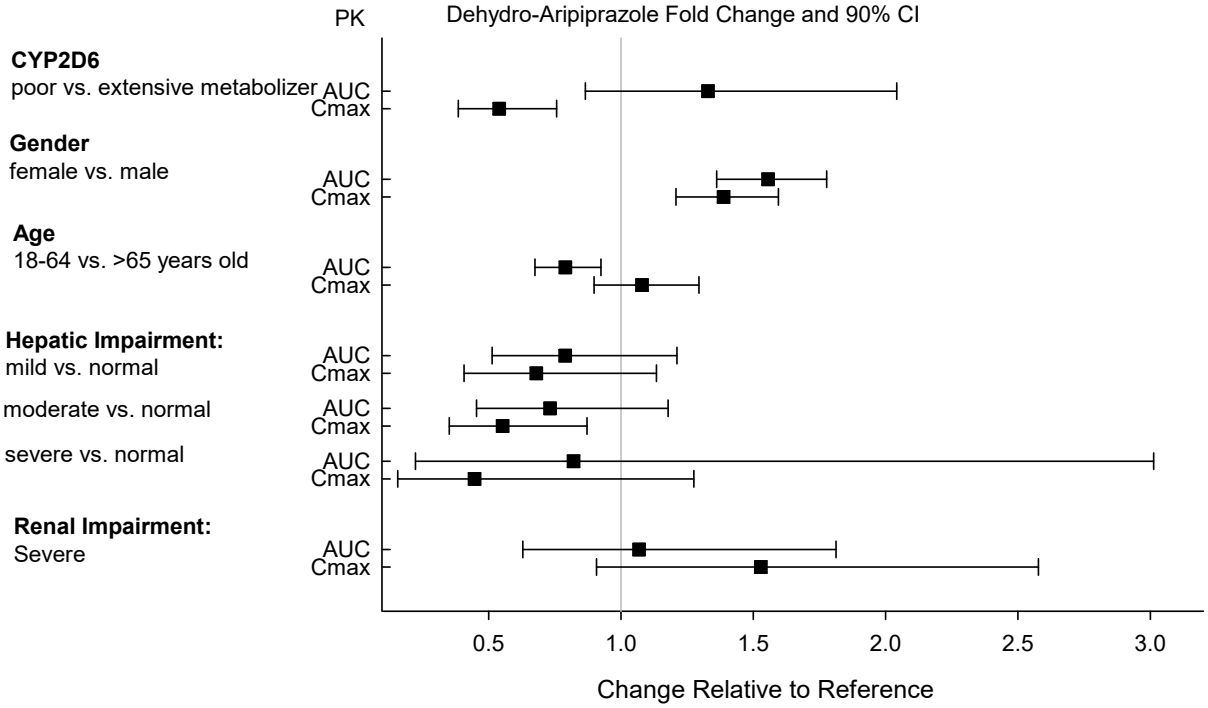


Figure 5: Effect of Intrinsic Factors on Dehydro-Aripiprazole Pharmacokinetics

Special Populations



13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Lifetime carcinogenicity studies were conducted in ICR mice, Sprague-Dawley (SD) rats, and F344 rats. Aripiprazole was administered for 2 years in the diet at doses of 1, 3, 10, and 30 mg/kg/day to ICR mice and 1, 3, and 10 mg/kg/day to F344 rats (0.2 to 5 times and 0.3 to 3 times the maximum recommended human dose [MRHD] based on mg/m^2, respectively). In addition, SD rats were dosed orally for 2 years at 10, 20, 40, and 60 mg/kg/day (3 to 19 times the MRHD based on mg/m^2). Aripiprazole did not induce tumors in male mice or male rats. In female mice, the incidences of pituitary gland adenomas and mammary gland adenocarcinomas and adenoacanthomas were increased at dietary doses of 3 to 30 mg/kg/day (0.1 to 0.9 times human exposure at MRHD based on AUC and 0.5 to 5 times the MRHD based on mg/m^2). In female rats, the incidence of mammary gland fibroadenomas was increased at a dietary dose of 10 mg/kg/day (0.1 times human exposure at MRHD based on AUC and 3 times the MRHD based on mg/m^2); and the incidences of adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas were increased at an oral dose of 60 mg/kg/day (14 times human exposure at MRHD based on AUC and 19 times the MRHD based on mg/m^2).

Proliferative changes in the pituitary and mammary gland of rodents have been observed following chronic administration of other antipsychotic agents and are considered prolactin-mediated. Serum prolactin was not measured in the aripiprazole carcinogenicity studies. However, increases in serum prolactin levels were observed in female mice in a 13-week dietary study at the doses associated with mammary gland and pituitary tumors. Serum prolactin was not increased in female rats in 4-week and 13-week dietary studies at the dose associated with mammary gland tumors. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown.

Mutagenesis

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

Impairment of Fertility

Female rats were treated with oral doses of 2, 6, and 20 mg/kg/day (0.6, 2, and 6 times the MRHD on a mg/m^2 basis) of aripiprazole from 2 weeks prior to mating through Day 7 of gestation. Estrus cycle irregularities and increased corpora lutea were seen at all doses, but no impairment of fertility was seen. Increased pre-implantation loss was seen at 6 and 20 mg/kg/day and decreased fetal weight was seen at 20 mg/kg/day.

Male rats were treated with oral doses of 20, 40, and 60 mg/kg/day (6, 13, and 19 times the MRHD on a mg/m^2 basis) of aripiprazole from 9 weeks prior to mating through mating.

Disturbances in spermatogenesis were seen at 60 mg/kg and prostate atrophy was seen at 40 and 60 mg/kg, but no impairment of fertility was seen.

13.2 Animal Toxicology and/or Pharmacology

Aripiprazole produced retinal degeneration in albino rats in a 26-week chronic toxicity study at a dose of 60 mg/kg and in a 2-year carcinogenicity study at doses of 40 and 60 mg/kg. The 40 and 60 mg/kg/day doses are 13 and 19 times the maximum recommended human dose (MRHD) based on mg/m^2 and 7 to 14 times human exposure at MRHD based on AUC. Evaluation of the retinas of albino mice and of monkeys did not reveal evidence of retinal degeneration. Additional studies to further evaluate the mechanism have not been performed. The relevance of this finding to human risk is unknown.

14 CLINICAL STUDIES

14.1 Overview of the Clinical Studies

The safety and efficacy of aripiprazole tablets for the treatment of adults with schizophrenia, acute treatment of adults with manic and mixed episodes associated with Bipolar I disorder, and adjunctive treatment of adults with major depressive disorder (MDD) has been established and is based on the following adequate and well-controlled trials of aripiprazole tablets:

- Four short-term trials and one maintenance trial in adult patients with schizophrenia *[see Clinical Studies (14.2)]*
- Four short-term monotherapy trials and one 6-week adjunctive trial in adult patients with manic or mixed episodes *[see Clinical Studies (14.3)]*
- One maintenance monotherapy trial and in one maintenance adjunctive trial in adult patients with bipolar I disorder *[see Clinical Studies (14.3)]*
- Two short-term trials in adult patients with MDD who had an inadequate response to antidepressant therapy during the current episode *[see Clinical Studies (14.4)]*

14.2 Schizophrenia

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

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

In a 4-week trial (n=414) comparing two fixed doses of aripiprazole tablets (15 or 30 mg/day) to placebo, both doses of aripiprazole tablets were superior to placebo in the PANSS total

score (Study 1 in Table 14), PANSS positive subscale, and CGI-severity score. In addition, the 15 mg dose was superior to placebo in the PANSS negative subscale.

In a 4-week trial (n=404) comparing two fixed doses of aripiprazole tablets (20 or 30 mg/day) to placebo, both doses of aripiprazole tablets were superior to placebo in the PANSS total score (Study 2 in Table 14), PANSS positive subscale, PANSS negative subscale, and CGI-severity score.

In a 6-week trial (n=420) comparing three fixed doses of aripiprazole tablets (10, 15, or 20 mg/day) to placebo, all three doses of aripiprazole tablets were superior to placebo in the PANSS total score (Study 3 in Table 14), PANSS positive subscale, and the PANSS negative subscale.

In a 6-week trial (n=367) comparing three fixed doses of aripiprazole tablets (2, 5, or 10 mg/day) to placebo, the 10 mg dose of aripiprazole tablets was superior to placebo in the PANSS total score (Study 4 in Table 14), the primary outcome measure of the study. The 2 and 5 mg doses did not demonstrate superiority to placebo on the primary outcome measure.

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

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

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

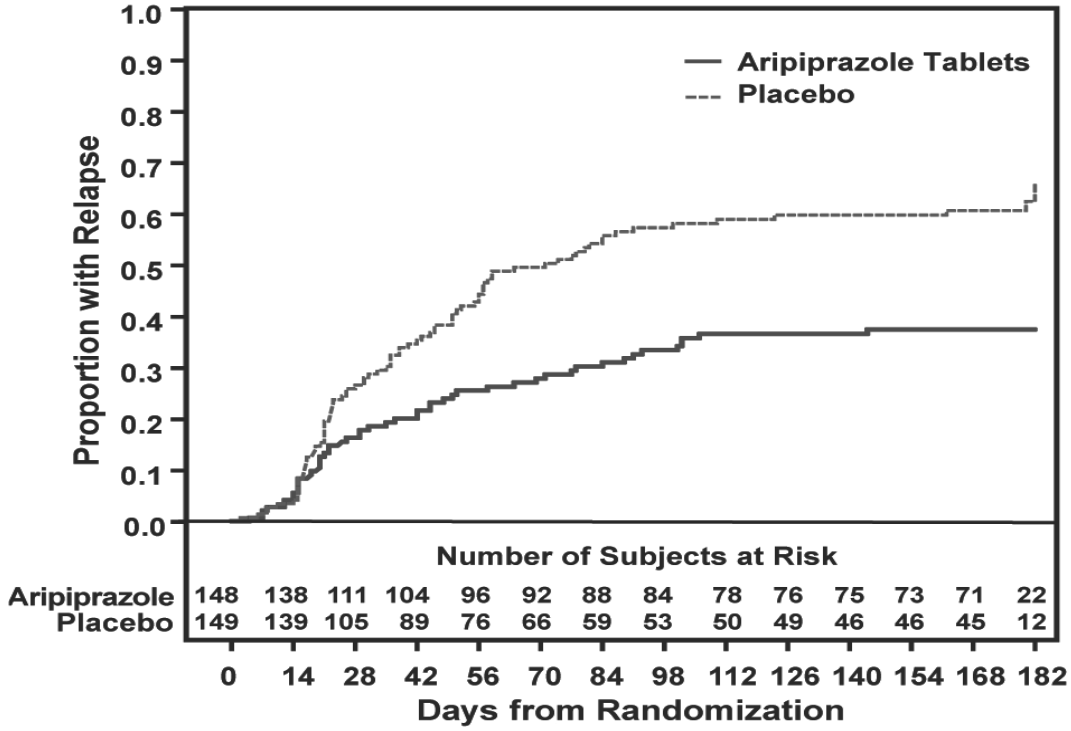
Table 14: Schizophrenia Studies

		Primary Efficacy Measure: PANSS		
Study Number	**Treatment Group**	**Mean Baseline Score (SD)**	**LS Mean Change from Baseline (SE)**	**Placebo-subtracted Difference* (95% CI)**
Study 1	Aripiprazole tablets (15 mg/day) †	98.5 (17.2)	-15.5 (2.40)	-12.6 (-18.9, -6.2)
	Aripiprazole tablets (30 mg/day) †	99.0 (19.2)	-11.4 (2.39)	-8.5 (-14.8, -2.1)
	Placebo	100.2 (16.5)	-2.9 (2.36)	--
Study 2	Aripiprazole tablets (20 mg/day) †	92.6 (19.5)	-14.5 (2.23)	-9.6 (-15.4, -3.8)
	Aripiprazole tablets (30 mg/day) †	94.2 (18.5)	-13.9 (2.24)	-9.0 (-14.8, -3.1)
	Placebo	94.3 (18.5)	-5.0 (2.17)	--

Study 3	Aripiprazole tablets (10 mg/day) †	92.7 (19.5)	-15.0 (2.38)	-12.7 (-19.00, -6.41)
	Aripiprazole tablets (15 mg/day) †	93.2 (21.6)	-11.7 (2.38)	-9.4 (-15.71, -3.08)
	Aripiprazole tablets (20 mg/day) †	92.5 (20.9)	-14.4 (2.45)	-12.1 (-18.53, -5.68)
	Placebo	92.3 (21.8)	-2.3 (2.35)	--
Study 4	Aripiprazole tablets (2 mg/day)	90.7 (14.5)	-8.2 (1.90)	-2.9 (-8.29, 2.47)
	Aripiprazole tablets (5 mg/day)	92.0 (12.6)	-10.6 (1.93)	-5.2 (-10.7, 0.19)
	Aripiprazole tablets (10 mg/day) †	90.0 (11.9)	-11.3 (1.88)	-5.9 (-11.3, -0.58)
	Placebo	90.8 (13.3)	-5.3 (1.97)	--

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

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



14.3 Bipolar Disorder

Acute Treatment of Manic and Mixed Episodes

Monotherapy

The efficacy of aripiprazole tablets as monotherapy in the acute treatment of manic and mixed episodes associated with bipolar I disorder was established in four 3-week placebo-controlled trials in hospitalized patients who met the DSM-IV criteria for bipolar I disorder with manic or mixed episodes. These studies included patients with or without psychotic features and two of the studies also included patients with or without a rapid-cycling course.

The primary instrument used for assessing manic symptoms was the Young Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology in a range from 0 (no manic features) to 60 (maximum score). A key secondary instrument included the Clinical Global Impression-Bipolar (CGI-BP) Scale.

In the four positive, 3-week placebo-controlled trials (n=268; n=248; n=480; n=485) which evaluated aripiprazole tablets in a range of 15 mg to 30 mg, once daily (with a starting dose of 30 mg/day in two studies and 15 mg/day in two studies), aripiprazole tablets were superior to placebo in the reduction of Y-MRS total score (Studies 1 to 4 in Table 15) and CGI-BP Severity of Illness score (mania). In the two studies with a starting dose of 15 mg/day, 48% and 44% of patients were on 15 mg/day at endpoint. In the two studies with a starting dose of 30 mg/day, 86% and 85% of patients were on 30 mg/day at endpoint.

Adjunctive Therapy

The efficacy of adjunctive aripiprazole tablets with concomitant lithium or valproate in the treatment of manic or mixed episodes associated with Bipolar I Disorder was established in a 6-week placebo-controlled study (n=384) with a 2-week lead-in mood stabilizer monotherapy phase in adult patients who met DSM-IV criteria for bipolar I disorder. This study included patients with manic or mixed episodes and with or without psychotic features.

Patients were initiated on open-label lithium (0.6 to 1.0 mEq/L) or valproate (50 to 125 mcg/mL) at therapeutic serum levels and remained on stable doses for 2 weeks. At the end of 2 weeks, patients demonstrating inadequate response (Y-MRS total score ≥16 and ≤25% improvement on the Y-MRS total score) to lithium or valproate were randomized to receive either aripiprazole tablets (15 mg/day or an increase to 30 mg/day as early as Day 7) or placebo as adjunctive therapy with open-label lithium or valproate. In the 6-week placebo-controlled phase, adjunctive aripiprazole tablets starting at 15 mg/day with concomitant lithium or valproate (in a therapeutic range of 0.6 to 1.0 mEq/L or 50 to 125 mcg/mL, respectively) was superior to lithium or valproate with adjunctive placebo in the reduction of the Y-MRS total score (Study 5 in Table 15) and CGI-BP Severity of Illness score (mania). Seventy-one percent of the patients coadministered valproate and 62% of the patients coadministered lithium were on 15 mg/day at 6-week endpoint.

Table 15: Bipolar Studies

		Primary Efficacy Measure: Y-MRS		
Study Number	**Treatment Group**	**Mean Baseline Score (SD)**	**LS Mean Change from Baseline (SE)**	**Placebo-subtracted Difference* (95% CI)**
Study 1	Aripiprazole tablets (30/15 mg/day)†	29.0 (5.9)	-12.52 (1.05)	-5.33 (-7.90, -2.76)
	Placebo	28.5 (4.6)	-7.19 (1.07)	--
Study 2	Aripiprazole tablets (30/15 mg/day)†	27.8 (5.7)	-8.15 (1.23)	-4.80 (-7.80, -1.80)
	Placebo	29.1 (6.9)	-3.35 (1.22)	--
Study 3	Aripiprazole tablets (15 to 30 mg/day)†	28.5 (5.6)	-12.64 (0.84)	-3.63 (-5.75, -1.51)
	Placebo	28.9 (5.9)	9.01 (0.81)	--
Study 4	Aripiprazole tablets (15 to 30 mg/day)†	28.0 (5.8)	-11.98 (0.80)	-2.28 (-4.44 , -0.11)
	Placebo	28.3 (5.8)	-9.70 (0.83)	--
Study 5	Aripiprazole tablets (15 or 30 mg/day)† + Lithium/Valproate	23.2 (5.7)	-13.31 (0.50)	-2.62 (-4.29 , -0.95)
	Placebo + Lithium/Valproate	23.0 (4.9)	-10.70 (0.69)	--

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

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

†Doses statistically significantly superior to placebo.

Maintenance Treatment of Bipolar I Disorder

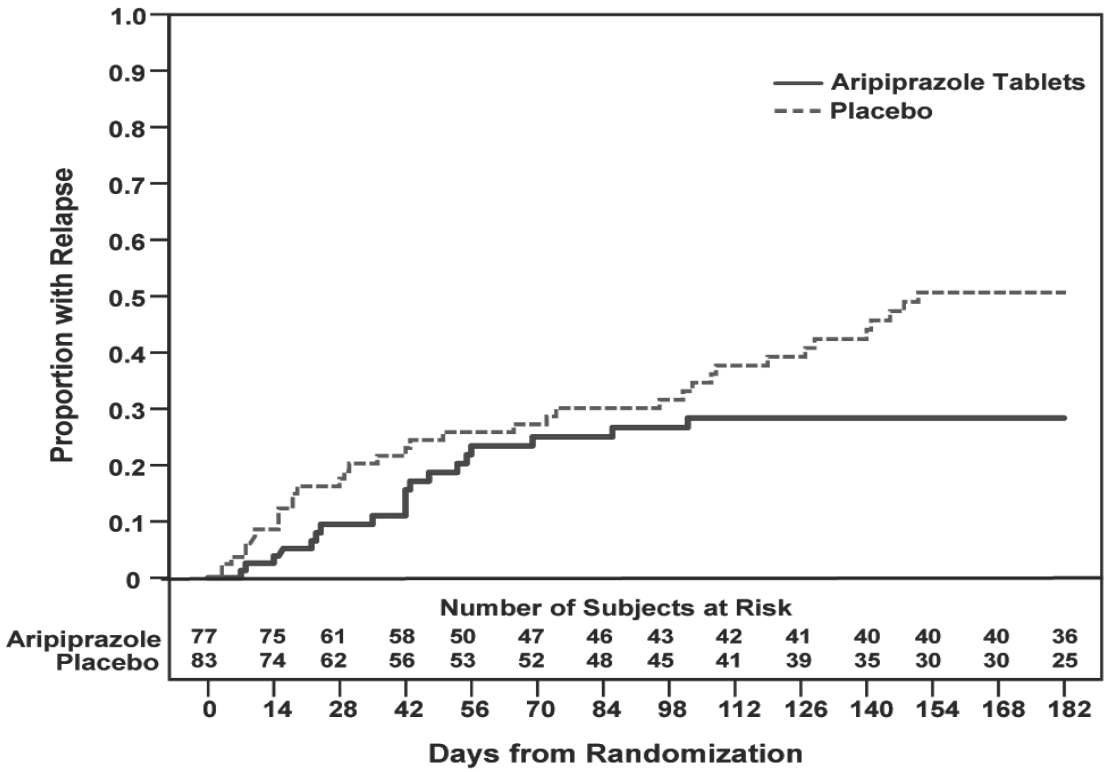
Monotherapy Maintenance Therapy

A maintenance trial was conducted in adult patients meeting DSM-IV criteria for bipolar I disorder with a recent manic or mixed episode who had been stabilized on open-label aripiprazole tablets and who had maintained a clinical response for at least 6 weeks. The first phase of this trial was an open-label stabilization period in which inpatients and outpatients were clinically stabilized and then maintained on open-label aripiprazole tablets (15 or 30 mg/day, with a starting dose of 30 mg/day) for at least 6 consecutive weeks. One hundred sixty-one outpatients were then randomized in a double-blind fashion to either the same dose of aripiprazole tablets they were on at the end of the stabilization and maintenance period or placebo and were then monitored for manic or depressive relapse. During the randomization phase, aripiprazole tablets were superior to placebo on time to the number of combined affective relapses (manic plus depressive), the primary outcome measure for this study (Study 7 in Figure 7). A total of 55 mood events were observed during the double-blind treatment phase. Nineteen were from the aripiprazole tablets group and 36 were from the placebo group. The number of observed manic episodes in the aripiprazole tablets group (6) were fewer than that in

the placebo group (19), while the number of depressive episodes in the aripiprazole tablets group (9) was similar to that in the placebo group (11).

An examination of population subgroups did not reveal any clear evidence of differential responsiveness on the basis of age and gender; however, there were insufficient numbers of patients in each of the ethnic groups to adequately assess inter-group differences.

Figure 7: Kaplan-Meier Estimation of Cumulative Proportion of Patients with Relapse (Bipolar Study 7)



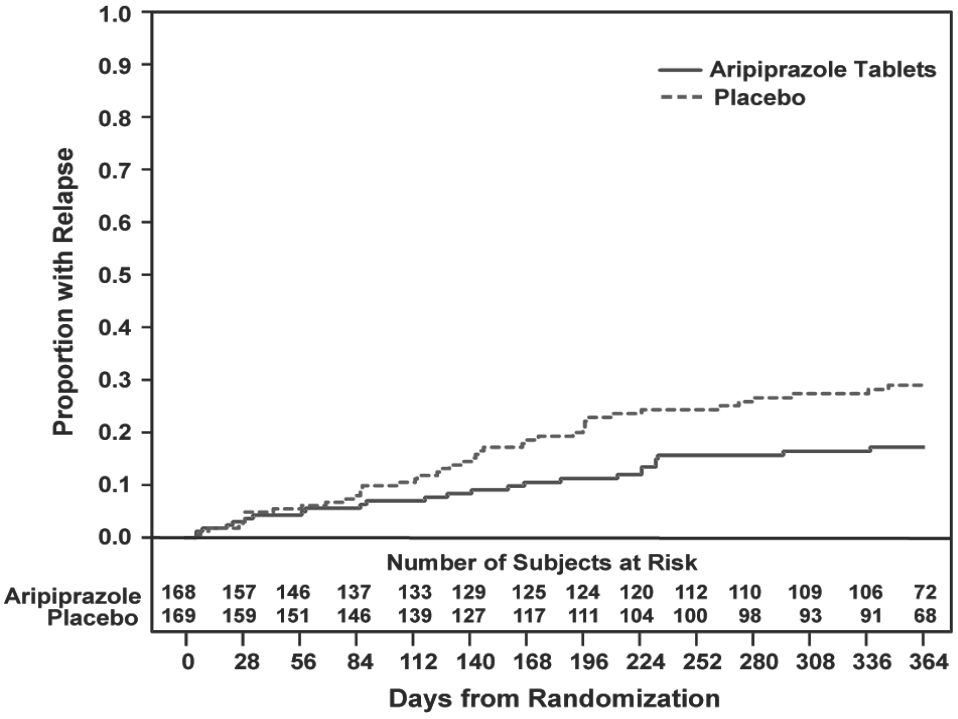
Adjunctive Maintenance Therapy

An adjunctive maintenance trial was conducted in adult patients meeting DSM-IV criteria for bipolar I disorder with a recent manic or mixed episode. Patients were initiated on open-label lithium (0.6 to 1.0 mEq/L) or valproate (50 to 125 mcg/mL) at therapeutic serum levels, and remained on stable doses for 2 weeks. At the end of 2 weeks, patients demonstrating inadequate response (Y-MRS total score ≥16 and ≤35% improvement on the Y-MRS total score) to lithium or valproate received aripiprazole tablets with a starting dose of 15 mg/day with the option to increase to 30 mg or reduce to 10 mg as early as Day 4, as adjunctive therapy with open-label lithium or valproate. Prior to randomization, patients on the combination of single-blind aripiprazole tablets and lithium or valproate were required to maintain stability (Y-MRS and MADRS total scores ≤12) for 12 consecutive weeks. Three hundred thirty-seven patients were then randomized in a double-blind fashion, to either the same dose of aripiprazole tablets they were on at the end of the stabilization period or placebo plus lithium or valproate and were then monitored for manic, mixed, or depressive relapse for a maximum of 52 weeks. Aripiprazole tablets were superior to placebo on the primary endpoint, time from randomization to relapse to any mood event (Study 8 in Figure 8). A mood event was defined as hospitalization for a manic, mixed, or depressive episode, study discontinuation due to lack of efficacy accompanied by Y-

MRS score >16 and/or a MADRS >16, or an SAE of worsening disease accompanied by Y-MRS score >16 and/or a MADRS >16. A total of 68 mood events were observed during the double-blind treatment phase. Twenty-five were from the aripiprazole group and 43 were from the placebo group. The number of observed manic episodes in the aripiprazole group (7) were fewer than that in the placebo group (19), while the number of depressive episodes in the aripiprazole group (14) was similar to that in the placebo group (18). The Kaplan-Meier curves of the time from randomization to relapse to any mood event during the 52-week double-blind treatment phase for aripiprazole tablets and placebo groups are shown in Figure 8.

An examination of population subgroups did not reveal any clear evidence of differential responsiveness on the basis of age and gender; however, there were insufficient numbers of patients in each of the ethnic groups to adequately assess inter-group differences.

Figure 8: Kaplan-Meier Estimation of Cumulative Proportion of Patients with Relapse to Any Mood Event (Bipolar Study 8)



14.4 Adjunctive Treatment of Adults with Major Depressive Disorder

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

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

In the two trials (n=381, n=362), aripiprazole tablets were superior to placebo in reducing mean MADRS total scores (Studies 1, 2 in Table 16). In one study, aripiprazole tablets were also superior to placebo in reducing the mean SDS score.

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

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

Table 16: Adjunctive Treatment of Major Depressive Disorder Studies

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

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

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

†Doses statistically significantly superior to placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

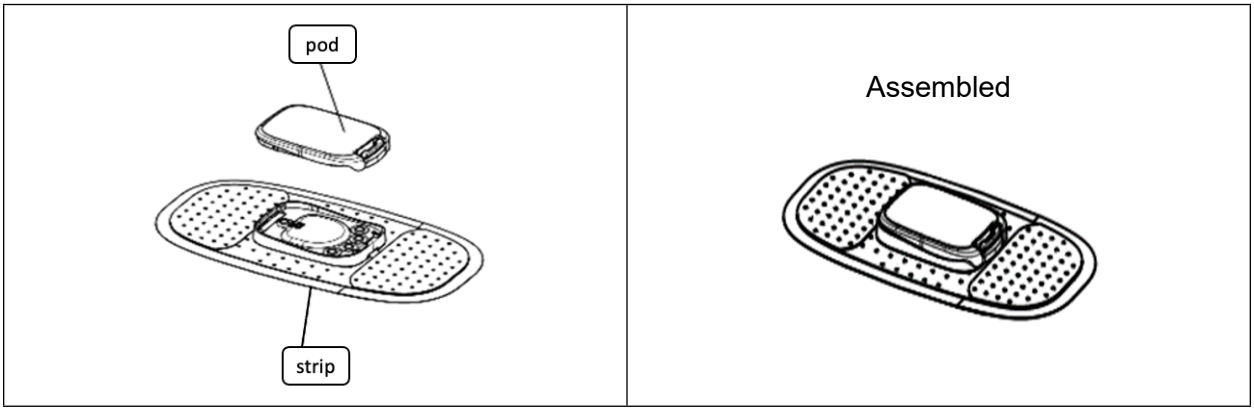
The ABILIFY MYCITE kit contains aripiprazole tablets embedded with an Ingestible Event Marker (IEM) sensor co-packaged with MYCITE Patches (wearable sensors) (referred to as the *patch*). The *patch* is available as a:

- 2-component patch, comprised of a removable electronics module (referred to as the “pod”) and an adhesive “strip” (see Table 18 and Figure 10). The pod contains electronic

components to record drug ingestion information and transfer the data to a compatible smartphone. The *30 Day Starter kits* contain (a) aripiprazole tablets with sensor, (b) strips, and (c) one pod; whereas, the *Maintenance kits* contain (a) aripiprazole tablets with sensor and (b) strips *[see Dosage and Administration (2.2)]*.

Each *patch* has a corresponding IFU within the *app*. The status of the *patch* is indicated by a status icon in the *app* to inform the user that the *patch* is properly adhered and fully functioning.

Figure 9: MYCITE Patch (2-component)



ABILIFY MYCITE Kits (2-component patch)

ABILIFY MYCITE kits are available in the following strengths and packages:

Strength	Color/ Shape	Markings	Pack Size and Components (2-component patch)[1]	NDC Code
2 mg	pale green modified rectangle	"DA-029" and "2"	**30 Day Starter kit:** Bottle of 30 tablets with sensor + 1 MYCITE pod and 7 MYCITE strips	59148-029-61
			Maintenance kit: Bottle of 30 tablets with sensor + 7 MYCITE strips[1]	59148-029-72
5 mg	pale blue modified rectangle	"DA-030 and "5"	**30 Day Starter kit:** Bottle of 30 tablets with sensor + 1 MYCITE pod and 7 MYCITE strips	59148-030-61
			Maintenance kit: Bottle of 30 tablets with sensor + 7 MYCITE strips[1]	59148-030-72
10 mg	off-white to pale pink modified rectangle	"DA-031" and "10"	**30 Day Starter kit:** Bottle of 30 tablets with sensor + 1 MYCITE pod and 7 MYCITE strips	59148-031-61
			Maintenance kit: Bottle of 30 tablets with sensor + 7 MYCITE strips[1]	59148-031-72
15 mg	pale yellow round	"DA-032" and "15"	**30 Day Starter kit:** Bottle of 30 tablets with sensor + 1 MYCITE pod and 7 MYCITE strips	59148-032-61
			Maintenance kit: Bottle of 30 tablets with sensor + 7 MYCITE strips[1]	59148-032-72
20 mg	white to pale yellowish white round	"DA-033" and "20"	**30 Day Starter kit:** Bottle of 30 tablets with sensor + 1 MYCITE pod and 7 MYCITE strips	59148-033-61
			Maintenance kit: Bottle of 30 tablets with sensor + 7 MYCITE strips[1]	59148-033-72

30 mg	off-white to pale pink round	"DA-034" and "30"	**30 Day Starter kit:** Bottle of 30 tablets with sensor + 1 MYCITE pod and 7 MYCITE strips	59148-034-61
			Maintenance kit: Bottle of 30 tablets with sensor + 7 MYCITE strips[1]	59148-034-72

[1] The Maintenance Kits do not include the pod.

16.2 Storage

Tablet bottle:

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

Do not store in conditions where tablets are exposed to humid conditions.

MYCITE Patch (Wearable Sensor):

Store between 5°C and 27°C (41°F to 81°F), 15% to 93% relative humidity.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (*Medication Guide)*.

General Instructions for Use

Instruct patients to:

- Refer to the app store to ensure compatibility with their specific smartphone.
- First download the MYCITE App and follow instructions provided by the app.

Advise patients that:

- The initial use should be facilitated by the healthcare provider *[see Dosage and Administration (2.1)]*.
- They need a functioning pod before using the Maintenance Kit *[see How Supplied/Storage and Handling (16.1)]*.

Advise patients that most ingestions will be detected within 30 minutes; however, in some cases it can take over two hours for the smartphone app and web portal to detect the ingestion of ABILIFY MYCITE. In some cases, the ingestion of the tablet may not be detected. If the tablet is not detected after ingestion, the dose should not be repeated.

Managing Lost or Disabled Smartphone

Advise patients that if their smartphone is lost, impaired or otherwise rendered unusable, some information collected by the system (synced) may be lost. Advise patients to change their MYCITE Patch immediately and connect to a new smartphone using their current account information. Information previously synced to the patients account will be available.

Using the MYCITE Patch in Different Environments

The MYCITE Patch will communicate with a paired device when it is within 9-foot proximity. The MYCITE Patch should remain on an individual whether they are showering, swimming, or exercising as it is intended to tolerate water or perspiration. Patients undergoing an MRI,

however, need to remove their patch and replace with a new one as soon as possible. In order for the MYCITE Patch to communicate with a smartphone, the device must be powered on and Bluetooth®-enabled.

Suicidal Thoughts and Behaviors

Advise patients and caregivers to look for the emergence of suicidality, especially early during treatment and when the dosage is adjusted up or down and instruct them to report such symptoms to the healthcare provider *[see Boxed Warning, Warnings and Precautions (5.2)]*.

Neuroleptic Malignant Syndrome (NMS)

Counsel patients about a potentially fatal adverse reaction referred to as Neuroleptic Malignant Syndrome (NMS) that has been reported in association with administration of antipsychotic drugs. Advise patients to contact a healthcare provider or report to the emergency room if they experience signs or symptoms of NMS *[see Warnings and Precautions (5.4)]*.

Tardive Dyskinesia

Advise patients that abnormal involuntary movements have been associated with the administration of antipsychotic drugs. Counsel patients on the signs and symptoms of tardive dyskinesia and to contact their healthcare provider if these abnormal movements occur *[see Warnings and Precautions (5.5)]*.

Metabolic Changes

Educate patients about the risk of metabolic changes, how to recognize symptoms of hyperglycemia and diabetes mellitus, and the need for specific monitoring, including blood glucose, lipids, and weight *[see Warnings and Precautions (5.6)]*.

Pathological Gambling and Other Compulsive Behaviors

Advise patients and their caregivers of the possibility that they may experience compulsive urges to shop, increased urges to gamble, compulsive sexual urges, binge eating and/or other compulsive urges and the inability to control these urges while taking aripiprazole. In some cases, but not all, the urges were reported to have stopped when the dose was reduced or stopped *[see Warnings and Precautions (5.7)]*.

Orthostatic Hypotension and Syncope

Educate patients about the risk of orthostatic hypotension and syncope especially early in treatment, when re-initiating treatment, or when increasing the dosage *[see Warnings and Precautions (5.8)]*.

Leukopenia, Neutropenia and Agranulocytosis

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

Interference with Cognitive and Motor Performance

Because ABILIFY MYCITE 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 ABILIFY MYCITE therapy does not affect them adversely *[see Warnings and Precautions (5.12)]*.

Heat Exposure and Dehydration

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

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)]*.

Pregnancy

Advise patients that ABILIFY MYCITE may cause extrapyramidal and/or withdrawal symptoms in a neonate and to notify their healthcare provider with a known or suspected pregnancy. Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ABILIFY MYCITE during pregnancy *[see Use In Specific Populations (8.1)]*.

Tablets with embedded IEM sensors Manufactured by Otsuka Pharmaceutical Co., Ltd., Tokyo, 101-8535 Japan

MYCITE Patches Manufactured for Otsuka America Pharmaceutical, Inc. 3956 Point Eden Way, Hayward, CA 94545 USA

Otsuka

Otsuka America Pharmaceutical, Inc.

Distributed and marketed by Otsuka America Pharmaceutical, Inc., Rockville, MD 20850 USA

12US23IBR0001

MEDICATION GUIDE

ABILIFY MYCITE® (a BIL ĭ fī - Mi SIHYT)

(aripiprazole tablets with sensor), for oral use

Important:

- **If you are taking ABILIFY MYCITE with other medicines for treatment of major depressive disorder (MDD), you should also read the Medication Guides or Patient Information that comes with the other medicines.**
- **The ABILIFY MYCITE System has 4 parts:**
  - Aripiprazole tablet with an Ingestible Event Marker (IEM) sensor inside it (ABILIFY MYCITE).
  - MYCITE Patch (wearable sensor) that picks up (detects) the signal from the IEM sensor after you take the ABILIFY MYCITE tablet and sends the information to a smartphone.
  - MYCITE App, which is a smartphone application (app) that is used with a compatible smartphone to show information about when you take your ABILIFY MYCITE tablet.
  - Web-based portal for healthcare providers and caregivers.
- **Download the MYCITE App before using the ABILIFY MYCITE System. Always follow the instructions provided within the MYCITE App when using the ABILIFY MYCITE System.**
- **Your healthcare provider should show you how to use the ABILIFY MYCITE System before you use it for the first time.**

What is the most important information I should know about ABILIFY MYCITE?

ABILIFY MYCITE may cause serious side effects, including:

- **Increased risk of death in elderly people with dementia-related psychosis**. Medicines like ABILIFY MYCITE can raise the risk of death in elderly people who have lost touch with reality (psychosis) due to confusion and memory loss (dementia). ABILIFY MYCITE is not approved for the treatment of people who have lost touch with reality (psychosis) due to confusion or memory loss (dementia).
- **Increased risk of suicidal thoughts or actions in children and young adults.** Antidepressant medicines may increase suicidal thoughts or actions in some children and young adults within the first few months of treatment and when the dose is changed. It is not known if ABILIFY MYCITE is safe and effective for use in children.
  - **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.

What is ABILIFY MYCITE?

ABILIFY MYCITE is a prescription medicine of aripiprazole tablets with an Ingestible Event Marker (IEM) sensor inside it used:

- To treat adults with schizophrenia
- To treat bipolar I disorder:
  - short-term (acute) treatment of adults with manic or mixed episodes alone or when used with the medicine lithium or valproate
  - maintenance treatment of adults alone or when used with the medicine lithium or valproate
- To treat adults with major depressive disorder (MDD) along with other antidepressant medicines

The ABILIFY MYCITE System is meant to track if you have taken your ABILIFY MYCITE.

It is not known if ABILIFY MYCITE can improve how well you take your aripiprazole (patient compliance) or for changing your dose of aripiprazole.

There may be a delay in the detection of the ABILIFY MYCITE tablet and sometimes the detection of the tablet might not happen at all. ABILIFY MYCITE is not for use as real-time or emergency monitoring.

It is not known if ABILIFY MYCITE is safe or effective for use in children.

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

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

- have diabetes or high blood sugar or have a family history of diabetes or high blood sugar. Your healthcare provider should check your blood sugar before you start and during treatment with ABILIFY MYCITE.
- have or had seizures (convulsions)
- have or had low or high blood pressure
- have or had heart problems or stroke
- have or had a low white blood cell count
- are pregnant or plan to become pregnant. Talk to your healthcare provider about the risk to your unborn baby if you take ABLIFY MYCITE during pregnancy.
    - Tell your healthcare provider if you become pregnant or think you are pregnant during treatment with ABILIFY MYCITE.
    - If you become pregnant during treatment with ABILIFY MYCITE, talk to your healthcare provider about registering with the National Pregnancy Registry for Atypical Antipsychotics. You can register by calling 1-866-961-2388 or go to http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/.
- are breastfeeding or plan to breastfeed. ABILIFY MYCITE can pass into your breast milk. Talk to your healthcare provider about the best way to feed your baby during treatment with ABILIFY MYCITE.

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

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

Your healthcare provider can tell you if it is safe to take ABILIFY MYCITE with your other medicines. Do not start or stop any other medicines during treatment with ABILIFY MYCITE 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 ABILIFY MYCITE?

- **See the MYCITE App for instructions about how to apply and wear the MYCITE Patch and how to use the ABILIFY MYCITE System the right way.**
- Take ABILIFY MYCITE exactly as your healthcare provider tells you to take it. Do not change the dose or stop taking ABILIFY MYCITE without first talking to your healthcare provider.
- Take ABILIFY MYCITE by mouth with or without food.

- Swallow ABILIFY MYCITE tablets whole. Do not divide, crush, or chew ABILIFY MYCITE tablets.
- The ABILIFY MYCITE tablet is usually detected within 30 minutes after you take it, but there may be a delay of more than 2 hours for the smartphone app and web portal to detect that you have taken ABILIFY MYCITE, and sometimes the ABILIFY MYCITE tablet might not be detected at all. If the tablet is not detected after you take it, **do not** repeat the dose.
- If over-exposure occurs, call your poison control center at 1-800-222-1222.

What should I avoid while taking ABILIFY MYCITE?

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

What are the possible side effects of ABILIFY MYCITE?

ABILIFY MYCITE may cause serious side effects, including:

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

    Call your healthcare provider if you have any of these symptoms of high blood sugar during treatment with ABILIFY MYCITE:
    - **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.

- **Unusual urges.** Some people taking ABILIFY MYCITE have had unusual urges, such as gambling, binge eating or eating that you cannot control (compulsive), compulsive shopping and sexual urges. If you or your family members notice that you are having unusual urges or behaviors, talk to your healthcare provider.
- **Decreased blood pressure (orthostatic hypotension).** You may feel lightheaded or faint when you rise too quickly from a sitting or lying position.
- **Falls**
- **Low white blood cell count.** Your healthcare provider may do blood tests during the first few months of treatment with ABILIFY MYCITE.
- **Seizures (convulsions)**
- **Problems controlling your body temperature so that you feel too warm.** See "What should I avoid while taking ABILIFY MYCITE?"
- **Difficulty swallowing**

The most common side effects of ABILIFY MYCITE in adults include:

- restlessness or need to move (akathisia)
- dizziness
- nausea
- insomnia
- shaking (tremor)
- anxiety
- constipation
- sedation

These are not all the possible side effects of ABILIFY MYCITE.

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 ABILIFY MYCITE?

- Store ABILIFY MYCITE tablets at room temperature, between 68°F to 77°F (20°C to 25°C).
- Store MYCITE Patches between 41°F to 81°F (5°C to 27°C).
- Keep ABILIFY MYCITE tablets and MYCITE Patches (wearable sensor) dry. Do not store ABILIFY MYCITE tablets and Patches (wearable sensor) in places with high humidity.

Keep ABILIFY MYCITE and all medicines out of the reach of children.

General information about the safe and effective use of ABILIFY MYCITE.

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

What are the ingredients in ABILIFY MYCITE?

Active ingredient: aripiprazole

Inactive ingredients: cornstarch, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, and microcrystalline cellulose, and Ingestible Event Marker (IEM). Colorants include ferric oxide (yellow or red) and FD&C Blue No. 2 Aluminum Lake. Ingredients of the IEM include aluminum, cuprous chloride, ethyl cellulose, gold, hydroxypropyl cellulose, magnesium, silicon, silicon dioxide, silicon nitride, titanium-tungsten, titanium and triethyl citrate.

Manufactured by:
Tablets with embedded IEM sensors Manufactured by Otsuka Pharmaceutical Co., Ltd., Tokyo, 101-8535 Japan
MYCITE Patches Manufactured for Otsuka America Pharmaceutical, Inc. 3956 Point Eden Way, Hayward, CA 94545 USA
Distributed and marketed by Otsuka America Pharmaceutical, Inc., Rockville, MD 20850 USA

Otsuka
Otsuka America Pharmaceutical, Inc.

For more information about ABILIFY MYCITE go to www.abilifymycite.com or call 1-844-692-4834.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 12/2020

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