

# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

***APPLICATION NUMBER:***

**021436Orig1s041**

***Trade Name:*** ABILIFY

***Generic or Proper Name:*** aripiprazole

***Sponsor:*** Otsuka

***Approval Date:*** August 18, 2016

***Indication:*** ABILIFY is an atypical antipsychotic. The oral formulations are indicated for:

- Schizophrenia
- Acute treatment of Manic and Mixed Episodes associated with Bipolar I
- Adjunctive treatment of Major Depressive Disorder
- Irritability Associated with Autistic Disorder
- Treatment of Tourette's disorder

The injection is indicated for:

- Agitation associated with schizophrenia or bipolar mania

# CENTER FOR DRUG EVALUATION AND RESEARCH

## 021436Orig1s041

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**021436Orig1s041**

**APPROVAL LETTER**



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 021436/S-041  
NDA 021713/S-032  
NDA 021729/S-024  
NDA 021866/S-026  
NDA 202971/S-009

**SUPPLEMENT APPROVAL**

Otsuka Pharmaceutical Development & Commercialization, Inc.  
U.S. Agent for Otsuka Pharmaceutical Company, Ltd.  
Attention: Dana Cahill, PhD  
Associate Director, Global Regulatory Affairs  
2440 Research Boulevard  
Rockville, MD 20850

Dear Dr. Cahill:

Please refer to your Supplemental New Drug Applications (sNDA) dated and received July 14, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Abilify (aripiprazole) 2, 5, 10, 15, 20, 30 mg tablets (NDA 021436); Abilify (aripiprazole) 1 mg/mL oral solution (NDA 021713); Abilify (aripiprazole) 10 and 15 mg Orally Disintegrating Tablets (NDA 021729); Abilify (aripiprazole) 9.75 mg/1.3 mL injection for IM use (NDA 021866); Abilify Maintena (aripiprazole) for extended-release injectable suspension, for intramuscular injection 300 mg/vial and 400 mg/vial (NDA 202971).

We also refer to our letter dated May 3, 2016, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for aripiprazole, pertaining to the risk of impulse-control problems.

These supplemental new drug applications provide for revisions to the Highlights, Warnings and Precautions (5), Patient Counseling Information section (17), and Medication Guide consistent with our May 3, 2016 letter.

**APPROVAL & LABELING**

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

We note that your July 14, 2016, submission includes final printed labeling (FPL) for your package insert and Medication Guide. We have not reviewed this FPL. You are responsible for

assuring that the wording in this printed labeling is identical to that of the approved content of labeling in the structured product labeling (SPL) format.

### **WAIVER OF HIGHLIGHTS SECTION**

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

### **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide), with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

### **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf> ).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf> ).

## **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, contact Danbi Lee, Regulatory Project Manager, at (240) 402-8986.

Sincerely,

*{See appended electronic signature page}*

Mitchell V. Mathis, MD  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

ENCLOSURE:  
Content of Labeling

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MITCHELL V Mathis  
08/18/2016

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**021436Orig1s041**

**LABELING**

## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ABILIFY® (aripiprazole) Tablets

ABILIFY DISCMELT® (aripiprazole) Orally Disintegrating Tablets

ABILIFY® (aripiprazole) Oral Solution

ABILIFY® (aripiprazole) Injection FOR INTRAMUSCULAR USE ONLY

Initial U.S. Approval: 2002

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

See full prescribing information for complete boxed warning.

- Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ABILIFY is not approved for the treatment of patients with dementia-related psychosis. (5.1)
- Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants. Monitor for worsening and emergence of suicidal thoughts and behaviors. (5.3)

## RECENT MAJOR CHANGES

Warnings and Precautions, Pathological Gambling and Other Compulsive Behaviors (5.7)

08/2016

## INDICATIONS AND USAGE

ABILIFY is an atypical antipsychotic. The oral formulations are indicated for:

- Schizophrenia (14.1)
- Acute Treatment of Manic and Mixed Episodes associated with Bipolar I (14.2)
- Adjunctive Treatment of Major Depressive Disorder (14.3)
- Irritability Associated with Autistic Disorder (14.4)
- Treatment of Tourette's disorder (14.5)

The injection is indicated for:

- Agitation associated with schizophrenia or bipolar mania (14.6)

## DOSAGE AND ADMINISTRATION

	Initial Dose	Recommended Dose	Maximum Dose
Schizophrenia – adults (2.1)	10-15 mg/day	10-15 mg/day	30 mg/day
Schizophrenia – adolescents (2.1)	2 mg/day	10 mg/day	30 mg/day
Bipolar mania – adults: monotherapy (2.2)	15 mg/day	15 mg/day	30 mg/day
Bipolar mania – adults: adjunct to lithium or valproate (2.2)	10-15 mg/day	15 mg/day	30 mg/day
Bipolar mania – pediatric patients: monotherapy or as an adjunct to lithium or valproate (2.2)	2 mg/day	10 mg/day	30 mg/day
Major Depressive Disorder – Adults adjunct to antidepressants (2.3)	2-5 mg/day	5-10 mg/day	15 mg/day
Irritability associated with autistic disorder – pediatric patients (2.4)	2 mg/day	5-10 mg/day	15 mg/day
Tourette's disorder – (2.5)	Patients < 50 kg	2 mg/day	10 mg/day
	Patients ≥ 50 kg	2 mg/day	20 mg/day
Agitation associated with schizophrenia or bipolar mania – adults (2.6)	9.75 mg /1.3 mL injected IM		30 mg/day injected IM

- Oral formulations: Administer once daily without regard to meals (2)
- IM injection: Wait at least 2 hours between doses. Maximum daily dose 30 mg (2.5)
- Known CYP2D6 poor metabolizers: Half of the usual dose (2.7)

## DOSAGE FORMS AND STRENGTHS

- Tablets: 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg (3)
- Orally Disintegrating Tablets: 10 mg and 15 mg (3)
- Oral Solution: 1 mg/mL (3)
- Injection: 9.75 mg/1.3 mL single-dose vial (3)

## CONTRAINDICATIONS

- Known hypersensitivity to ABILIFY (4)

## WARNINGS AND PRECAUTIONS

- Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis** Increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack, including fatalities) (5.2)
- Neuroleptic Malignant Syndrome** Manage with immediate discontinuation and close monitoring (5.4)
- Tardive Dyskinesia** Discontinue if clinically appropriate (5.5)
- Metabolic Changes** Atypical antipsychotic drugs have been associated with metabolic changes that include hyperglycemia/diabetes mellitus, dyslipidemia, and body weight gain (5.6)
  - Hyperglycemia/Diabetes Mellitus** Monitor glucose regularly in patients with and at risk for diabetes (5.6)
  - Dyslipidemia** Undesirable alterations in lipid levels have been observed in patients treated with atypical antipsychotics (5.6)
  - Weight Gain** Weight gain has been observed with atypical antipsychotic use. Monitor weight (5.6)
- 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** have been reported with antipsychotics including ABILIFY. Patients with a history of a clinically significant low white blood cell count (WBC) or a drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of ABILIFY should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors (5.9)
- Seizures/Convulsions** Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold (5.10)
- Potential for Cognitive and Motor Impairment** Use caution when operating machinery (5.11)
- Suicide** The possibility of a suicide attempt is inherent in schizophrenia and bipolar disorder. Closely supervise high-risk patients (5.13)

## ADVERSE REACTIONS

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

- Adult patients with schizophrenia: akathisia
- Pediatric patients (13 to 17 years) with schizophrenia: extrapyramidal disorder, somnolence, and tremor
- Adult patients (monotherapy) with bipolar mania: akathisia, sedation, restlessness, tremor, and extrapyramidal disorder
- Adult patients (adjunctive therapy with lithium or valproate) with bipolar mania: akathisia, insomnia, and extrapyramidal disorder
- Pediatric patients (10 to 17 years) with bipolar mania: somnolence, extrapyramidal disorder, fatigue, nausea, akathisia, blurred vision, salivary hypersecretion, and dizziness
- Adult patients with major depressive disorder (adjunctive treatment to antidepressant therapy): akathisia, restlessness, insomnia, constipation, fatigue, and blurred vision
- Pediatric patients (6 to 17 years) with autistic disorder: sedation, fatigue, vomiting, somnolence, tremor, pyrexia, drooling, decreased appetite, salivary hypersecretion, extrapyramidal disorder, and lethargy
- Pediatric patients (6 to 18 years) with Tourette's disorder: sedation, somnolence, nausea, headache, nasopharyngitis, fatigue, increased appetite
- Adult patients with agitation associated with schizophrenia or bipolar mania: nausea

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

Strong CYP3A4 inducers	Double usual dose over 1 to 2 weeks
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## ----- DRUG INTERACTIONS -----

*Dosage adjustment due to drug interactions (7.1)*

Factors	Dosage Adjustments for ABILIFY
Known CYP2D6 Poor Metabolizers	Administer half of usual dose
Known CYP2D6 Poor Metabolizers and strong CYP3A4 inhibitors	Administer a quarter of usual dose
Strong CYP2D6 or CYP3A4 inhibitors	Administer half of usual dose
Strong CYP2D6 and CYP3A4 inhibitors	Administer a quarter of usual dose

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 08/2016

## FULL PRESCRIBING INFORMATION: CONTENTS\*

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

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## FULL PRESCRIBING INFORMATION

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

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

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

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

## 1 INDICATIONS AND USAGE

ABILIFY Oral Tablets, Orally-Disintegrating Tablets, and Oral Solution are indicated for the treatment of:

- Schizophrenia [see [CLINICAL STUDIES \(14.1\)](#)]
- Acute Treatment of Manic and Mixed Episodes associated with Bipolar I Disorder [see [CLINICAL STUDIES \(14.2\)](#)]
- Adjunctive Treatment of Major Depressive Disorder [see [CLINICAL STUDIES \(14.3\)](#)]
- Irritability Associated with Autistic Disorder [see [CLINICAL STUDIES \(14.4\)](#)]
- Treatment of Tourette's Disorder [see [CLINICAL STUDIES \(14.5\)](#)]

ABILIFY Injection is indicated for the treatment of:

- Agitation associated with schizophrenia or bipolar mania [*see [CLINICAL STUDIES \(14.6\)](#)*]

## **2 DOSAGE AND ADMINISTRATION**

### **2.1 Schizophrenia**

#### **Adults**

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

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

#### **Adolescents**

The recommended target dose of ABILIFY is 10 mg/day. Aripiprazole was studied in adolescent patients 13 to 17 years of age with schizophrenia at daily doses of 10 mg and 30 mg. The starting daily dose of the tablet formulation in these patients was 2 mg, which was titrated to 5 mg after 2 days and to the target dose of 10 mg after 2 additional days. Subsequent dose increases should be administered in 5 mg increments. The 30 mg/day dose was not shown to be more efficacious than the 10 mg/day dose. ABILIFY can be administered without regard to meals [*see [CLINICAL STUDIES \(14.1\)](#)*]. Patients should be periodically reassessed to determine the need for maintenance treatment.

#### **Switching from Other Antipsychotics**

There are no systematically collected data to specifically address switching patients with schizophrenia from other antipsychotics to ABILIFY or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia, more gradual discontinuation

may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized.

## **2.2 Bipolar I Disorder**

### **Acute Treatment of Manic and Mixed Episodes**

Adults: The recommended starting dose in adults is 15 mg given once daily as monotherapy and 10 mg to 15 mg given once daily as adjunctive therapy with lithium or valproate. ABILIFY can be given without regard to meals. The recommended target dose of ABILIFY is 15 mg/day, as monotherapy or as adjunctive therapy with lithium or valproate. The dose may be increased to 30 mg/day based on clinical response. The safety of doses above 30 mg/day has not been evaluated in clinical trials.

Pediatrics: The recommended starting dose in pediatric patients (10 to 17 years) as monotherapy is 2 mg/day, with titration to 5 mg/day after 2 days, and a target dose of 10 mg/day after 2 additional days. Recommended dosing as adjunctive therapy to lithium or valproate is the same. Subsequent dose increases, if needed, should be administered in 5 mg/day increments. ABILIFY can be given without regard to meals [*see [CLINICAL STUDIES \(14.2\)](#)*].

## **2.3 Adjunctive Treatment of Major Depressive Disorder**

### **Adults**

The recommended starting dose for ABILIFY as adjunctive treatment for patients already taking an antidepressant is 2 to 5 mg/day. The recommended dosage range is 2 to 15 mg/day. Dosage adjustments of up to 5 mg/day should occur gradually, at intervals of no less than 1 week [*see [CLINICAL STUDIES \(14.3\)](#)*]. Patients should be periodically reassessed to determine the continued need for maintenance treatment.

## **2.4 Irritability Associated with Autistic Disorder**

### **Pediatric Patients (6 to 17 years)**

The recommended dosage range for the treatment of pediatric patients with irritability associated with autistic disorder is 5 to 15 mg/day.

Dosing should be initiated at 2 mg/day. The dose should be increased to 5 mg/day, with subsequent increases to 10 or 15 mg/day if needed. Dose adjustments of up to 5 mg/day should occur gradually, at intervals of no less than 1 week [*see [CLINICAL STUDIES \(14.4\)](#)*]. Patients should be periodically reassessed to determine the continued need for maintenance treatment.

## **2.5 Tourette's Disorder**

### **Pediatric Patients (6 to 18 years)**

The recommended dosage range for Tourette's Disorder is 5 to 20 mg/day.

For patients weighing less than 50 kg, dosing should be initiated at 2 mg/day with a target dose of 5 mg/day after 2 days. The dose can be increased to 10 mg/day in patients who do not achieve optimal control of tics. Dosage adjustments should occur gradually at intervals of no less than 1 week.

For patients weighing 50 kg or more, dosing should be initiated at 2 mg/day for 2 days, and then increased to 5 mg/day for 5 days, with a target dose of 10 mg/day on day 8. The dose can be increased up to 20 mg/day for patients who do not achieve optimal control of tics. Dosage adjustments should occur gradually in increments of 5 mg/day at intervals of no less than 1 week. [*see [CLINICAL STUDIES \(14.5\)](#)*].

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

## **2.6 Agitation Associated with Schizophrenia or Bipolar Mania (Intramuscular Injection)**

### **Adults**

The recommended dose in these patients is 9.75 mg. The recommended dosage range is 5.25 to 15 mg. No additional benefit was demonstrated for 15 mg compared to 9.75 mg. A lower dose of 5.25 mg may be considered when clinical factors warrant. If agitation warranting a second dose persists following the initial dose, cumulative doses up to a total of 30 mg/day may be given. However, the efficacy of repeated doses of ABILIFY injection in agitated patients has not been systematically evaluated in controlled clinical trials. The safety of total daily doses greater than 30 mg or injections given more frequently than every 2 hours have not been adequately evaluated in clinical trials [*see [CLINICAL STUDIES \(14.6\)](#)*].

If ongoing ABILIFY therapy is clinically indicated, oral ABILIFY in a range of 10 to 30 mg/day should replace ABILIFY injection as soon as possible [*see [DOSAGE AND ADMINISTRATION \(2.1 and 2.2\)](#)*].

### **Administration of ABILIFY Injection**

To administer ABILIFY Injection, draw up the required volume of solution into the syringe as shown in Table 1. Discard any unused portion.

**Table 1: ABILIFY Injection Dosing Recommendations**

Single-Dose	Required Volume of Solution
5.25 mg	0.7 mL
9.75 mg	1.3 mL
15 mg	2 mL

ABILIFY Injection is intended for intramuscular use only. Do not administer intravenously or subcutaneously. Inject slowly, deep into the muscle mass.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

## 2.7 Dosage Adjustments for Cytochrome P450 Considerations

Dosage adjustments are recommended in patients who are known CYP2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors or strong CYP3A4 inducers (see Table 2). When the coadministered drug is withdrawn from the combination therapy, ABILIFY dosage should then be adjusted to its original level. When the coadministered CYP3A4 inducer is withdrawn, ABILIFY dosage should be reduced to the original level over 1 to 2 weeks. Patients who may be receiving a combination of strong, moderate, and weak inhibitors of CYP3A4 and CYP2D6 (e.g., a strong CYP3A4 inhibitor and a moderate CYP2D6 inhibitor or a moderate CYP3A4 inhibitor with a moderate CYP2D6 inhibitor), the dosing may be reduced to one-quarter (25%) of the usual dose initially and then adjusted to achieve a favorable clinical response.

**Table 2: Dose Adjustments for ABILIFY 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
Known CYP2D6 Poor Metabolizers	Administer half of usual dose
Known CYP2D6 Poor Metabolizers taking concomitant strong CYP3A4 inhibitors (e.g., itraconazole, clarithromycin)	Administer a quarter of usual dose
Strong CYP2D6 (e.g., quinidine, fluoxetine, paroxetine) or CYP3A4 inhibitors (e.g., itraconazole, clarithromycin)	Administer half of usual dose
Strong CYP2D6 and CYP3A4 inhibitors	Administer a quarter of usual dose

Strong CYP3A4 inducers (e.g., carbamazepine, rifampin)	Double usual dose over 1 to 2 weeks
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When adjunctive ABILIFY is administered to patients with major depressive disorder, ABILIFY should be administered without dosage adjustment as specified in [DOSAGE AND ADMINISTRATION \(2.3\)](#).

## 2.8 Dosing of Oral Solution

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

## 2.9 Dosing of Orally Disintegrating Tablets

The dosing for ABILIFY Orally Disintegrating Tablets is the same as for the oral tablets [see [DOSAGE AND ADMINISTRATION \(2.1, 2.2, 2.3, and 2.4\)](#)].

## 3 DOSAGE FORMS AND STRENGTHS

ABILIFY<sup>®</sup> (aripiprazole) Tablets are available as described in Table 3.

**Table 3: ABILIFY Tablet Presentations**

Tablet Strength	Tablet Color/Shape	Tablet Markings
2 mg	green modified rectangle	“A-006” and “2”
5 mg	blue modified rectangle	“A-007” and “5”
10 mg	pink modified rectangle	“A-008” and “10”
15 mg	yellow round	“A-009” and “15”
20 mg	white round	“A-010” and “20”
30 mg	pink round	“A-011” and “30”

ABILIFY DISCMELT<sup>®</sup> (aripiprazole) Orally Disintegrating Tablets are available as described in Table 4.

**Table 4: ABILIFY DISCMELT Orally Disintegrating Tablet Presentations**

<b>Tablet Strength</b>	<b>Tablet Color/Shape</b>	<b>Tablet Markings</b>
<b>10 mg</b>	pink (with scattered specks) round	“A” and “640” “10”
<b>15 mg</b>	yellow (with scattered specks) round	“A” and “641” “15”

ABILIFY® (aripiprazole) Oral Solution (1 mg/mL) is a clear, colorless to light-yellow solution, supplied in child-resistant bottles along with a calibrated oral dosing cup.

ABILIFY® (aripiprazole) Injection for Intramuscular Use is a clear, colorless solution available as a ready-to-use, 9.75 mg/1.3 mL (7.5 mg/mL) solution in clear, Type 1 glass vials.

## 4 CONTRAINDICATIONS

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

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

#### Increased Mortality

**Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ABILIFY (aripiprazole) is not approved for the treatment of patients with dementia-related psychosis [*see* [BOXED WARNING](#)].**

#### ***Safety Experience in Elderly Patients with Psychosis Associated with Alzheimer’s Disease***

In three, 10-week, placebo-controlled studies of ABILIFY in elderly patients with psychosis associated with Alzheimer’s disease (n=938; mean age: 82.4 years; range: 56-99 years), the adverse reactions that were reported at an incidence of  $\geq 3\%$  and ABILIFY incidence at least twice that for placebo were lethargy [placebo 2%, ABILIFY 5%], somnolence (including sedation) [placebo 3%, ABILIFY 8%], and incontinence (primarily, urinary incontinence) [placebo

1%, ABILIFY 5%], excessive salivation [placebo 0%, ABILIFY 4%], and lightheadedness [placebo 1%, ABILIFY 4%].

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

## **5.2 Cerebrovascular Adverse Events, Including Stroke**

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

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

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

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, Obsessive Compulsive Disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in

over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 5.

**Table 5:**

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

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

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

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

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for MDD as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence

of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

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

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

**Screening Patients for Bipolar Disorder:** A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

It should be noted that ABILIFY is not approved for use in treating depression in the pediatric population.

## **5.4 Neuroleptic Malignant Syndrome (NMS)**

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) may occur with administration of antipsychotic drugs, including ABILIFY. Rare cases of NMS occurred during ABILIFY treatment in the worldwide clinical database. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia,

diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

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

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

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

## **5.5 Tardive Dyskinesia**

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

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

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress

(or partially suppress) the signs and symptoms of the syndrome and, thereby, may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

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

## **5.6 Metabolic Changes**

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

### **Hyperglycemia/Diabetes Mellitus**

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. There have been reports of hyperglycemia in patients treated with ABILIFY [see [ADVERSE REACTIONS \(6.1, 6.2\)](#)]. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of hyperglycemia-related adverse reactions in patients treated with the atypical antipsychotics. Because ABILIFY was not marketed at the time these studies were performed, it is not known if ABILIFY is associated with this increased risk. Precise risk estimates for hyperglycemia-related adverse reactions in patients treated with atypical antipsychotics are not available.

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

## Adults

In an analysis of 13 placebo-controlled monotherapy trials in adults, primarily with schizophrenia or bipolar disorder, the mean change in fasting glucose in ABILIFY-treated patients (+4.4 mg/dL; median exposure 25 days; N=1057) was not significantly different than in placebo-treated patients (+2.5 mg/dL; median exposure 22 days; N=799). Table 6 shows the proportion of ABILIFY-treated patients with normal and borderline fasting glucose at baseline (median exposure 25 days) that had treatment-emergent high fasting glucose measurements compared to placebo-treated patients (median exposure 22 days).

**Table 6: Changes in Fasting Glucose From Placebo-Controlled Monotherapy Trials in Adult Patients**

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

At 24 weeks, the mean change in fasting glucose in ABILIFY-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 ABILIFY-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 7 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 7: Changes in Fasting Glucose From Placebo-Controlled Adjunctive Trials in Adult Patients with Major Depressive Disorder**

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

### Pediatric Patients and Adolescents

In an analysis of two placebo-controlled trials in adolescents with schizophrenia (13 to 17 years) and pediatric patients with bipolar disorder (10 to 17 years), the mean change in fasting glucose in ABILIFY-treated patients (+4.8 mg/dL; with a median exposure of 43 days; N=259) was not significantly different than in placebo-treated patients (+1.7 mg/dL; with a median exposure of 42 days; N=123).

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

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

Table 8 shows the proportion of patients with changes in fasting glucose levels from the pooled adolescent schizophrenia and pediatric bipolar patients (median exposure of 42-43 days), from two placebo-controlled trials in pediatric patients (6 to 17 years) with irritability associated with autistic disorder (median exposure of 56 days), and from the two placebo-controlled trials in pediatric patients (6 to 18 year) with Tourette’s Disorder (median exposure 57 days).

**Table 8: Changes in Fasting Glucose From Placebo-Controlled Trials in Pediatric and Adolescent Patients**

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

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

### Dyslipidemia

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

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

### Adults

Table 9 shows the proportion of adult patients, primarily from pooled schizophrenia and 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 9: Changes in Blood Lipid Parameters From Placebo-Controlled Monotherapy Trials in Adults**

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

In monotherapy trials in adults, the proportion of patients at 12 weeks and 24 weeks with changes from Normal to High in total cholesterol (fasting/nonfasting), fasting triglycerides, and fasting LDL cholesterol were similar between ABILIFY- 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 10 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 10: Changes in Blood Lipid Parameters From Placebo-Controlled Adjunctive Trials in Adult Patients with Major Depressive Disorder**

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

### Pediatric Patients and Adolescents

Table 11 shows the proportion of adolescents with schizophrenia (13 to 17 years) and pediatric patients with bipolar disorder (10 to 17 years) with changes in total cholesterol and HDL cholesterol (pooled from two placebo-controlled trials; median exposure 42 to 43 days) and fasting triglycerides (pooled from two placebo-controlled trials; median exposure 42 to 44 days).

**Table 11: Changes in Blood Lipid Parameters From Placebo-Controlled Monotherapy Trials in Pediatric and Adolescent Patients in Schizophrenia and Bipolar Disorder**

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

In monotherapy trials of adolescents with schizophrenia and pediatric patients with bipolar disorder, 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 ABILIFY- and placebo-treated patients: at 12 weeks, Total Cholesterol (fasting/nonfasting), 0/57 (0%) vs. 0/15 (0%); Fasting Triglycerides, 2/72 (2.8%) vs. 1/14 (7.1%),

respectively; and at 24 weeks, Total Cholesterol (fasting/nonfasting), 0/36 (0%) vs. 0/12 (0%); Fasting Triglycerides, 1/47 (2.1%) vs. 1/10 (10.0%), respectively.

Table 12 shows the proportion of patients with changes in total cholesterol (fasting/nonfasting) and fasting triglycerides (median exposure 56 days) and HDL cholesterol (median exposure 55 to 56 days) from two placebo-controlled trials in pediatric patients (6 to 17 years) with irritability associated with autistic disorder.

**Table 12: Changes in Blood Lipid Parameters From Placebo-Controlled Trials in Pediatric Patients with Autistic Disorder**

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

Table 13 shows the proportion of patients with changes in total cholesterol (fasting/nonfasting) and fasting triglycerides (median exposure 57 days) and HDL cholesterol (median exposure 57 days) from two placebo-controlled trials in pediatric patients (6 to 18 years) with Tourette's Disorder.

**Table 13: Changes in Blood Lipid Parameters From Placebo-Controlled Trials in Pediatric Patients with Tourette's Disorder**

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

## Weight Gain

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

### Adults

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

In the trials adding ABILIFY to antidepressants, patients first received 8 weeks of antidepressant treatment followed by 6 weeks of adjunctive ABILIFY or placebo in addition to their ongoing antidepressant treatment. The mean change in body weight in patients receiving adjunctive ABILIFY was +1.7 kg (N=347) compared to +0.4 kg (N=330) in patients receiving adjunctive placebo.

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

**Table 14: Percentage of Patients From Placebo-Controlled Trials in Adult Patients with Weight Gain  $\geq 7\%$  of Body Weight**

Weight gain $\geq 7\%$ of body weight	Indication	Treatment Arm	N	Patients n (%)
	Schizophrenia <sup>a</sup>	ABILIFY	852	69 (8.1)
		Placebo	379	12 (3.2)
	Bipolar Mania <sup>b</sup>	ABILIFY	719	16 (2.2)
		Placebo	598	16 (2.7)
	Major Depressive Disorder (Adjunctive Therapy) <sup>c</sup>	ABILIFY	347	18 (5.2)
		Placebo	330	2 (0.6)

<sup>a</sup> 4-6 weeks duration. <sup>b</sup> 3 weeks duration. <sup>c</sup> 6 weeks duration.

### Pediatric Patients and Adolescents

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

body weight in ABILIFY-treated patients was +5.8 kg (n=62) compared to +1.4 kg (n=13) in placebo-treated patients.

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

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

Table 15 shows the percentage of pediatric and adolescent patients with weight gain  $\geq 7\%$  of body weight by indication.

**Table 15: Percentage of Patients From Placebo-Controlled Monotherapy Trials in Pediatric and Adolescent Patients with Weight Gain  $\geq 7\%$  of Body Weight**

	Indication	Treatment Arm	N	Patients n (%)
<b>Weight gain <math>\geq 7\%</math> of body weight</b>	Pooled Schizophrenia and Bipolar Mania <sup>a</sup>	ABILIFY	381	20 (5.2)
		Placebo	187	3 (1.6)
	Irritability Associated with Autistic Disorder <sup>b</sup>	ABILIFY	209	55 (26.3)
		Placebo	98	7 (7.1)
	Tourette's Disorder <sup>c</sup>	ABILIFY	105	21 (20.0)
		Placebo	66	5 (7.6)

<sup>a</sup> 4-6 weeks duration. <sup>b</sup> 8 weeks duration. <sup>c</sup> 8-10 weeks duration.

In an open-label trial that enrolled patients from the two placebo-controlled trials of adolescents with schizophrenia (13 to 17 years) and pediatric patients with bipolar disorder (10 to 17 years), 73.2% of patients (238/325) completed 26 weeks of therapy with ABILIFY. After 26 weeks, 32.8% of patients gained  $\geq 7\%$  of their body weight, not adjusted for normal growth. To adjust for normal growth, z-scores were derived (measured in standard deviations [SD]), which normalize for the natural growth of pediatric patients and adolescents by comparisons to age- and gender-matched population standards. A z-score change  $< 0.5$  SD is considered not clinically significant. After 26 weeks, the mean change in z-score was 0.09 SD.

In an open-label trial that enrolled patients from two short-term, placebo-controlled trials, patients (6 to 17 years) with irritability associated with autistic disorder, as well as *de novo* patients, 60.3% (199/330) completed one year of

therapy with ABILIFY. The mean change in weight z-score was 0.26 SDs for patients receiving >9 months of treatment.

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

## **5.7 Pathological Gambling and Other Compulsive Behaviors**

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

## **5.8 Orthostatic Hypotension**

ABILIFY may cause orthostatic hypotension, perhaps due to its  $\alpha_1$ -adrenergic receptor antagonism. The incidence of orthostatic hypotension-associated events from short-term, placebo-controlled trials of adult patients on oral ABILIFY (n=2467) included (ABILIFY incidence, placebo incidence) orthostatic hypotension (1%, 0.3%), postural dizziness (0.5%, 0.3%), and syncope (0.5%, 0.4%); of pediatric patients 6 to 18 years of age (n=732) on oral ABILIFY included orthostatic hypotension (0.5%, 0%), postural dizziness (0.4%, 0%), and syncope (0.2%, 0%); and of patients on ABILIFY Injection (n=501) included orthostatic hypotension (0.6%, 0%), postural dizziness (0.2%, 0.5%), and syncope (0.4%, 0%). [see [ADVERSE REACTIONS \(6.1\)](#)]

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

ABILIFY-treated patients aged 6 to 18 years (0.4%, 1%), or in ABILIFY injection-treated patients (3%, 2%).

ABILIFY 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 \(7.1\)](#)].

If parenteral benzodiazepine therapy is deemed necessary in addition to ABILIFY injection treatment, patients should be monitored for excessive sedation and for orthostatic hypotension [see [DRUG INTERACTIONS \(7.1\)](#)].

## **5.9 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 ABILIFY. 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 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 in patients with severe neutropenia (absolute neutrophil count <1000/mm<sup>3</sup>) and follow their WBC counts until recovery.

## **5.10 Seizures/Convulsions**

In short-term, placebo-controlled trials, patients with a history of seizures excluded seizures/convulsions occurred in 0.1% (3/2467) of undiagnosed adult patients treated with oral ABILIFY, in 0.1% (1/732) of pediatric patients (6 to 18 years), and in 0.2% (1/501) of adult ABILIFY injection-treated patients.

As with other antipsychotic drugs, ABILIFY 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.

## 5.11 Potential for Cognitive and Motor Impairment

ABILIFY, like other antipsychotics, may have the potential to impair judgment, thinking, or motor skills. For example, in short-term, placebo-controlled trials, somnolence (including sedation) was reported as follows (ABILIFY incidence, placebo incidence): in adult patients (n=2467) treated with oral ABILIFY (11%, 6%), in pediatric patients ages 6 to 17 (n=611) (24%, 6%), and in adult patients (n=501) on ABILIFY Injection (9%, 6%). Somnolence (including sedation) led to discontinuation in 0.3% (8/2467) of adult patients and 3% (20/732) of pediatric patients (6 to 18 years) on oral ABILIFY in short-term, placebo-controlled trials, but did not lead to discontinuation of any adult patients on ABILIFY Injection.

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

## 5.12 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 for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, (e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration) [*see* [ADVERSE REACTIONS \(6.2\)](#)].

## 5.13 Suicide

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

## 5.14 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use, including ABILIFY. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. ABILIFY and other antipsychotic drugs should be used

cautiously in patients at risk for aspiration pneumonia [see [WARNINGS AND PRECAUTIONS \(5.1\)](#) and [ADVERSE REACTIONS \(6.2\)](#)].

## 6 ADVERSE REACTIONS

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

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

- Increased Mortality in Elderly Patients with Dementia-Related Psychosis [see [BOXED WARNING](#) and [WARNINGS AND PRECAUTIONS \(5.1\)](#)]
- Cerebrovascular Adverse Events, Including Stroke [see [WARNINGS AND PRECAUTIONS \(5.2\)](#)]
- Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults [see [BOXED WARNING](#) and [WARNINGS AND PRECAUTIONS \(5.3\)](#)]
- Neuroleptic Malignant Syndrome (NMS) [see [WARNINGS AND PRECAUTIONS \(5.4\)](#)]
- Tardive Dyskinesia [see [WARNINGS AND PRECAUTIONS \(5.5\)](#)]
- Metabolic Changes [see [WARNINGS AND PRECAUTIONS \(5.6\)](#)]
- *Pathological Gambling and Other Compulsive Behaviors* [see [WARNINGS AND PRECAUTIONS \(5.7\)](#)]
- Orthostatic Hypotension [see [WARNINGS AND PRECAUTIONS \(5.8\)](#)]
- Leukopenia, Neutropenia, and Agranulocytosis [see [WARNINGS AND PRECAUTIONS \(5.9\)](#)]
- Seizures/Convulsions [see [WARNINGS AND PRECAUTIONS \(5.10\)](#)]
- Potential for Cognitive and Motor Impairment [see [WARNINGS AND PRECAUTIONS \(5.11\)](#)]
- Body Temperature Regulation [see [WARNINGS AND PRECAUTIONS \(5.12\)](#)]
- Suicide [see [WARNINGS AND PRECAUTIONS \(5.13\)](#)]

- Dysphagia [*see* [WARNINGS AND PRECAUTIONS \(5.14\)](#)]

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

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

ABILIFY has been evaluated for safety in 13,543 adult patients who participated in multiple-dose, clinical trials in schizophrenia, bipolar disorder, major depressive disorder, Dementia of the Alzheimer's type, Parkinson's disease, and alcoholism, and who had approximately 7619 patient-years of exposure to oral ABILIFY and 749 patients with exposure to ABILIFY injection. A total of 3390 patients were treated with oral ABILIFY for at least 180 days and 1933 patients treated with oral ABILIFY had at least 1 year of exposure.

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

The conditions and duration of treatment with ABILIFY (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.

## **6.1 Clinical Trials Experience**

### **Adult Patients with Schizophrenia**

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

#### *Commonly Observed Adverse Reactions*

The only commonly observed adverse reaction associated with the use of ABILIFY in patients with schizophrenia (incidence of 5% or greater and

ABILIFY incidence at least twice that for placebo) was akathisia (ABILIFY 8%; placebo 4%).

## **Adult Patients with Bipolar Mania**

### ***Monotherapy***

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

#### ***Commonly Observed Adverse Reactions***

Commonly observed adverse reactions associated with the use of ABILIFY in patients with bipolar mania (incidence of 5% or greater and ABILIFY incidence at least twice that for placebo) are shown in Table 16.

**Table 16: Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials of Adult Patients with Bipolar Mania Treated with Oral ABILIFY Monotherapy**

<b>Preferred Term</b>	<b>Percentage of Patients Reporting Reaction</b>	
	<b>ABILIFY (n=917)</b>	<b>Placebo (n=753)</b>
Akathisia	13	4
Sedation	8	3
Restlessness	6	3
Tremor	6	3
Extrapyramidal Disorder	5	2

### **Less Common Adverse Reactions in Adults**

Table 17 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 ABILIFY (doses  $\geq 2$  mg/day) and for which the incidence in patients treated with ABILIFY was greater than the incidence in patients treated with placebo in the combined dataset.

**Table 17: Adverse Reactions in Short-Term, Placebo-Controlled Trials in Adult Patients Treated with Oral ABILIFY**

<b>System Organ Class Preferred Term</b>	<b>Percentage of Patients Reporting Reaction<sup>a</sup></b>	
	<b>ABILIFY (n=1843)</b>	<b>Placebo (n=1166)</b>
Eye Disorders		

Blurred Vision	3	1
<b>Gastrointestinal Disorders</b>		
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
<b>General Disorders and Administration Site Conditions</b>		
Fatigue	6	4
Pain	3	2
<b>Musculoskeletal and Connective Tissue Disorders</b>		
Musculoskeletal Stiffness	4	3
Pain in Extremity	4	2
Myalgia	2	1
Muscle Spasms	2	1
<b>Nervous System Disorders</b>		
Headache	27	23
Dizziness	10	7
Akathisia	10	4
Sedation	7	4
Extrapyramidal Disorder	5	3
Tremor	5	3
Somnolence	5	3
<b>Psychiatric Disorders</b>		
Agitation	19	17
Insomnia	18	13
Anxiety	17	13
Restlessness	5	3
<b>Respiratory, Thoracic, and Mediastinal Disorders</b>		
Pharyngolaryngeal Pain	3	2
Cough	3	2

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<sup>a</sup> Adverse reactions reported by at least 2% of patients treated with oral ABILIFY, except adverse reactions which had an incidence equal to or less than placebo.

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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 ABILIFY was administered at doses of 15 or 30 mg/day as adjunctive therapy with lithium or valproate.

#### *Adverse Reactions Associated with Discontinuation of Treatment*

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 ABILIFY compared to 6% for patients treated with adjunctive placebo. The most common adverse drug reactions associated with discontinuation in the adjunctive ABILIFY-treated compared to placebo-treated patients were akathisia (5% and 1%, respectively) and tremor (2% and 1%, respectively).

#### *Commonly Observed Adverse Reactions*

The commonly observed adverse reactions associated with adjunctive ABILIFY 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.

#### **Less Common Adverse Reactions in Adult Patients with Adjunctive Therapy in Bipolar Mania**

Table 18 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 ABILIFY (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 18: Adverse Reactions in a Short-Term, Placebo-Controlled Trial of Adjunctive Therapy in Patients with Bipolar Disorder**

System Organ Class Preferred Term	Percentage of Patients Reporting Reaction <sup>a</sup>	
	ABILIFY + Li or Val* (n=253)	Placebo + Li or Val* (n=130)
<b>Gastrointestinal Disorders</b>		
Nausea	8	5
Vomiting	4	0
Salivary Hypersecretion	4	2
Dry Mouth	2	1
<b>Infections and Infestations</b>		
Nasopharyngitis	3	2
<b>Investigations</b>		
Weight Increased	2	1
<b>Nervous System Disorders</b>		
Akathisia	19	5
Tremor	9	6
Extrapyramidal Disorder	5	1
Dizziness	4	1

Sedation	4	2
<b>Psychiatric Disorders</b>		
Insomnia	8	4
Anxiety	4	1
Restlessness	2	1
<sup>a</sup> Adverse reactions reported by at least 2% of patients treated with oral ABILIFY, except adverse reactions which had an incidence equal to or less than placebo.		
* Lithium or Valproate		

### **Pediatric Patients (13 to 17 years) with Schizophrenia**

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

#### *Adverse Reactions Associated with Discontinuation of Treatment*

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

#### *Commonly Observed Adverse Reactions*

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

### **Pediatric Patients (10 to 17 years) with Bipolar Mania**

The following findings are based on one 4-week, placebo-controlled trial in which oral ABILIFY was administered in doses of 10 or 30 mg/day.

#### *Adverse Reactions Associated with Discontinuation of Treatment*

The incidence of discontinuation due to adverse reactions between ABILIFY-treated and placebo-treated pediatric patients (10 to 17 years) was 7% and 2%, respectively.

#### *Commonly Observed Adverse Reactions*

Commonly observed adverse reactions associated with the use of ABILIFY in pediatric patients with bipolar mania (incidence of 5% or greater and ABILIFY incidence at least twice that for placebo) are shown in Table 19.

**Table 19:** Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials of Pediatric Patients (10 to 17 years) with Bipolar Mania Treated with Oral ABILIFY

Preferred Term	Percentage of Patients Reporting Reaction	
	ABILIFY (n=197)	Placebo (n=97)
Somnolence	23	3
Extrapyramidal Disorder	20	3
Fatigue	11	4
Nausea	11	4
Akathisia	10	2
Blurred Vision	8	0
Salivary Hypersecretion	6	0
Dizziness	5	1

### **Pediatric Patients (6 to 17 years) with Autistic Disorder**

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

#### *Adverse Reactions Associated with Discontinuation of Treatment*

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

#### *Commonly Observed Adverse Reactions*

Commonly observed adverse reactions associated with the use of ABILIFY in pediatric patients with autistic disorder (incidence of 5% or greater and ABILIFY incidence at least twice that for placebo) are shown in Table 20.

**Table 20:** Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials of Pediatric Patients (6 to 17 years) with Autistic Disorder Treated with Oral ABILIFY

Preferred Term	Percentage of Patients Reporting Reaction	
	ABILIFY (n=212)	Placebo (n=101)
Sedation	21	4
Fatigue	17	2
Vomiting	14	7
Somnolence	10	4
Tremor	10	0
Pyrexia	9	1

Drooling	9	0
Decreased Appetite	7	2
Salivary Hypersecretion	6	1
Extrapyramidal Disorder	6	0
Lethargy	5	0

### **Pediatric Patients (6 to 18 years) with Tourette's Disorder**

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

#### *Adverse Reactions Associated with Discontinuation of Treatment*

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

#### *Commonly Observed Adverse Reactions*

Commonly observed adverse reactions associated with the use of ABILIFY in pediatric patients with Tourette's disorder (incidence of 5% or greater and ABILIFY incidence at least twice that for placebo) are shown in Table 21.

**Table 21: Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials of Pediatric Patients (6 to 18 years) with Tourette's Disorder Treated with Oral ABILIFY**

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

### **Less Common Adverse Reactions in Pediatric Patients (6 to 18 years) with Schizophrenia, Bipolar Mania, Autistic Disorder, or Tourette's Disorder**

Table 22 enumerates the pooled incidence, rounded to the nearest percent, of adverse reactions that occurred during acute therapy (up to 6 weeks in schizophrenia, up to 4 weeks in bipolar mania, up to 8 weeks in autistic disorder, and up to 10 weeks in Tourette's disorder), including only those

reactions that occurred in 2% or more of pediatric patients treated with ABILIFY (doses  $\geq 2$  mg/day) and for which the incidence in patients treated with ABILIFY was greater than the incidence in patients treated with placebo.

**Table 22: Adverse Reactions in Short-Term, Placebo-Controlled Trials of Pediatric Patients (6 to 18 years) Treated with Oral ABILIFY**

System Organ Class Preferred Term	Percentage of Patients Reporting Reaction <sup>a</sup>	
	ABILIFY (n=732)	Placebo (n=370)
<b>Eye Disorders</b>		
Blurred Vision	3	0
<b>Gastrointestinal Disorders</b>		
Abdominal Discomfort	2	1
Vomiting	8	7
Nausea	8	4
Diarrhea	4	3
Salivary Hypersecretion	4	1
Abdominal Pain Upper	3	2
Constipation	2	2
<b>General Disorders and Administration Site Conditions</b>		
Fatigue	10	2
Pyrexia	4	1
Irritability	2	1
Asthenia	2	1
<b>Infections and Infestations</b>		
Nasopharyngitis	6	3
<b>Investigations</b>		
Weight Increased	3	1
<b>Metabolism and Nutrition Disorders</b>		
Increased Appetite	7	3
Decreased Appetite	5	4
<b>Musculoskeletal and Connective Tissue Disorders</b>		
Musculoskeletal Stiffness	2	1
Muscle Rigidity	2	1
<b>Nervous System Disorders</b>		
Somnolence	16	4
Headache	12	10
Sedation	9	2
Tremor	9	1
Extrapyramidal Disorder	6	1
Akathisia	6	4
Drooling	3	0
Lethargy	3	0
Dizziness	3	2
Dystonia	2	1
<b>Respiratory, Thoracic, and Mediastinal Disorders</b>		

Epistaxis	2	1
<b>Skin and Subcutaneous Tissue Disorders</b>		
Rash	2	1
<sup>a</sup> Adverse reactions reported by at least 2% of pediatric patients treated with oral ABILIFY, except adverse reactions which had an incidence equal to or less than placebo.		

## Adult Patients Receiving ABILIFY 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 ABILIFY was administered at doses of 2 mg to 20 mg as adjunctive treatment to continued antidepressant therapy.

### *Adverse Reactions Associated with Discontinuation of Treatment*

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

### *Commonly Observed Adverse Reactions*

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

### *Less Common Adverse Reactions in Adult Patients with Major Depressive Disorder*

Table 23 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 ABILIFY (doses  $\geq 2$  mg/day) and for which the incidence in patients treated with adjunctive ABILIFY was greater than the incidence in patients treated with adjunctive placebo in the combined dataset.

**Table 23: Adverse Reactions in Short-Term, Placebo-Controlled Adjunctive Trials in Patients with Major Depressive Disorder**

System Organ Class Preferred Term	Percentage of Patients Reporting Reaction <sup>a</sup>	
	ABILIFY + ADT* (n=371)	Placebo + ADT* (n=366)
<b>Eye Disorders</b>		
Blurred Vision	6	1
<b>Gastrointestinal Disorders</b>		

Constipation	5	2
<b>General Disorders and Administration Site Conditions</b>		
Fatigue	8	4
Feeling Jittery	3	1
<b>Infections and Infestations</b>		
Upper Respiratory Tract Infection	6	4
<b>Investigations</b>		
Weight Increased	3	2
<b>Metabolism and Nutrition Disorders</b>		
Increased Appetite	3	2
<b>Musculoskeletal and Connective Tissue Disorders</b>		
Arthralgia	4	3
Myalgia	3	1
<b>Nervous System Disorders</b>		
Akathisia	25	4
Somnolence	6	4
Tremor	5	4
Sedation	4	2
Dizziness	4	2
Disturbance in Attention	3	1
Extrapyramidal Disorder	2	0
<b>Psychiatric Disorders</b>		
Restlessness	12	2
Insomnia	8	2
<sup>a</sup> Adverse reactions reported by at least 2% of patients treated with adjunctive ABILIFY, except adverse reactions which had an incidence equal to or less than placebo.		
* Antidepressant Therapy		

### **Patients with Agitation Associated with Schizophrenia or Bipolar Mania (Intramuscular Injection)**

The following findings are based on a pool of three placebo-controlled trials of patients with agitation associated with schizophrenia or bipolar mania in which ABILIFY injection was administered at doses of 5.25 mg to 15 mg.

#### *Commonly Observed Adverse Reactions*

There was one commonly observed adverse reaction (nausea) associated with the use of ABILIFY injection in patients with agitation associated with schizophrenia and bipolar mania (incidence of 5% or greater and ABILIFY incidence at least twice that for placebo).

#### *Less Common Adverse Reactions in Patients with Agitation Associated with Schizophrenia or Bipolar Mania*

Table 24 enumerates the pooled incidence, rounded to the nearest percent, of adverse reactions that occurred during acute therapy (24-hour), including only

those adverse reactions that occurred in 2% or more of patients treated with ABILIFY injection (doses  $\geq 5.25$  mg/day) and for which the incidence in patients treated with ABILIFY injection was greater than the incidence in patients treated with placebo in the combined dataset.

**Table 24: Adverse Reactions in Short-Term, Placebo-Controlled Trials in Patients Treated with ABILIFY Injection**

System Organ Class Preferred Term	Percentage of Patients Reporting Reaction <sup>a</sup>	
	ABILIFY (n=501)	Placebo (n=220)
<b>Cardiac Disorders</b>		
Tachycardia	2	<1
<b>Gastrointestinal Disorders</b>		
Nausea	9	3
Vomiting	3	1
<b>General Disorders and Administration Site Conditions</b>		
Fatigue	2	1
<b>Nervous System Disorders</b>		
Headache	12	7
Dizziness	8	5
Somnolence	7	4
Sedation	3	2
Akathisia	2	0

<sup>a</sup> Adverse reactions reported by at least 2% of patients treated with ABILIFY injection, except adverse reactions which had an incidence equal to or less than placebo.

## Dose-Related Adverse Reactions

### ***Schizophrenia***

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

In the study of pediatric patients (13 to 17 years of age) with schizophrenia, three common adverse reactions appeared to have a possible dose response relationship: extrapyramidal disorder (incidences were placebo, 5.0%; 10 mg, 13.0%; 30 mg, 21.6%); somnolence (incidences were placebo, 6.0%; 10 mg, 11.0%; 30 mg, 21.6%); and tremor (incidences were placebo, 2.0%; 10 mg, 2.0%; 30 mg, 11.8%).

### ***Bipolar Mania***

In the study of pediatric patients (10 to 17 years of age) with bipolar mania, four common adverse reactions had a possible dose response relationship at 4 weeks; extrapyramidal disorder (incidences were placebo, 3.1%; 10 mg, 12.2%; 30 mg, 27.3%); somnolence (incidences were placebo, 3.1%; 10 mg, 19.4%; 30 mg, 26.3%); akathisia (incidences were placebo, 2.1%; 10 mg, 8.2%; 30 mg, 11.1%); and salivary hypersecretion (incidences were placebo, 0%; 10 mg, 3.1%; 30 mg, 8.1%).

### ***Autistic Disorder***

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

### ***Tourette's Disorder***

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

## **Extrapyramidal Symptoms**

### ***Schizophrenia***

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

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

Similarly, in a long-term (26-week), placebo-controlled trial of schizophrenia in adults, objectively collected data on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia), and the Assessments of Involuntary Movement Scales (for dyskinesias) did not show a difference between ABILIFY 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 ABILIFY-treated patients was 16% vs. 8% for placebo and the incidence of akathisia-related events for monotherapy ABILIFY-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 ABILIFY-treated patients was 15% vs. 8% for adjunctive placebo and the incidence of akathisia-related events for adjunctive ABILIFY-treated patients was 19% vs. 5% for adjunctive placebo. In the short-term, placebo-controlled trial in bipolar mania in pediatric (10 to 17 years) patients, the incidence of reported EPS-related events, excluding events related to akathisia, for ABILIFY-treated patients was 26% vs. 5% for placebo and the incidence of akathisia-related events for ABILIFY-treated patients was 10% vs. 2% for placebo.

In the adult bipolar mania trials with monotherapy ABILIFY, the Simpson Angus Rating Scale and the Barnes Akathisia Scale showed a significant difference between ABILIFY and placebo (ABILIFY, 0.50; placebo, -0.01 and ABILIFY, 0.21; placebo, -0.05). Changes in the Assessments of Involuntary Movement Scales were similar for the ABILIFY and placebo groups. In the bipolar mania trials with ABILIFY as adjunctive therapy with either lithium or valproate, the Simpson Angus Rating Scale and the Barnes Akathisia Scale showed a significant difference between adjunctive ABILIFY and adjunctive placebo (ABILIFY, 0.73; placebo, 0.07 and ABILIFY, 0.30; placebo, 0.11). Changes in the Assessments of Involuntary Movement Scales were similar for adjunctive ABILIFY and adjunctive placebo. In the pediatric (10 to 17 years), short-term, bipolar mania trial, the Simpson Angus Rating Scale showed a significant difference between ABILIFY and placebo (ABILIFY, 0.90; placebo, -0.05). Changes in the Barnes Akathisia Scale and the Assessments of Involuntary Movement Scales were similar for the ABILIFY and placebo groups.

### ***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 ABILIFY-treated patients was 8% vs. 5% for adjunctive placebo-treated patients; and the incidence of akathisia-related events for adjunctive ABILIFY-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 ABILIFY and adjunctive placebo (ABILIFY, 0.31; placebo, 0.03 and ABILIFY, 0.22; placebo, 0.02). Changes in the Assessments of Involuntary Movement Scales were similar for the adjunctive ABILIFY and adjunctive placebo groups.

### ***Autistic Disorder***

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

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

### ***Tourette's Disorder***

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

In the pediatric (6 to 18 years) short-term Tourette's disorder trials, changes in the Simpson Angus Rating Scale, Barnes Akathisia Scale and Assessments of Involuntary Movement Scale were not clinically meaningfully different for ABILIFY and placebo.

### ***Agitation Associated with Schizophrenia or Bipolar Mania***

In the placebo-controlled trials in patients with agitation associated with schizophrenia or bipolar mania, the incidence of reported EPS-related events excluding events related to akathisia for ABILIFY-treated patients was 2% vs. 2% for placebo and the incidence of akathisia-related events for ABILIFY-treated patients was 2% vs. 0% for placebo. Objectively collected data on the Simpson Angus Rating Scale (for EPS) and the Barnes Akathisia Scale (for akathisia) for all treatment groups did not show a difference between ABILIFY and placebo.

### **Dystonia**

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

### **Additional Findings Observed in Clinical Trials**

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

The adverse reactions reported in a 26-week, double-blind trial comparing oral ABILIFY 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 ABILIFY 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  $\leq$ 49 days), and were of limited duration (7/12  $\leq$ 10 days). Tremor infrequently led to discontinuation (<1%) of ABILIFY. In addition, in a long-term (52 week), active-controlled study, the incidence of tremor was 5% (40/859) for ABILIFY. 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 the Premarketing Evaluation of ABILIFY**

The following listing does not include reactions: 1) already listed in previous tables or elsewhere in labeling, 2) for which a drug cause was remote, 3) which

were so general as to be uninformative, 4) which were not considered to have significant clinical implications, or 5) which occurred at a rate equal to or less than placebo.

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

### ***Adults - Oral Administration***

#### *Blood and Lymphatic System Disorders:*

*rare* - thrombocytopenia

#### *Cardiac Disorders:*

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

#### *Eye Disorders:*

*infrequent* – photophobia; *rare* - diplopia

#### *Gastrointestinal Disorders:*

*infrequent* - gastroesophageal reflux disease

#### *General Disorders and Administration Site Conditions:*

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

#### *Hepatobiliary Disorders:*

*rare* - hepatitis, jaundice

#### *Immune System Disorders:*

*rare* - hypersensitivity

#### *Injury, Poisoning, and Procedural Complications:*

*infrequent* – fall; *rare* – heat stroke

#### *Investigations:*

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

*Metabolism and Nutrition Disorders:*

*frequent* – anorexia; *infrequent* - *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, myoclonus, bradykinesia; *rare* – akinesia, myoclonus, coordination abnormal, speech disorder, Grand Mal convulsion; <1/10,000 patients - choreoathetosis

*Psychiatric Disorders:*

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

*Renal and Urinary Disorders:*

*rare* - urinary retention, nocturia

*Reproductive System and Breast Disorders:*

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

*Respiratory, Thoracic, and Mediastinal Disorders:*

*infrequent* - nasal congestion, dyspnea

*Skin and Subcutaneous Tissue Disorders:*

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

*Vascular Disorders:*

*infrequent* – hypotension, hypertension

### ***Pediatric Patients - Oral Administration***

Most adverse events observed in the pooled database of 1,686 pediatric patients, aged 6 to 18 years, were also observed in the adult population. Additional adverse reactions observed in the pediatric population are listed below.

#### *Eye Disorders*

*infrequent* - oculogyric crisis

#### *Gastrointestinal Disorders:*

*infrequent* -tongue dry, tongue spasm

#### *Investigations:*

*frequent* - blood insulin increased

#### *Nervous System Disorders:*

*infrequent* - sleep talking

#### *Renal and Urinary Disorders*

*frequent* – enuresis

#### *Skin and Subcutaneous Tissue Disorders:*

*infrequent* - hirsutism

### ***Adults - Intramuscular Injection***

Most adverse reactions observed in the pooled database of 749 adult patients treated with ABILIFY injection, were also observed in the adult population treated with oral ABILIFY. Additional adverse reactions observed in the ABILIFY injection population are listed below.

#### *General Disorders and Administration Site Conditions:*

$\geq 1/100$  patients - injection site reaction;  $\geq 1/1000$  patients and  $< 1/100$  patients - venipuncture site bruise

## **6.2 Postmarketing Experience**

The following adverse reactions have been identified during post-approval use of ABILIFY. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to establish a causal relationship to

drug exposure: occurrences of allergic reaction (anaphylactic reaction, angioedema, laryngospasm, pruritus/urticaria, or oropharyngeal spasm), pathological gambling, hiccups and blood glucose fluctuation.

## 7 DRUG INTERACTIONS

### 7.1 Drugs Having Clinically Important Interactions with ABILIFY

**Table 25: Clinically Important Drug Interactions with ABILIFY:**

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 ABILIFY with strong CYP 3A4 or CYP2D6 inhibitors increased the exposure of aripiprazole compared to the use of ABILIFY alone [see <a href="#">CLINICAL PHARMACOLOGY (12.3)</a> ].	With concomitant use of ABILIFY with a strong CYP3A4 inhibitor or CYP2D6 inhibitor, reduce the ABILIFY dosage [see <a href="#">DOSAGE AND ADMINISTRATION (2.7)</a> ].
Strong CYP3A4 Inducers (e.g., carbamazepine, rifampin)	The concomitant use of ABILIFY and carbamazepine decreased the exposure of aripiprazole compared to the use of ABILIFY alone [see <a href="#">CLINICAL PHARMACOLOGY (12.3)</a> ].	With concomitant use of ABILIFY with a strong CYP3A4 inducer, consider increasing the ABILIFY dosage [see <a href="#">DOSAGE AND ADMINISTRATION (2.7)</a> ].
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 <a href="#">WARNINGS AND PRECAUTIONS (5.8)</a> ].
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 <a href="#">WARNINGS AND PRECAUTIONS (5.7)</a> ].	Monitor sedation and blood pressure. Adjust dose accordingly.

## 7.2 Drugs Having No Clinically Important Interactions with ABILIFY

Based on pharmacokinetic studies, no dosage adjustment of ABILIFY 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. Additionally, no dosage adjustment is necessary for valproate, lithium, lamotrigine, lorazepam, or sertraline when co-administered with ABILIFY. [see [CLINICAL PHARMACOLOGY \(12.3\)](#)].

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

*Pregnancy Category C*

*Pregnancy Exposure Registry*

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ABILIFY 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) during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms. Adequate and well controlled studies with ABILIFY have not been conducted in pregnant women. Animal reproduction studies were conducted with aripiprazole in rats and rabbits during organogenesis, and in rats during the pre- and post-natal period. Oral and intravenous aripiprazole administration during organogenesis in rats and/or rabbits at doses higher than the maximum recommended human dose (MRHD) produced fetal death, decreased fetal weight, undescended testicles, delayed skeletal ossification, skeletal abnormalities, and diaphragmatic hernia. Oral and intravenous aripiprazole administration during the pre- and post-natal period in rats at doses higher than the maximum recommended human dose (MRHD) produced prolonged

gestation, stillbirths, decreased pup weight, and decreased pup survival. Administer ABILIFY during pregnancy only if the potential benefit justifies the potential risk to the fetus.

### *Clinical Considerations*

#### Fetal/Neonatal Adverse Reactions

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

### Data

#### Animal Data

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

Pregnant rats were treated with oral doses of 3, 10, and 30 mg/kg/day (1, 3, and 10 times the maximum recommended human dose [MRHD] on a mg/m<sup>2</sup> 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  $\text{mg/m}^2$ ) 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  $\text{mg/m}^2$ .

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 a  $\text{mg/m}^2$  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.

## **8.2 Labor and Delivery**

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

## **8.3 Nursing Mothers**

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

## 8.4 Pediatric Use

Safety and effectiveness in pediatric patients with major depressive disorder or agitation associated with schizophrenia or bipolar mania have not been established.

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

### *Schizophrenia*

Safety and effectiveness in pediatric patients with schizophrenia were established in a 6-week, placebo-controlled clinical trial in 202 pediatric patients aged 13 to 17 years [see [DOSAGE AND ADMINISTRATION \(2.1\)](#), [ADVERSE REACTIONS \(6.1\)](#), and [CLINICAL STUDIES \(14.1\)](#)]. Although maintenance efficacy in pediatric patients has not been systematically evaluated, maintenance efficacy can be extrapolated from adult data along with comparisons of aripiprazole pharmacokinetic parameters in adult and pediatric patients.

### *Bipolar I Disorder*

Safety and effectiveness in pediatric patients with bipolar mania were established in a 4-week, placebo-controlled clinical trial in 197 pediatric patients aged 10 to 17 years [see [DOSAGE AND ADMINISTRATION \(2.2\)](#), [ADVERSE REACTIONS \(6.1\)](#), and [CLINICAL STUDIES \(14.2\)](#)]. Although maintenance efficacy in pediatric patients has not been systematically evaluated, maintenance efficacy can be extrapolated from adult data along with comparisons of aripiprazole pharmacokinetic parameters in adult and pediatric patients.

The efficacy of adjunctive ABILIFY with concomitant lithium or valproate in the treatment of manic or mixed episodes in pediatric patients has not been systematically evaluated. However, such efficacy and lack of pharmacokinetic interaction between aripiprazole and lithium or valproate can be extrapolated from adult data, along with comparisons of aripiprazole pharmacokinetic parameters in adult and pediatric patients.

### *Irritability Associated with Autistic Disorder*

Safety and effectiveness in pediatric patients demonstrating irritability associated with autistic disorder were established in two 8-week, placebo-controlled clinical trials in 212 pediatric patients aged 6 to 17 years [see

[INDICATIONS AND USAGE \(1\), DOSAGE AND ADMINISTRATION \(2.4\), ADVERSE REACTIONS \(6.1\), and CLINICAL STUDIES \(14.4\)](#)]. A maintenance trial was conducted in pediatric patients (6 to 17 years of age) with irritability associated with autistic disorder. The first phase of this trial was an open-label, flexibly dosed (aripiprazole 2 to 15 mg/day) phase in which patients were stabilized (defined as > 25% improvement on the ABC-I subscale, and a CGI-I rating of “much improved” or “very much improved”) on ABILIFY for 12 consecutive weeks. Overall, 85 patients were stabilized and entered the second, 16-week, double-blind phase where they were randomized to either continue ABILIFY treatment or switch to placebo. In this trial, the efficacy of ABILIFY for the maintenance treatment of irritability associated with autistic disorder was not established.

#### *Tourette’s Disorder*

Safety and effectiveness of aripiprazole in pediatric patients with Tourette’s Disorder were established in one 8-week (aged 7 to 17) and one 10-week trial (aged 6 to 18) in 194 pediatric patients [see [DOSAGE AND ADMINISTRATION \(2.5\), ADVERSE REACTIONS \(6.1\), and CLINICAL STUDIES \(14.5\)](#)]. Maintenance efficacy in pediatric patients has not been systematically evaluated.

#### **Juvenile Animal Studies**

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

were reversible after a 2-month recovery period, and most of the drug effects in juvenile rats were also observed in adult rats from previously conducted studies.

Aripiprazole in juvenile dogs (2 months old) caused CNS clinical signs of tremors, hypoactivity, ataxia, recumbency and limited use of hind limbs when administered orally for 6 months at 3, 10, 30 mg/kg/day. Mean body weight and weight gain were decreased up to 18% in females in all drug groups relative to control values. A NOAEL could not be determined and, at the lowest tested dose of 3 mg/kg/day, there is no safety margin relative to the systemic exposures (AUC<sub>0-24</sub>) for aripiprazole or its major active metabolite in adolescents at the maximum recommended pediatric dose of 15 mg/day. All drug-related effects were reversible after a 2-month recovery period.

## 8.5 Geriatric Use

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

Of the 13,543 patients treated with oral ABILIFY in clinical trials, 1073 (8%) were  $\geq 65$  years old and 799 (6%) were  $\geq 75$  years old. Placebo-controlled studies of oral ABILIFY in schizophrenia, bipolar mania, or major depressive disorder did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Of the 749 patients treated with ABILIFY injection in clinical trials, 99 (13%) were  $\geq 65$  years old and 78 (10%) were  $\geq 75$  years old. Placebo-controlled studies of ABILIFY injection in patients with agitation associated with schizophrenia or bipolar mania did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

ABILIFY is not approved for the treatment of patients with psychosis associated with Alzheimer's disease [see [BOXED WARNING](#) and [WARNINGS AND PRECAUTIONS \(5.1\)](#)].

## 8.6 CYP2D6 Poor Metabolizers

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

## 8.7 Hepatic and Renal Impairment

No dosage adjustment for ABILIFY 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 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 is not a controlled substance.

## 9.2 Abuse

ABILIFY 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 misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

## 9.3 Dependence

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

# 10 OVERDOSAGE

MedDRA terminology has been used to classify the adverse reactions.

## 10.1 Human Experience

In clinical trials and in postmarketing experience, adverse reactions of deliberate or accidental overdose with oral ABILIFY have been reported worldwide.

These include overdoses with oral ABILIFY alone and in combination with other substances. No fatality was reported with ABILIFY alone. The largest known dose with a known outcome involved acute ingestion of 1260 mg of oral ABILIFY (42 times the maximum recommended daily dose) by a patient who fully recovered. Deliberate or accidental overdosage was also reported in children (age 12 and younger) involving oral ABILIFY ingestions up to 195 mg with no fatalities.

Common adverse reactions (reported in at least 5% of all overdose cases) reported with oral ABILIFY 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 ABILIFY 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. 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.

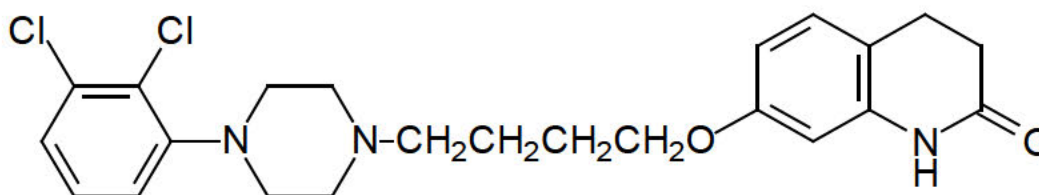
*Charcoal:* In the event of an overdose of ABILIFY, an early charcoal administration may be useful in partially preventing the absorption of aripiprazole. Administration of 50 g of activated charcoal, one hour after a single 15 mg oral dose of ABILIFY, decreased the mean AUC and C<sub>max</sub> of aripiprazole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

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

## **11 DESCRIPTION**

Aripiprazole is a psychotropic drug that is available as ABILIFY<sup>®</sup> (aripiprazole) Tablets, ABILIFY DISC MELT<sup>®</sup> (aripiprazole) Orally Disintegrating Tablets,

ABILIFY® (aripiprazole) Oral Solution, and ABILIFY® (aripiprazole) Injection, a solution for intramuscular injection. Aripiprazole is 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyrl. The empirical formula is C<sub>23</sub>H<sub>27</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>2</sub> and its molecular weight is 448.38. The chemical structure is:



ABILIFY Tablets are available in 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg strengths. Inactive ingredients 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.

ABILIFY DISCMELT Orally Disintegrating Tablets are available in 10 mg and 15 mg strengths. Inactive ingredients include acesulfame potassium, aspartame, calcium silicate, croscarmellose sodium, crospovidone, crème de vanilla (natural and artificial flavors), magnesium stearate, microcrystalline cellulose, silicon dioxide, tartaric acid, and xylitol. Colorants include ferric oxide (yellow or red) and FD&C Blue No. 2 Aluminum Lake.

ABILIFY Oral Solution is a clear, colorless to light-yellow solution available in a concentration of 1 mg/mL. The inactive ingredients for this solution include disodium edetate, fructose, glycerin, dl-lactic acid, methylparaben, propylene glycol, propylparaben, sodium hydroxide, sucrose, and purified water. The oral solution is flavored with natural orange cream and other natural flavors.

ABILIFY Injection is available in single-dose vials as a ready-to-use, 9.75 mg/1.3 mL (7.5 mg/mL) clear, colorless, sterile, aqueous solution for intramuscular use only. Inactive ingredients for this solution include 199.5mg of sulfobutylether β-cyclodextrin (SBECD), 10.4 mg of tartaric acid, qs to pH 4.3 of sodium hydroxide, and qs to 1.33 mL of water for injection.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The mechanism of action of aripiprazole in schizophrenia or bipolar mania, is unknown. However, the efficacy of aripiprazole could be mediated through a

combination of partial agonist activity at D<sub>2</sub> and 5-HT<sub>1A</sub> receptors and antagonist activity at 5-HT<sub>2A</sub> receptors. Actions at receptors other than D<sub>2</sub>, 5-HT<sub>1A</sub>, and 5-HT<sub>2A</sub> may explain some of the other clinical effects of aripiprazole (e.g., the orthostatic hypotension observed with aripiprazole may be explained by its antagonist activity at adrenergic alpha1 receptors).

## 12.2 Pharmacodynamics

Aripiprazole exhibits high affinity for dopamine D<sub>2</sub> and D<sub>3</sub>, serotonin 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptors (K<sub>i</sub> values of 0.34 nM, 0.8 nM, 1.7 nM, and 3.4 nM, respectively), moderate affinity for dopamine D<sub>4</sub>, serotonin 5-HT<sub>2C</sub> and 5-HT<sub>7</sub>, alpha1-adrenergic and histamine H<sub>1</sub> receptors (K<sub>i</sub> values of 44 nM, 15 nM, 39 nM, 57 nM, and 61 nM, respectively), and moderate affinity for the serotonin reuptake site (K<sub>i</sub>=98 nM). Aripiprazole has no appreciable affinity for cholinergic muscarinic receptors (IC<sub>50</sub>>1000 nM). [Aripiprazole functions as a partial agonist at the dopamine D<sub>2</sub> and the serotonin 5-HT<sub>1A</sub> receptors, and as an antagonist at serotonin 5-HT<sub>2A</sub> receptor.]

## 12.3 Pharmacokinetics

ABILIFY 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<sub>2</sub> 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.

Pharmacokinetic studies showed that ABILIFY DISCMELT Orally Disintegrating Tablets are bioequivalent to ABILIFY Tablets.

## ORAL ADMINISTRATION

### Absorption

*Tablet:* Aripiprazole is well absorbed after administration of the tablet, with peak plasma concentrations occurring within 3 hours to 5 hours; the absolute oral bioavailability of the tablet formulation is 87%. ABILIFY can be administered with or without food. Administration of a 15 mg ABILIFY Tablet

with a standard high-fat meal did not significantly affect the C<sub>max</sub> or AUC of aripiprazole or its active metabolite, dehydro-aripiprazole, but delayed T<sub>max</sub> by 3 hours for aripiprazole and 12 hours for dehydro-aripiprazole.

*Oral Solution:* Aripiprazole is well absorbed when administered orally as the solution. At equivalent doses, the plasma concentrations of aripiprazole from the solution were higher than that from the tablet formulation. In a relative bioavailability study comparing the pharmacokinetics of 30 mg aripiprazole as the oral solution to 30 mg aripiprazole tablets in healthy subjects, the solution to tablet ratios of geometric mean C<sub>max</sub> and AUC values were 122% and 114%, respectively [see [DOSAGE AND ADMINISTRATION \(2.6\)](#)]. The single-dose pharmacokinetics of aripiprazole were linear and dose-proportional between the doses of 5 mg to 30 mg.

### **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<sub>2</sub> receptor occupancy indicating brain penetration of aripiprazole in humans.

### **Metabolism and Elimination**

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

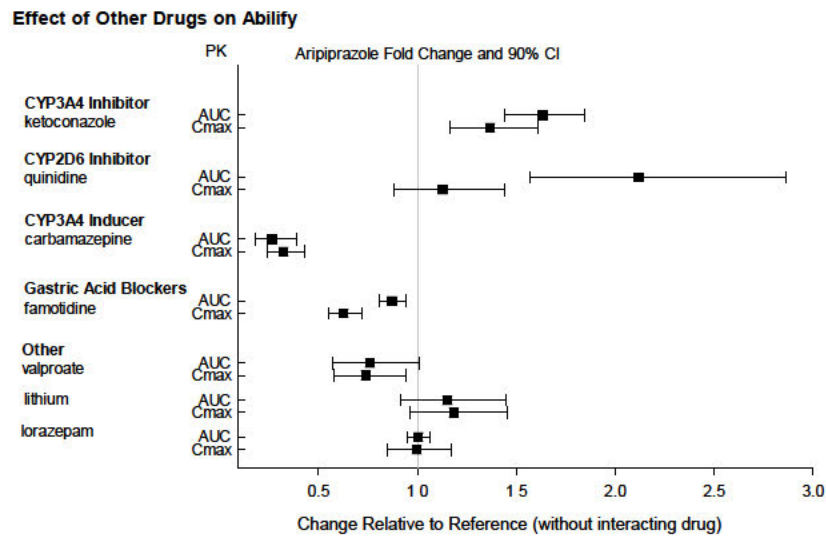
Following a single oral dose of [14C]-labeled aripiprazole, approximately 25% and 55% of the administered radioactivity was recovered in the urine and feces, respectively. Less than 1% of unchanged aripiprazole was excreted in the urine and approximately 18% of the oral dose was recovered unchanged in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

### **Drug Interaction Studies**

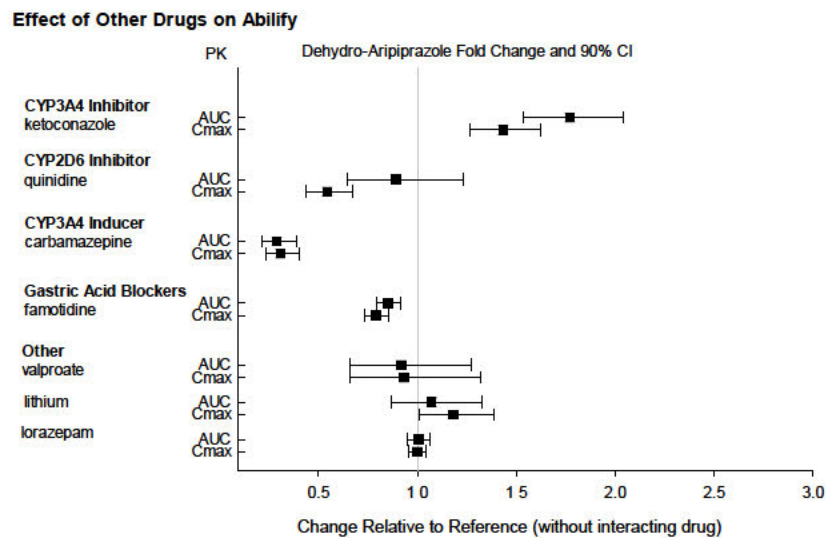
Effects of other drugs on the exposures of aripiprazole and dehydro-aripiprazole are summarized in Figure 1 and Figure 2, respectively. Based on simulation, a 4.5-fold increase in mean C<sub>max</sub> and AUC values at steady-state is expected when extensive metabolizers of CYP2D6 are administered with both strong

CYP2D6 and CYP3A4 inhibitors. A 3-fold increase in mean C<sub>max</sub> and AUC values at steady-state is expected in poor metabolizers of CYP2D6 administered with strong CYP3A4 inhibitors.

**Figure 1: The effects of other drugs on aripiprazole pharmacokinetics**



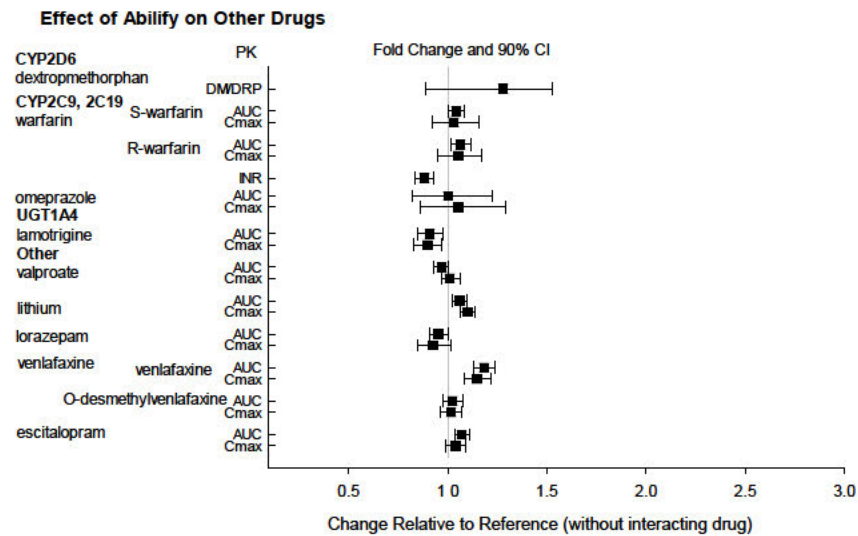
**Figure 2: The effects of other drugs on dehydro-aripiprazole pharmacokinetics**



The effects of ABILIFY 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.

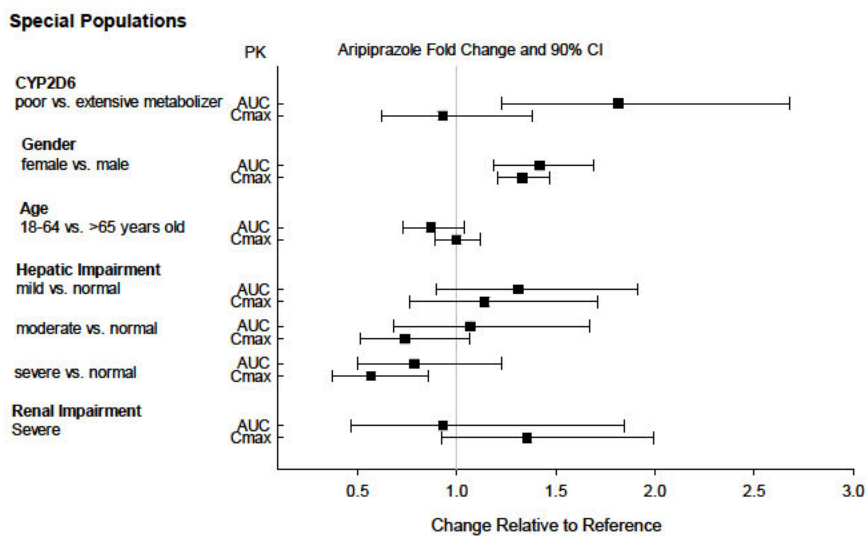
**Figure 3: The effects of ABILIFY on pharmacokinetics of other drugs**



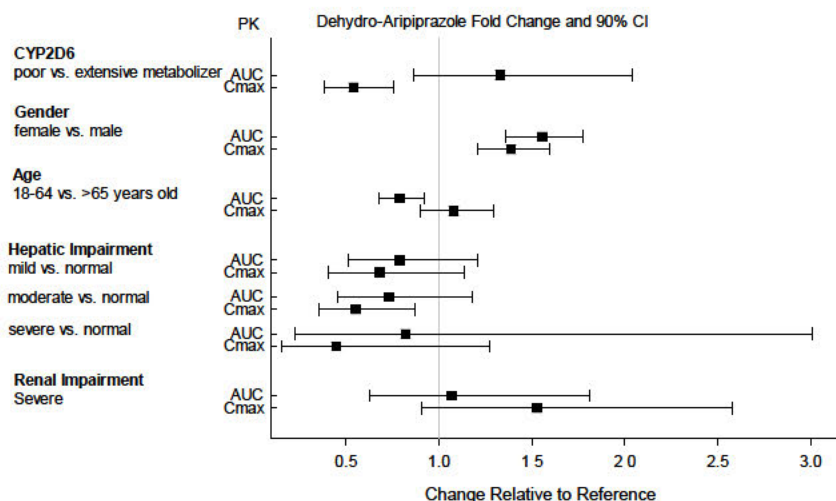
## Studies in Specific Populations

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

**Figure 4: Effects of intrinsic factors on aripiprazole pharmacokinetics**



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



## INTRAMUSCULAR ADMINISTRATION

In two pharmacokinetic studies of aripiprazole injection administered intramuscularly to healthy subjects, the median times to the peak plasma concentrations were at 1 hour and 3 hours. A 5 mg intramuscular injection of aripiprazole had an absolute bioavailability of 100%. The geometric mean maximum concentration achieved after an intramuscular dose was on average 19% higher than the C<sub>max</sub> of the oral tablet. While the systemic exposure over 24 hours was generally similar between aripiprazole injection given intramuscularly and after oral tablet administration, the aripiprazole AUC in the first 2 hours after an intramuscular injection was 90% greater than the AUC after the same dose as a tablet. In stable patients with schizophrenia or schizoaffective disorder, the pharmacokinetics of aripiprazole after intramuscular administration were linear over a dose range of 1 mg to 45 mg. Although the metabolism of aripiprazole injection was not systematically evaluated, the intramuscular route of administration would not be expected to alter the metabolic pathways.

## 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  $\text{mg}/\text{m}^2$ , respectively). In addition, SD rats were dosed orally for 2 years at 10, 20, 40, and 60  $\text{mg}/\text{kg}/\text{day}$  (3 to 19 times the MRHD based on  $\text{mg}/\text{m}^2$ ). 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  $\text{mg}/\text{kg}/\text{day}$  (0.1 to 0.9 times human exposure at MRHD based on AUC and 0.5 to 5 times the MRHD based on  $\text{mg}/\text{m}^2$ ). In female rats, the incidence of mammary gland fibroadenomas was increased at a dietary dose of 10  $\text{mg}/\text{kg}/\text{day}$  (0.1 times human exposure at MRHD based on AUC and 3 times the MRHD based on  $\text{mg}/\text{m}^2$ ); and the incidences of adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas were increased at an oral dose of 60  $\text{mg}/\text{kg}/\text{day}$  (14 times human exposure at MRHD based on AUC and 19 times the MRHD based on  $\text{mg}/\text{m}^2$ ).

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  $\text{mg}/\text{kg}/\text{day}$  (0.6, 2, and 6 times the maximum recommended human dose [MRHD] on a  $\text{mg}/\text{m}^2$  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<sup>2</sup> 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<sup>2</sup> and 7 to 14 times human exposure at MRHD based on AUC. Evaluation of the retinas of albino mice and of monkeys did not reveal evidence of retinal degeneration. Additional studies to further evaluate the mechanism have not been performed. The relevance of this finding to human risk is unknown.

## **14 CLINICAL STUDIES**

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

- Four short-term trials and one maintenance trial in adult patients and one short-term trial in adolescents (ages 13-17) with schizophrenia [*see [CLINICAL STUDIES \(14.1\)](#)*]
- Four short-term monotherapy trials and one 6-week adjunctive trial in adult patients and one short-term monotherapy trial in pediatric patients (ages 10-17) with manic or mixed episodes [*see [CLINICAL STUDIES \(14.2\)](#)*]
- One maintenance monotherapy trial and in one maintenance adjunctive trial in adult patients with bipolar I disorder [*see [CLINICAL STUDIES \(14.2\)](#)*]
- Two short-term trials in adult patients with MDD who had an inadequate response to antidepressant therapy during the current episode [*see [CLINICAL STUDIES \(14.3\)](#)*]
- Two short-term trials in pediatric patients (ages 6-17 years) for the treatment of irritability associated with autistic disorder [*see [CLINICAL STUDIES \(14.4\)](#)*]

- Two short-term trials in pediatric patients (ages 6-18 years) with Tourette's disorder [see [CLINICAL STUDIES \(14.5\)](#)]

Efficacy of the injectable formulation of ABILIFY (aripiprazole) was established in the following adequate and well-controlled trials:

- Three 24-hour trials in agitated adult patients with schizophrenia or manic/mixed episodes of bipolar I disorder [see [CLINICAL STUDIES \(14.6\)](#)]

## 14.1 Schizophrenia

### Adults

The efficacy of ABILIFY 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 ABILIFY 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 ABILIFY and the active comparators.

In the four positive trials for ABILIFY, 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 ABILIFY (15 or 30 mg/day) to placebo, both doses of ABILIFY were superior to placebo in the PANSS total score (Study 1 in Table 26), PANSS positive subscale, and CGI-severity score. In addition, the 15 mg dose was superior to placebo in the PANSS negative subscale.

In a 4-week trial (n=404) comparing two fixed doses of ABILIFY (20 or 30 mg/day) to placebo, both doses of ABILIFY were superior to placebo in the PANSS total score (Study 2 in Table 26), PANSS positive subscale, PANSS negative subscale, and CGI-severity score.

In a 6-week trial (n=420) comparing three fixed doses of ABILIFY (10, 15, or 20 mg/day) to placebo, all three doses of ABILIFY were superior to placebo in the PANSS total score (Study 3 in Table 26), PANSS positive subscale, and the PANSS negative subscale.

In a 6-week trial (n=367) comparing three fixed doses of ABILIFY (2, 5, or 10 mg/day) to placebo, the 10 mg dose of ABILIFY was superior to placebo in the PANSS total score (Study 4 in Table 26), the primary outcome measure of the study. The 2 and 5 mg doses did not demonstrate superiority to placebo on the primary outcome measure.

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

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

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

### **Pediatric Patients**

The efficacy of ABILIFY (aripiprazole) in the treatment of schizophrenia in pediatric patients (13 to 17 years of age) was evaluated in one 6-week, placebo-controlled trial of outpatients who met DSM-IV criteria for schizophrenia and had a PANSS score  $\geq 70$  at baseline. In this trial (n=302) comparing two fixed doses of ABILIFY (10 or 30 mg/day) to placebo, ABILIFY was titrated starting from 2 mg/day to the target dose in 5 days in the 10 mg/day treatment arm and in 11 days in the 30 mg/day treatment arm. Both doses of ABILIFY were superior to placebo in the PANSS total score (Study 6 in Table 26), the primary outcome measure of the study. The 30 mg/day dosage was not shown to be more efficacious than the 10 mg/day dose. Although maintenance efficacy in pediatric patients has not been systematically evaluated, maintenance efficacy

can be extrapolated from adult data along with comparisons of aripiprazole pharmacokinetic parameters in adult and pediatric patients.

**Table 26: Schizophrenia Studies**

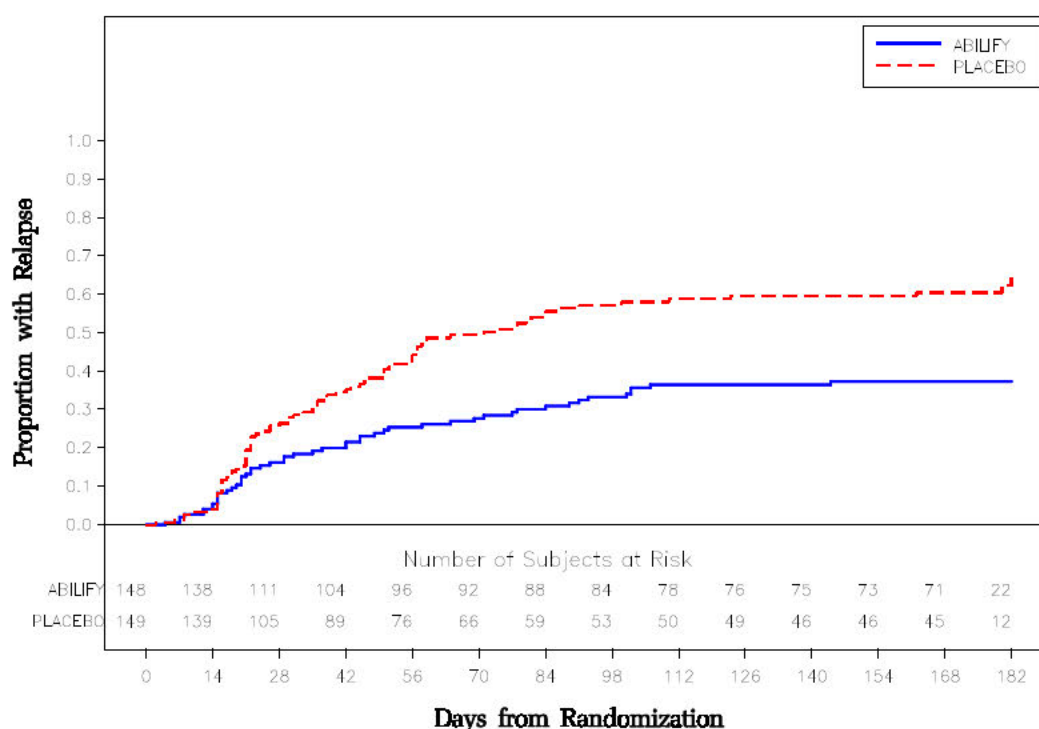
Study Number	Treatment Group		Primary Efficacy Measure: PANSS		
			Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference <sup>a</sup> (95% CI)
Study 1	ABILIFY mg/day)*	(15)	98.5 (17.2)	-15.5 (2.40)	-12.6 (-18.9, -6.2)
	ABILIFY mg/day)*	(30)	99.0 (19.2)	-11.4 (2.39)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

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

<sup>a</sup> 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)**



## 14.2 Bipolar Disorder

### Acute Treatment of Manic and Mixed Episodes

#### Adults

#### Monotherapy

The efficacy of ABILIFY as monotherapy in the acute treatment of manic episodes 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 ABILIFY 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), ABILIFY was superior to placebo in the reduction of Y-MRS total score (Studies 1-4 in Table 27) 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 ABILIFY with concomitant lithium or valproate in the treatment of manic or mixed episodes 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 µg/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  $\geq 16$  and  $\leq 25\%$  improvement on the Y-MRS total score) to lithium or valproate were randomized to receive either ABILIFY (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 ABILIFY 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 µg/mL, respectively) was superior to lithium or valproate with adjunctive placebo in the reduction of the Y-MRS total score (Study 5 in Table 27) 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.

### **Pediatric Patients**

The efficacy of ABILIFY in the treatment of bipolar I disorder in pediatric patients (10 to 17 years of age) was evaluated in one 4-week, placebo-controlled trial (n=296) of outpatients who met DSM-IV criteria for bipolar I disorder manic or mixed episodes with or without psychotic features and had a Y-MRS score  $\geq 20$  at baseline. This double-blind, placebo-controlled trial compared two fixed doses of ABILIFY (10 or 30 mg/day) to placebo. The ABILIFY dose was started at 2 mg/day, which was titrated to 5 mg/day after 2 days, and to the target dose in 5 days in the 10 mg/day treatment arm, and in 13 days in the

30 mg/day treatment arm. Both doses of ABILIFY were superior to placebo in change from baseline to week 4 on the Y-MRS total score (Study 6 in Table 27).

**Table 27: Bipolar Studies**

Study Number	Treatment Group	Primary Efficacy Measure: Y-MRS		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference <sup>a</sup> (95% CI)
Study 1	ABILIFY (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	ABILIFY (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	ABILIFY (15 - 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	ABILIFY (15 -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	ABILIFY (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)	--
Study 6 (Pediatric, 10-17 years)	ABILIFY (10 mg/day)*	29.8 (6.5)	-14.2 (0.89)	-5.99 (-8.49, -3.50)
	ABILIFY (30 mg/day)*	29.5 (6.3)	-16.5 (0.87)	-8.26 (-10.7, -5.77)
	Placebo	30.7 (6.8)	-8.2 (0.91)	--

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

<sup>a</sup> Difference (drug minus placebo) in least-squares mean change from baseline.

\* Doses statistically significantly superior to placebo.

## Maintenance Treatment of Bipolar I Disorder

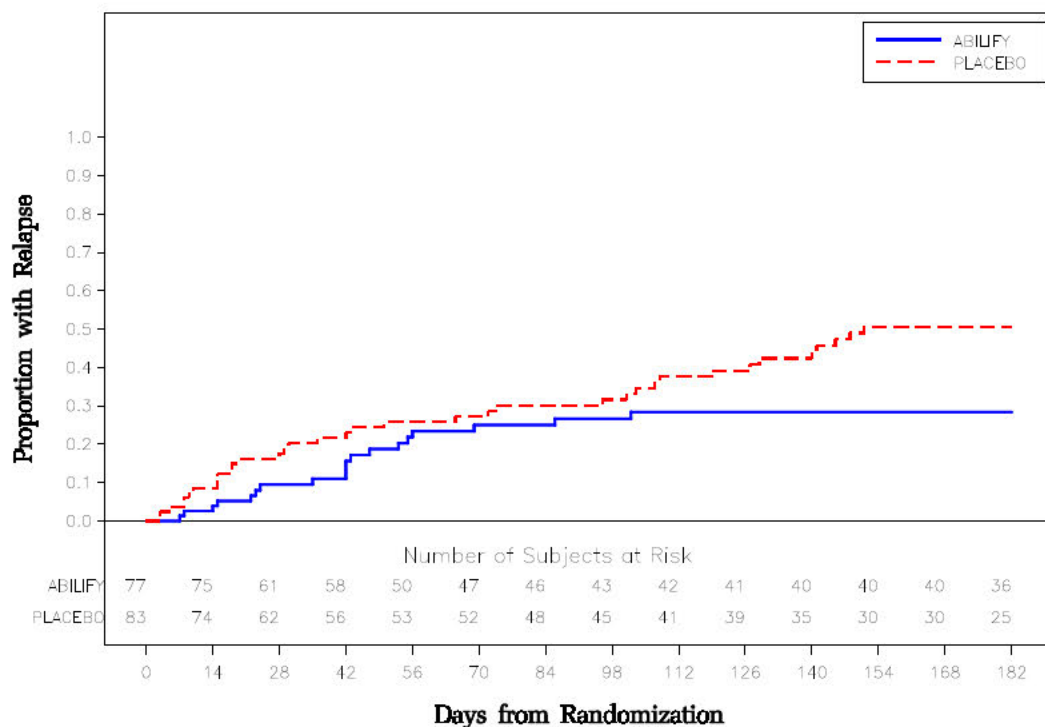
### ***Monotherapy Maintenance Therapy***

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 ABILIFY 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 ABILIFY (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 ABILIFY 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, ABILIFY was 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 ABILIFY group and 36 were from the placebo group. The number of observed manic episodes in the ABILIFY group (6) were fewer than that in the placebo group (19), while the number of depressive episodes in the ABILIFY 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.

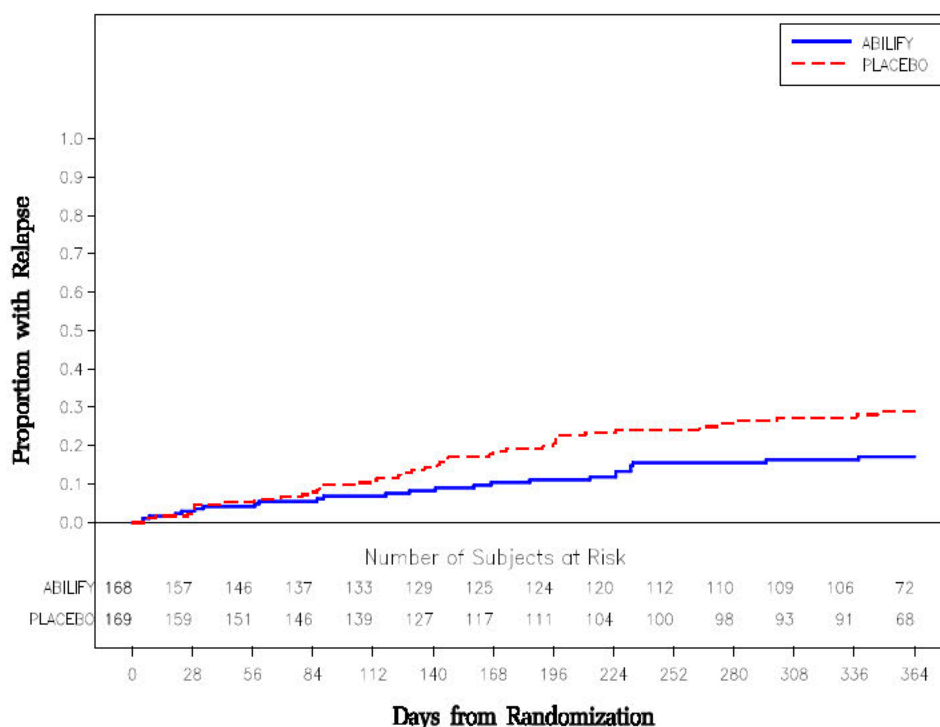
**Figure 7: Kaplan-Meier Estimation of Cumulative Proportion of Patients with Relapse (Bipolar Study 7)**



### ***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 µg/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  $\geq 16$  and  $\leq 35\%$  improvement on the Y-MRS total score) to lithium or valproate received ABILIFY 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 ABILIFY and lithium or valproate were required to maintain stability (Y-MRS and MADRS total scores  $\leq 12$ ) for 12 consecutive weeks. Three hundred thirty-seven patients were then randomized in a double-blind fashion, to either the same dose of ABILIFY 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. ABILIFY was 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 ABILIFY group and 43 were from the placebo group. The number of observed manic episodes in the ABILIFY group (7) were fewer than that in the placebo group (19), while the number of depressive episodes in the ABILIFY 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 ABILIFY and placebo groups are shown in Figure 8.

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

### 14.3 Adjunctive Treatment of Major Depressive Disorder

#### Adults

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

perceived by the patient after a minimum of 6 weeks of antidepressant therapy at or above the minimal effective dose.

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

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

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

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

**Table 28: Adjunctive Treatment of Major Depressive Disorder Studies**

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

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

<sup>a</sup> Difference (drug minus placebo) in least-squares mean change from baseline.

\* Doses statistically significantly superior to placebo.

## 14.4 Irritability Associated with Autistic Disorder

### Pediatric Patients

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

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

The results of these trials are as follows:

In one of the 8-week, placebo-controlled trials, children and adolescents with autistic disorder (n=98), aged 6 to 17 years, received daily doses of placebo or ABILIFY 2 to 15 mg/day. ABILIFY, starting at 2 mg/day with increases allowed up to 15 mg/day based on clinical response, significantly improved

scores on the ABC-I subscale and on the CGI-I scale compared with placebo. The mean daily dose of ABILIFY at the end of 8-week treatment was 8.6 mg/day (Study 1 in Table 29).

In the other 8-week, placebo-controlled trial in children and adolescents with autistic disorder (n=218), aged 6 to 17 years, three fixed doses of ABILIFY (5 mg/day, 10 mg/day, or 15 mg/day) were compared to placebo. ABILIFY dosing started at 2 mg/day and was increased to 5 mg/day after one week. After a second week, it was increased to 10 mg/day for patients in the 10 and 15 mg dose arms, and after a third week, it was increased to 15 mg/day in the 15 mg/day treatment arm (Study 2 in Table 29). All three doses of ABILIFY significantly improved scores on the ABC-I subscale compared with placebo.

**Table 29: Irritability Associated with Autistic Disorder Studies (Pediatric)**

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

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

<sup>a</sup> Difference (drug minus placebo) in least-squares mean change from baseline.

\* Doses statistically significantly superior to placebo.

## 14.5 Tourette's Disorder

### Pediatric Patients

The efficacy of ABILIFY (aripiprazole) in the treatment of Tourette's disorder was established in one 8-week (7 to 17 years of age) and one 10-week (6 to 18 years of age), placebo-controlled trials in pediatric patients (6 to 18 years of age) who met the DSM-IV criteria for Tourette's disorder and had a Total Tic score (TTS)  $\geq 20$  - 22 on the Yale Global Tic Severity Scale (YGTSS). The YGTSS is a fully validated scale designed to measure current tic severity.

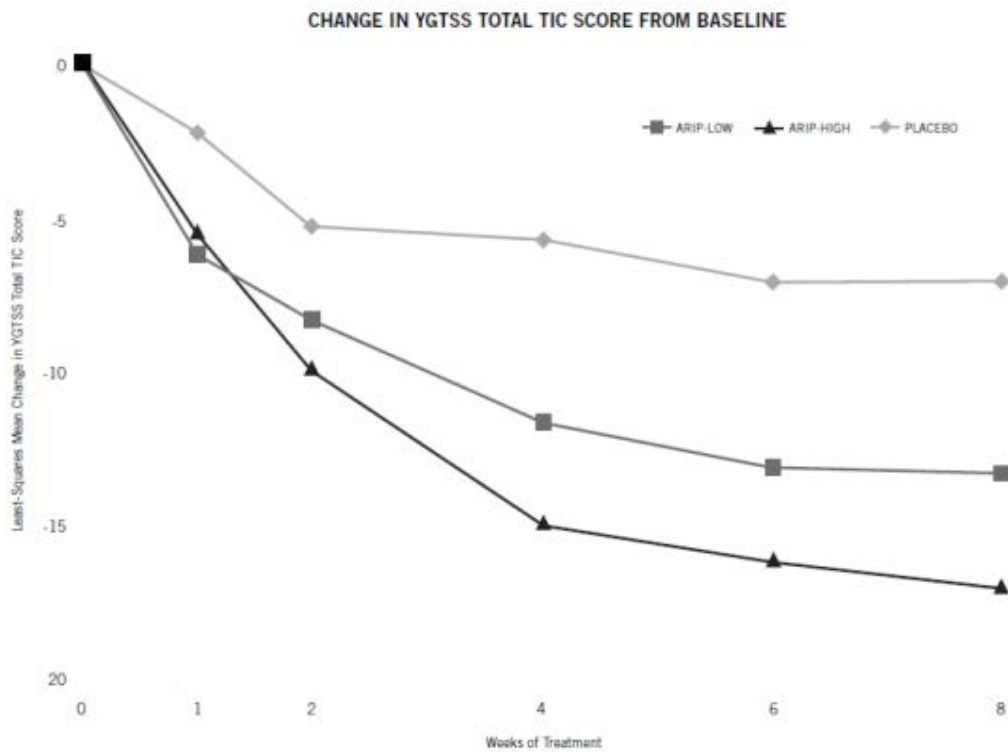
Efficacy was evaluated using two assessment scales: 1) the Total Tic score (TTS) of the YGTSS and 2) the Clinical Global Impressions Scale for Tourette's Syndrome (CGI-TS), a clinician-determined summary measure that takes into account all available patient information. Over 65% of these patients were under 13 years of age.

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

The results of these trials are as follows:

In the 8-week, placebo-controlled, fixed-dose trial, children and adolescents with Tourette's disorder (n=133), aged 7 to 17 years, were randomized 1:1:1 to low dose ABILIFY, high dose ABILIFY, or placebo. The target doses for the low and high dose ABILIFY groups were based on weight. Patients < 50 kg in the low dose ABILIFY group started at 2 mg per day with a target dose of 5 mg per day after 2 days. Patients  $\geq$  50 kg in the low dose ABILIFY group, started at 2 mg per day increased to 5 mg per day after 2 days, with a subsequent increase to a target dose of 10 mg per day at day 7. Patients <50 kg in the high dose ABILIFY group started at 2 mg per day increased to 5 mg per day after 2 days, with a subsequent increase to a target dose of 10 mg per day at day 7. Patients  $\geq$  50 kg in the high dose ABILIFY group, started at 2 mg per day increased to 5 mg per day after 2 days, with a subsequent increase to a dose of 10 mg per day at day 7 and were allowed weekly increases of 5 mg per day up to a target dose 20 mg per day at Day 21. ABILIFY (both high and low dose groups) demonstrated statistically significantly improved scores on the YGTSS TTS (Study 1 in Table 30) and on the CGI-TS scale compared with placebo. The estimated improvements on the YGTSS TTS over the course of the study are displayed in Figure 9.

**Figure 9: Least Square Means of Change from Baseline in YGTSS TTS by Week (Tourette's Disorder Study 1)**



In the 10-week, placebo-controlled, flexible-dose trial in children and adolescents with Tourette's disorder (n=61), aged 6 to 18 years, patients received daily doses of placebo or ABILIFY, starting at 2 mg/day with increases allowed up to 20 mg/day based on clinical response. ABILIFY demonstrated statistically significantly improved scores on the YGTSS TTS scale compared with placebo (Study 2 in Table 30). The mean daily dose of ABILIFY at the end of 10-week treatment was 6.54 mg/day.

**Table 30: Tourette's Disorder Studies (Pediatric)**

Study Number	Treatment Group	Primary Efficacy Measure: YGTSS TTS		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference <sup>a</sup> (95% CI)
Study 1	ABILIFY (low dose)*	29.2 (5.63)	-13.4 (1.59)	-6.3 (-10.2, -2.3)
	ABILIFY (high dose)*	31.2 (6.40)	-16.9 (1.61)	-9.9 (-13.8, -5.9)
	Placebo	30.7 (5.95)	-7.1 (1.55)	--
Study 2	ABILIFY (2-20 mg/day)*	28.3 (5.51)	-15.0 (1.51)	-5.3 (-9.8, -0.9)
	Placebo	29.5 (5.60)	-9.6 (1.64)	--

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

<sup>a</sup> Difference (drug minus placebo) in least-squares mean change from baseline.

\* Doses statistically significantly superior to placebo.

## 14.6 Agitation Associated with Schizophrenia or Bipolar Mania

The efficacy of intramuscular ABILIFY for injection for the treatment of agitation was established in three short-term (24-hour), placebo-controlled trials in agitated inpatients from two diagnostic groups: schizophrenia and bipolar I disorder (manic or mixed episodes, with or without psychotic features). Each of the trials included a single active comparator treatment arm of either haloperidol injection (schizophrenia studies) or lorazepam injection (bipolar mania study). Patients could receive up to three injections during the 24-hour treatment periods; however, patients could not receive the second injection until after the initial 2-hour period when the primary efficacy measure was assessed. Patients enrolled in the trials needed to be: (1) judged by the clinical investigators as clinically agitated and clinically appropriate candidates for treatment with intramuscular medication, and (2) exhibiting a level of agitation that met or exceeded a threshold score of  $\geq 15$  on the five items comprising the Positive and Negative Syndrome Scale (PANSS) Excited Component (i.e., poor impulse control, tension, hostility, uncooperativeness, and excitement items) with at least two individual item scores  $\geq 4$  using a 1-7 scoring system (1 = absent, 4 = moderate, 7 = extreme). In the studies, the mean baseline PANSS Excited Component score was 19, with scores ranging from 15 to 34 (out of a maximum score of 35), thus suggesting predominantly moderate levels of agitation with some patients experiencing mild or severe levels of agitation. The primary efficacy measure used for assessing agitation signs and symptoms in these trials was the change from baseline in the PANSS Excited Component at 2 hours

post-injection. A key secondary measure was the Clinical Global Impression of Improvement (CGI-I) Scale. The results of the trials follow:

In a placebo-controlled trial in agitated inpatients predominantly meeting DSM-IV criteria for schizophrenia (n=350), four fixed ABILIFY injection doses of 1 mg, 5.25 mg, 9.75 mg, and 15 mg were evaluated. At 2 hours post-injection, the 5.25 mg, 9.75 mg, and 15 mg doses were statistically superior to placebo in the PANSS Excited Component (Study 1 in Table 31) and on the CGI-I Scale.

In a second placebo-controlled trial in agitated inpatients predominantly meeting DSM-IV criteria for schizophrenia (n=445), one fixed ABILIFY injection dose of 9.75 mg was evaluated. At 2 hours post-injection, ABILIFY for injection was statistically superior to placebo in the PANSS Excited Component (Study 2 in Table 31) and on the CGI-I Scale.

In a placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for bipolar I disorder (manic or mixed) (n=291), two fixed ABILIFY injection doses of 9.75 mg and 15 mg were evaluated. At 2 hours post-injection, both doses were statistically superior to placebo in the PANSS Excited Component (Study 3 in Table 31).

Examination of population subsets (age, race, and gender) did not reveal any differential responsiveness on the basis of these subgroupings.

**Table 31: Agitation Associated with Schizophrenia or Bipolar Mania Studies**

Study Number	Treatment Group	Primary Efficacy Measure: PANSS Excited Component		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference <sup>a</sup> (95% CI)
Agitation Associated with Schizophrenia				

Study 1	ABILIFY (1 mg)	19.16 (3.26)	-4.47 (0.72)	-1.19 (-2.96 , 0.59)
	ABILIFY (5.25 mg)*	19.41 (3.31)	-5.65 (0.68)	-2.37 (-4.10 , -0.63)
	ABILIFY (9.75 mg)*	19.42 (2.80)	-6.69 (0.72)	-3.40 (-5.18 , -1.62)
	ABILIFY (15 mg)*	19.34 (2.38)	-5.72 (0.72)	-2.44 (-4.21 , -0.68)
	Placebo	19.18 (2.95)	-3.28 (0.70)	--
Study 2	ABILIFY (9.75 mg)*	18.82 (2.67)	-7.27 (0.59)	-2.48 (-3.77, -1.19)
	Placebo	18.74 (2.71)	-4.78 (0.69)	--
<b>Agitation Associated with Bipolar Mania</b>				
Study 3	ABILIFY (9.75 mg)*	18.77 (2.45)	-8.74 (0.57)	-2.99 (-4.53, -1.44)
	ABILIFY (15 mg)*	18.29 (2.49)	-8.67 (0.57)	-2.91 (-4.44, -1.38)
	Placebo	17.95 (2.63)	-5.76 (0.58)	--

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

<sup>a</sup> 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

ABILIFY<sup>®</sup> (aripiprazole) Tablets have markings on one side and are available in the strengths and packages listed in Table 32.

**Table 32: ABILIFY Tablet Presentations**

Tablet Strength	Tablet Color/Shape	Tablet Markings	Pack Size	NDC Code
<b>2 mg</b>	green modified rectangle	“A-006” and “2”	Bottle of 30	59148-006-13
			Blister of 100	59148-006-35
<b>5 mg</b>	blue modified rectangle	“A-007” and “5”	Bottle of 30	59148-007-13
			Blister of 100	59148-007-35
<b>10 mg</b>	pink modified rectangle	“A-008” and “10”	Bottle of 30	59148-008-13
			Blister of 100	59148-008-35
<b>15 mg</b>	yellow round	“A-009” and “15”	Bottle of 30	59148-009-13
			Blister of 100	59148-009-35
<b>20 mg</b>	white round	“A-010” and “20”	Bottle of 30	59148-010-13
			Blister of 100	59148-010-35
<b>30 mg</b>	pink round	“A-011” and “30”	Bottle of 30	59148-011-13
			Blister of 100	59148-011-35

ABILIFY DISCMELT<sup>®</sup> (aripiprazole) Orally Disintegrating Tablets are round tablets with markings on either side. ABILIFY DISCMELT is available in the strengths and packages listed in Table 33.

**Table 33: ABILIFY DISCMELT Orally Disintegrating Tablet Presentations**

Tablet Strength	Tablet Color	Tablet Markings	Pack Size	NDC Code
10 mg	pink (with scattered specks)	“A” and “640” “10”	Blister of 30	59148-640-23
15 mg	yellow (with scattered specks)	“A” and “641” “15”	Blister of 30	59148-641-23

ABILIFY® (aripiprazole) Oral Solution (1 mg/mL) is supplied in child-resistant bottles along with a calibrated oral dosing cup. ABILIFY Oral Solution is available as follows:

150 mL bottle                      NDC 59148-013-15

ABILIFY® (aripiprazole) Injection for intramuscular use is available as a ready-to-use, 9.75 mg/1.3 mL (7.5 mg/mL) solution in clear, Type 1 glass vials as follows:

9.75 mg/1.3 mL single-dose vial                      NDC 59148-016-65

## 16.2 Storage

### Tablets

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

### Oral Solution

Store at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [*see USP Controlled Room Temperature*]. Opened bottles of ABILIFY Oral Solution can be used for up to 6 months after opening, but not beyond the expiration date on the bottle. The bottle and its contents should be discarded after the expiration date.

### Injection

Store at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [*see USP Controlled Room Temperature*]. Protect from light by storing in the original container. Retain in carton until time of use.

## 17 PATIENT COUNSELING INFORMATION

[\*See Medication Guide\*](#)

**Discuss the following issues with patients prescribed ABILIFY:**

### **Clinical Worsening of Depression and Suicide Risk**

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

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

### **Pathological Gambling and Other Compulsive Behaviors**

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

## **Use of Orally Disintegrating Tablet**

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

## **Interference with Cognitive and Motor Performance**

Because ABILIFY 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 therapy does not affect them adversely [[see WARNINGS AND PRECAUTIONS \(5.11\)](#)].

## **Nursing**

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

## **Concomitant Medication**

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

## **Heat Exposure and Dehydration**

Patients should be advised regarding appropriate care in avoiding overheating and dehydration [[see WARNINGS AND PRECAUTIONS \(5.12\)](#)].

## **Sugar Content**

Patients should be advised that each mL of ABILIFY Oral Solution contains 400 mg of sucrose and 200 mg of fructose.

## **Phenylketonurics**

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

Tablets manufactured by Otsuka Pharmaceutical Co., Ltd., Tokyo, 101-8535 Japan

Orally Disintegrating Tablets, Oral Solution, and Injection manufactured by Bristol-Myers Squibb Company, Princeton, NJ 08543 USA

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

ABILIFY is a trademark of Otsuka Pharmaceutical Company.



Otsuka

Otsuka America Pharmaceutical, Inc.

Rev 08/2016

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## MEDICATION GUIDE

ABILIFY® (a BIL ĭ fĭ) (aripiprazole) Tablets intramuscular use	ABILIFY® (a BIL ĭ fĭ) (aripiprazole) Orally Disintegrating Tablets	ABILIFY® (a BIL ĭ fĭ) (aripiprazole) Oral Solution	ABILIFY® (a BIL ĭ fĭ) (aripiprazole) Injection, for
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### What is the most important information I should know about ABILIFY?

(For other side effects, also see “What are the possible side effects of ABILIFY?”)

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

- **Increased risk of death in elderly patients with dementia-related psychosis:** Medicines like ABILIFY can raise the risk of death in elderly people who have lost touch with reality (psychosis) due to confusion and memory loss (dementia). ABILIFY is not approved for the treatment of patients with dementia-related psychosis.
- **Risk of suicidal thoughts or actions:** Antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions:
  1. **Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.**
  2. **Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions.** These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.
  3. **How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?**
    - Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
    - Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
    - Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

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

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

### What else do I need to know about antidepressant medicines?

- **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.

- **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
- **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
- **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information.

#### **What is ABILIFY?**

- **ABILIFY Oral Tablets, Orally-Disintegrating Tablets, and Oral Solution are prescription medicines used to treat:**
  - Schizophrenia
  - manic or mixed episodes that happen with bipolar I disorder
  - major depressive disorder (MDD) when ABILIFY is used with antidepressant medicines
  - irritability associated with autistic disorder
  - Tourette's disorder
- **ABILIFY Injection is a prescription medicine used to treat:**
  - agitation associated with schizophrenia or bipolar mania

#### **It is not known if ABILIFY is safe or effective in children:**

- under 13 years of age with schizophrenia
- under 10 years of age with bipolar I disorder
- under 6 years of age with irritability associated with autistic disorder
- under 6 years of age with Tourette's disorder

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

#### **Before taking ABILIFY, tell your healthcare provider** about all your medical conditions, including if **you have or had:**

- diabetes or high blood sugar in you or your family; your healthcare provider should check your blood sugar before you start ABILIFY and also during therapy.
- seizures (convulsions).
- low or high blood pressure.
- heart problems or stroke.
- pregnancy or plans to become pregnant. It is not known if ABILIFY will harm your unborn baby.
- breast-feeding or plans to breast-feed. ABILIFY can pass into your breast milk and may harm your baby. Talk to your healthcare provider about the best way to feed your baby if you receive ABILIFY.
- low white blood cell count.
- phenylketonuria. ABILIFY DISCMELT Orally Disintegrating Tablets contain phenylalanine.

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

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

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

- Take ABILIFY exactly as your healthcare provider tells you to take it. Do not change the dose or stop taking ABILIFY yourself.

- ABILIFY can be taken with or without food.
- ABILIFY tablets should be swallowed whole.
- If you miss a dose of ABILIFY, take the missed dose as soon as you remember. If it is almost time for the next dose, just skip the missed dose and take your next dose at the regular time. Do not take two doses of ABILIFY at the same time.
- If you have been prescribed ABILIFY DISCMELT, take it as follows:
  - Do not open the blister until ready to take the DISCMELT tablet.
  - To remove one DISCMELT tablet, open the package and peel back the foil on the blister to expose the tablet.
  - Do not push the tablet through the foil because this could damage the tablet.
  - Immediately upon opening the blister, using dry hands, remove the tablet and place the entire ABILIFY DISCMELT Orally Disintegrating Tablet on the tongue.
  - Tablet disintegration occurs rapidly in saliva. It is recommended that ABILIFY DISCMELT be taken without liquid. However, if needed, it can be taken with liquid.
  - Do not attempt to split the DISCMELT tablet.
- If you take too much ABILIFY, call your healthcare provider or poison control center at 1-800-222-1222 right away, or go to the nearest hospital emergency room.

#### **What should I avoid while taking ABILIFY?**

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

#### **What are the possible side effects of ABILIFY?**

**ABILIFY may cause serious side effects, including:**

- **See “What is the most important information I should know about ABILIFY?”**
  - **Stroke in elderly people (cerebrovascular problems) that can lead to death**
  - **Neuroleptic malignant syndrome (NMS).** Tell your healthcare provider right away if you have some or all of the following symptoms: high fever, stiff muscles, confusion, sweating, changes in pulse, heart rate, and blood pressure. These may be symptoms of a rare and serious condition that can lead to death. Call your healthcare provider right away if you have any of these symptoms.
  - **Uncontrolled body movements (tardive dyskinesia).** ABILIFY may cause movements that you cannot control in your face, tongue, or other body parts. Tardive dyskinesia may not go away, even if you stop receiving ABILIFY. Tardive dyskinesia may also start after you stop receiving ABILIFY.
  - **Problems with your metabolism such as:**
    - **High blood sugar (hyperglycemia) and diabetes.** Increases in blood sugar can happen in some people who take ABILIFY. 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 ABILIFY and during your treatment.
- Call your healthcare provider if you have any of these symptoms of high blood sugar while receiving ABILIFY:**
- 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 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.
- **Orthostatic hypotension (decreased blood pressure).** Lightheadedness or fainting may happen when rising too quickly from a sitting or lying position.
- **Low white blood cell count**
- **Seizures (convulsions)**
- **Problems with control of your body temperature especially when you exercise a lot or are in an area that is very hot. It is important for you to drink water to avoid dehydration.** See “What should I avoid while receiving ABILIFY?”
- **Difficulty swallowing that can cause food or liquid to get into your lungs.**

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

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

**The most common side effects of ABILIFY in children include:**

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

These are not all the possible side effects of ABILIFY.

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?**

- Store ABILIFY at room temperature, between 68°F to 77°F (20°C to 25°C).
- Opened bottles of ABILIFY Oral Solution can be used for up to 6 months after opening, but not beyond the expiration date on the bottle.

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

#### **General information about the safe and effective use of ABILIFY**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ABILIFY for a condition for which it was not prescribed. Do not give ABILIFY 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 that was written for healthcare professionals.

## What are the ingredients in ABILIFY?

**Active ingredient:** aripiprazole

### Inactive ingredients:

**Tablets:** 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

**ABILIFY DISCMELT Orally Disintegrating Tablets:** acesulfame potassium, aspartame (which contains phenylalanine), calcium silicate, croscarmellose sodium, crospovidone, crème de vanilla (natural and artificial flavors), magnesium stearate, microcrystalline cellulose, silicon dioxide, tartaric acid, and xylitol. Colorants include ferric oxide (yellow or red) and FD&C Blue No. 2 Aluminum Lake

**ABILIFY Oral Solution:** disodium edetate, fructose (200 mg per mL), glycerin, dl-lactic acid, methylparaben, propylene glycol, propylparaben, sodium hydroxide, sucrose (400 mg per mL), and purified water. The oral solution is flavored with natural orange cream and other natural flavors

For more information about ABILIFY go to [www.abilify.com](http://www.abilify.com) or call 1-800-438-6055.

Tablets manufactured by Otsuka Pharmaceutical Co., Ltd., Tokyo, 101-8535 Japan

Orally Disintegrating Tablets, Oral Solution, and Injection manufactured by Bristol-Myers Squibb Company, Princeton, NJ 08543 USA

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

ABILIFY is a trademark of Otsuka Pharmaceutical Company.



Otsuka

Otsuka America Pharmaceutical, Inc.

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## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ABILIFY MAINTENA® (aripiprazole) for extended-release injectable suspension, for intramuscular use  
Initial U.S. Approval: 2002

### WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

See full prescribing information for complete boxed warning.

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

## RECENT MAJOR CHANGES

Dosage and Administration: Pre-filled Dual Chamber Syringe (2.5), Vial (2.6) 07/2015  
Warnings and Precautions, Pathological Gambling and Other Compulsive Behaviors (5.6) 08/2016

## INDICATIONS AND USAGE

ABILIFY MAINTENA is an atypical antipsychotic indicated for the treatment of schizophrenia (1)

## DOSAGE AND ADMINISTRATION

- Only to be administered by intramuscular injection in the deltoid or gluteal muscle by a healthcare professional (2.1)
- For patients naïve to aripiprazole, establish tolerability with oral aripiprazole prior to initiating ABILIFY MAINTENA (2.1)
- Recommended starting and maintenance dose is 400 mg administered monthly as a single injection. Dose can be reduced to 300 mg in patients with adverse reactions (2.1)
- In conjunction with first dose, take 14 consecutive days of concurrent oral aripiprazole (10 mg to 20 mg) or current oral antipsychotic (2.1)
- Dosage adjustments are required for missed doses (2.2)
- Known CYP2D6 poor metabolizers: Recommended starting and maintenance dose is 300 mg administered monthly as a single injection (2.3)
- ABILIFY MAINTENA comes in two types of kits. See instructions for reconstitution/injection/disposal procedures for 1) Pre-filled Dual Chamber Syringe (2.5), and 2) Vials (2.6).

## DOSAGE FORMS AND STRENGTHS

For extended-release injectable suspension 300 mg and 400 mg strength lyophilized powder for reconstitution in (3):

- single-dose pre-filled dual chamber syringe
- single-dose vial

## CONTRAINDICATIONS

Known hypersensitivity to aripiprazole (4)

## WARNINGS AND PRECAUTIONS

- **Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis** Increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack, including fatalities) (5.2)
- **Neuroleptic Malignant Syndrome** Manage with immediate discontinuation and close monitoring (5.3)
- **Tardive Dyskinesia** Discontinue if clinically appropriate (5.4)

- **Metabolic Changes** Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and weight gain (5.5)
  - **Hyperglycemia and Diabetes Mellitus** Monitor patients for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Monitor glucose regularly in patients with and at risk for diabetes (5.5)
  - **Dyslipidemia** Undesirable alterations have been observed in patients treated with atypical antipsychotics (5.5)
  - **Weight Gain** Gain in body weight has been observed; clinical monitoring of weight is recommended (5.5)
- **Pathological Gambling and Other Compulsive Behaviors** Consider dose reduction or discontinuation (5.6)
- **Orthostatic Hypotension** Use with caution in patients with known cardiovascular or cerebrovascular disease (5.7)
- **Leukopenia, Neutropenia, and Agranulocytosis** Perform complete blood 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 (5.8)
- **Seizures** Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold (5.9)
- **Potential for Cognitive and Motor Impairment** Use caution when operating machinery (5.10)

## ADVERSE REACTIONS

Most commonly observed adverse reactions with ABILIFY MAINTENA (incidence  $\geq 5\%$  and at least twice that for placebo) were increased weight, akathisia, injection site pain, and sedation (6.1)

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](http://www.fda.gov/medwatch).

## DRUG INTERACTIONS

Dosage adjustments for patients taking CYP2D6 inhibitors, CYP3A4 inhibitors, or CYP3A4 inducers for greater than 14 days (2.3):

Factors	Adjusted Dose
<b>CYP2D6 Poor Metabolizers</b>	
CYP2D6 Poor Metabolizers taking concomitant CYP3A4 inhibitors	200 mg <sup>1</sup>
<b>Patients Taking 400 mg of ABILIFY MAINTENA</b>	
Strong CYP2D6 <b>or</b> CYP3A4 inhibitors	300 mg
CYP2D6 <b>and</b> CYP3A4 inhibitors	200 mg <sup>1</sup>
CYP3A4 inducers	Avoid use
<b>Patients Taking 300 mg of ABILIFY MAINTENA</b>	
Strong CYP2D6 <b>or</b> CYP3A4 inhibitors	200 mg <sup>1</sup>
CYP2D6 <b>and</b> CYP3A4 inhibitors	160 mg <sup>1</sup>
CYP3A4 inducers	Avoid use

<sup>1</sup>200 mg and 160 mg dose adjustments are obtained only by using the 300 mg or 400 mg strength vials.

## 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: 08/2016

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**FULL PRESCRIBING INFORMATION: CONTENTS\******WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS*****1 INDICATIONS AND USAGE****2 DOSAGE AND ADMINISTRATION**

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\*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***

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

## 1 INDICATIONS AND USAGE

ABILIFY MAINTENA (aripiprazole) is indicated for the treatment of schizophrenia [see [CLINICAL STUDIES \(14\)](#)].

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Dosage Overview for the Treatment of Schizophrenia

ABILIFY MAINTENA is only to be administered by intramuscular injection by a healthcare professional. The recommended starting and maintenance dose of ABILIFY MAINTENA is 400 mg monthly (no sooner than 26 days after the previous injection).

For patients who have never taken aripiprazole, establish tolerability with oral aripiprazole prior to initiating treatment with ABILIFY MAINTENA. Due to the half-life of oral aripiprazole, it may take up to 2 weeks to fully assess tolerability.

After the first ABILIFY MAINTENA injection, administer oral aripiprazole (10 mg to 20 mg) for 14 consecutive days to achieve therapeutic aripiprazole concentrations during initiation of therapy. For patients already stable on another oral antipsychotic (and known to tolerate aripiprazole), after the first ABILIFY MAINTENA injection, continue treatment with the antipsychotic for 14 consecutive days to maintain therapeutic antipsychotic concentrations during initiation of therapy.

If there are adverse reactions with the 400 mg dosage, consider reducing the dosage to 300 mg once monthly.

### 2.2 Dosage Adjustments for Missed Doses

If the second or third doses are missed:

- **If more than 4 weeks and less than 5 weeks have elapsed since the last injection,** administer the injection as soon as possible.
- **If more than 5 weeks have elapsed since the last injection,** restart concomitant oral aripiprazole for 14 days with the next administered injection.

If the fourth or subsequent doses are missed:

- **If more than 4 weeks and less than 6 weeks have elapsed since the last injection,** administer the injection as soon as possible.
- **If more than 6 weeks have elapsed since the last injection,** restart concomitant oral aripiprazole for 14 days with the next administered injection.

## 2.3 Dosage Adjustments for Cytochrome P450 Considerations

Dosage adjustments are recommended in patients who are CYP2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors for greater than 14 days (see [Table 1](#)). Dosage adjustments for 200 mg and 160 mg are obtained only by using the 300 mg or 400 mg strength vials for intramuscular deltoid or gluteal injection.

If the CYP3A4 inhibitor or CYP2D6 inhibitor is withdrawn, the ABILIFY MAINTENA dosage may need to be increased [*see [DOSAGE AND ADMINISTRATION \(2.1\)](#)*].

Avoid the concomitant use of CYP3A4 inducers with ABILIFY MAINTENA for greater than 14 days because the blood levels of aripiprazole are decreased and may be below the effective levels.

Dosage adjustments are not recommended for patients with concomitant use of CYP3A4 inhibitors, CYP2D6 inhibitors or CYP3A4 inducers for less than 14 days.

**Table 1: Dose Adjustments of ABILIFY MAINTENA in Patients who are known CYP2D6 Poor Metabolizers and Patients Taking Concomitant CYP2D6 Inhibitors, 3A4 Inhibitors, and/or CYP3A4 Inducers for Greater than 14 days**

Factors	Adjusted Dose
<b>CYP2D6 Poor Metabolizers</b>	
Known CYP2D6 Poor Metabolizers	300 mg
Known CYP2D6 Poor Metabolizers taking concomitant CYP3A4 inhibitors	200 mg <sup>1</sup>
<b>Patients Taking 400 mg of ABILIFY MAINTENA</b>	
Strong CYP2D6 <u>or</u> CYP3A4 inhibitors	300 mg
CYP2D6 <u>and</u> CYP3A4 inhibitors	200 mg <sup>1</sup>
CYP3A4 inducers	Avoid use
<b>Patients Taking 300 mg of ABILIFY MAINTENA</b>	
Strong CYP2D6 <u>or</u> CYP3A4 inhibitors	200 mg <sup>1</sup>
CYP2D6 <u>and</u> CYP3A4 inhibitors	160 mg <sup>1</sup>
CYP3A4 inducers	Avoid use

1. 200 mg and 160 mg dosage adjustments are obtained only by using the 300 mg or 400 mg strength vials.

ABILIFY MAINTENA comes in two types of kits. See instructions for reconstitution/injection/disposal procedures for 1) Pre-filled Dual Chamber Syringe ([2.5](#)), and 2) Vials ([2.6](#)).

## 2.4 Different Aripiprazole Formulations and Kits

There are two aripiprazole formulations for intramuscular use with different dosages, dosing frequencies, and indications. ABILIFY MAINTENA is a long-acting aripiprazole formulation with 4 week dosing intervals indicated for the treatment of schizophrenia. In contrast, aripiprazole injection (9.75 mg per vial) is a short-acting formulation indicated for agitation in patients with schizophrenia or mania. Do not substitute these products. Refer to the prescribing information for aripiprazole injection for more information about aripiprazole injection.

ABILIFY MAINTENA comes in two types of kits. See instructions for reconstitution/injection/disposal procedures for 1) Pre-filled Dual Chamber Syringe available in 300 mg or 400 mg strength syringes [see [DOSAGE AND ADMINISTRATION \(2.5\)](#)], and 2) Single-use vials available in 300 mg or 400 mg strength vials [see [DOSAGE AND ADMINISTRATION \(2.6\)](#)].

The 200 mg and 160 mg dosage adjustments are obtained only by using the 300 mg or 400 mg strength vials.

## 2.5 Pre-filled Dual Chamber Syringe: Preparation and Administration Instructions

### Preparation Prior to Reconstitution

For deep intramuscular deltoid or gluteal injection by healthcare professionals only. Do not administer by any other route. Inject full syringe contents immediately following reconstitution. Administer once monthly.

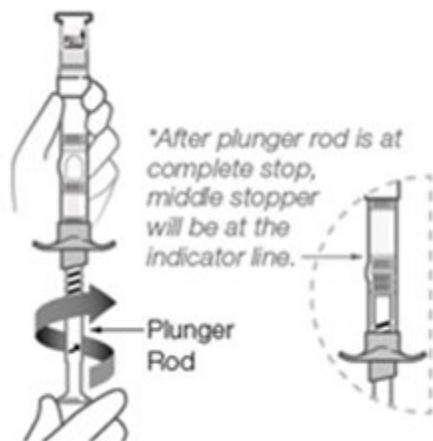
Lay out and confirm that components listed below are provided in the kit:

- One ABILIFY MAINTENA (aripiprazole) pre-filled dual chamber syringe (400 mg or 300 mg as appropriate) for extended release injectable suspension containing lyophilized powder and Sterile Water for Injection
- One 23 gauge, 1 inch (25 mm) hypodermic safety needle with needle protection device for deltoid administration in non-obese patients
- One 22 gauge, 1.5 inch (38 mm) hypodermic safety needle with needle protection device for gluteal administration in non-obese patients or deltoid administration in obese patients
- One 21 gauge, 2 inch (50 mm) hypodermic safety needle with needle protection device for gluteal administration in obese patients

## Reconstitution of Lyophilized Powder in Pre-filled Dual Chamber Syringe

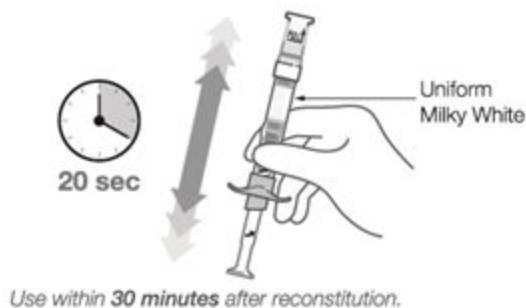
### Reconstitute at room temperature.

- a) Push plunger rod slightly to engage threads. And then, rotate plunger rod until the rod stops rotating to release diluent. After plunger rod is at complete stop, middle stopper will be at the indicator line (See [Figure 1](#)).



**Figure 1**

- b) Vertically shake the syringe vigorously for 20 seconds until drug is uniformly milky-white (See [Figure 2](#)).



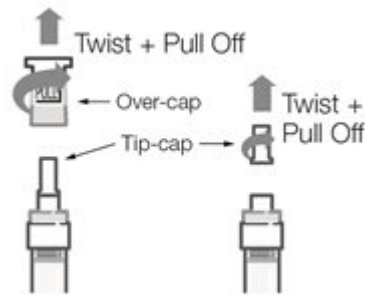
**Figure 2**

- c) Visually inspect the syringe for particulate matter and discoloration prior to administration. The reconstituted ABILIFY MAINTENA suspension should appear to be a uniform, homogeneous suspension that is opaque and milky-white in color.

### Injection Procedure

*Use appropriate aseptic techniques throughout injection procedure. For deep intramuscular injection only.*

- a) Twist and pull off Over-cap and Tip-cap (See [Figure 3](#)).



**Figure 3**

- b) Select appropriate needle (See [Figure 4](#)).

Body Type	Injection Site	Needle Size
Non-obese	Deltoid	1 inch (23G)
	Gluteus	1.5 inch (22G)
Obese	Deltoid	1.5 inch (22G)
	Gluteus	2 inch (21G)

**Figure 4**

For deltoid administration:

- 23 gauge, 1 inch (25 mm) hypodermic safety needle with needle protection device for non-obese patients
- 22 gauge, 1.5 inch (38 mm) hypodermic safety needle with needle protection device for obese patients

For gluteal administration:

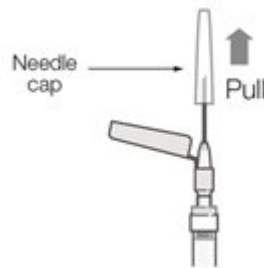
- 22 gauge, 1.5 inch (38 mm) hypodermic safety needle with needle protection device for non-obese patients
- 21 gauge, 2 inch (50 mm) hypodermic safety needle with needle protection device for obese patients

- c) While holding the needle cap, ensure the needle is firmly seated on the safety device with a push. Twist clockwise until SNUGLY fitted (See [Figure 5](#)).



**Figure 5**

- d) Then **PULL** needle-cap straight up (see [Figure 6](#)).



**Figure 6**

- e) Hold syringe UPRIGHT and **ADVANCE PLUNGER ROD SLOWLY TO EXPEL THE AIR**. Expel air until suspension fills needle base. If it's not possible to advance plunger rod to expel the air, check that plunger rod is rotated to a complete stop (See [Figure 7](#)).

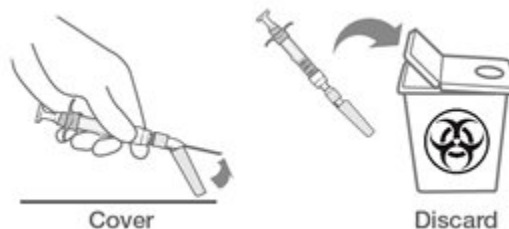


**Figure 7**

- f) **Inject slowly into the deltoid or gluteal muscle.** Do **not** massage the injection site.

### Disposal Procedure

- a) Engage the needle safety device and safely discard all kit components (See [Figure 8](#)). **ABILIFY MAINTENA pre-filled dual chamber syringe is for single-use only.**



**Figure 8**

- b) Rotate sites of injections between the two deltoid or gluteal muscles.

## **2.6 Vial: Preparation and Administration Instructions**

### **Preparation Prior to Reconstitution**

**For deep intramuscular injection by healthcare professionals only. Do not administer by any other route. Inject immediately after reconstitution. Administer once monthly.**

- a) Lay out and confirm that components listed below are provided in the kit:
- Vial of ABILIFY MAINTENA (aripiprazole) for extended-release injectable suspension lyophilized powder
  - 5 mL vial of Sterile Water for Injection, USP
  - One 3 mL luer lock syringe with pre-attached 21 gauge, 1.5 inch (38 mm) hypodermic safety needle with needle protection device
  - One 3 mL luer lock disposable syringe with luer lock tip
  - One vial adapter
  - One 23 gauge, 1 inch (25 mm) hypodermic safety needle with needle protection device for deltoid administration in non-obese patients
  - One 22 gauge, 1.5 inch (38 mm) hypodermic safety needle with needle protection device for gluteal administration in non-obese patients or deltoid administration in obese patients
  - One 21 gauge, 2 inch (50 mm) hypodermic safety needle with needle protection device for gluteal administration in obese patients
- b) ABILIFY MAINTENA should be suspended using the Sterile Water for Injection as supplied in the kit.
- c) The Sterile Water for Injection and ABILIFY MAINTENA vials are for single-use only.
- d) Use appropriate aseptic techniques throughout reconstitution and reconstitute at room temperature.
- e) Select the amount of Sterile Water for Injection needed for reconstitution (see [Table 2](#)).

**Table 2: Amount of Sterile Water for Injection Needed for Reconstitution**

<b>400 mg Vial</b>		<b>300 mg Vial</b>	
Dose	Sterile Water for Injection	Dose	Sterile Water for Injection
400 mg	1.9 mL	300 mg	1.5 mL

**Important:** There is more Sterile Water for Injection in the vial than is needed to reconstitute ABILIFY MAINTENA (aripiprazole) for extended-release injectable suspension. The vial will have excess Sterile Water for Injection; discard any unused portion.

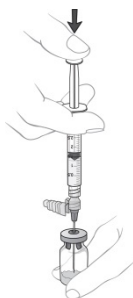
**Reconstitution of Lyophilized Powder in Vial**

- Remove the cap of the vial of Sterile Water for Injection and remove the cap of the vial containing ABILIFY MAINTENA lyophilized powder and wipe the tops with a sterile alcohol swab.
- Using the syringe with pre-attached hypodermic safety needle, withdraw the pre-determined Sterile Water for Injection volume from the vial of Sterile Water for Injection into the syringe (see [Figure 9](#)). Residual Sterile Water for Injection will remain in the vial following withdrawal; discard any unused portion.



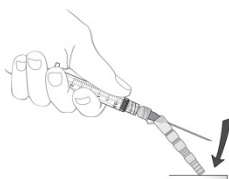
**Figure 9**

- Slowly inject the Sterile Water for Injection into the vial containing the ABILIFY MAINTENA lyophilized powder (see [Figure 10](#)).



**Figure 10**

- d) Withdraw air to equalize the pressure in the vial by pulling back slightly on the plunger. Subsequently, remove the needle from the vial. Engage the needle safety device by using the one-handed technique (see [Figure 11](#)). Gently press the sheath against a flat surface until the needle is firmly engaged in the needle protection sheath. Visually confirm that the needle is fully engaged into the needle protection sheath, and discard.



**Figure 11**

- e) Shake the vial vigorously for 30 seconds until the reconstituted suspension appears uniform (see [Figure 12](#)).



**Figure 12**

- f) Visually inspect the reconstituted suspension for particulate matter and discoloration prior to administration. The reconstituted ABILIFY MAINTENA is a uniform, homogeneous suspension that is opaque and milky-white in color.
- g) If the injection is not performed immediately after reconstitution keep the vial at room temperature and shake the vial vigorously for at least 60 seconds to re-suspend prior to injection.
- h) Do not store the reconstituted suspension in a syringe.

### **Preparation Prior to Injection**

- a) Use appropriate aseptic techniques throughout injection of the reconstituted ABILIFY MAINTENA suspension.
- b) Remove the cover from the vial adapter package (see [Figure 13](#)). Do not remove the vial adapter from the package.



**Figure 13**

- c) Using the vial adapter package to handle the vial adapter, attach the prepackaged luer lock syringe to the vial adapter (see [Figure 14](#)).



**Figure 14**

- d) Use the luer lock syringe to remove the vial adapter from the package and discard the vial adapter package (see [Figure 15](#)). Do not touch the spike tip of the adapter at any time.



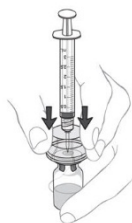
**Figure 15**

- e) Determine the recommended volume for injection ([Table 3](#)).

**Table 3: ABILIFY MAINTENA Reconstituted Suspension Volume to Inject**

400 mg Vial		300 mg Vial	
Dose	Volume to Inject	Dose	Volume to Inject
400 mg	2 mL	---	---
300 mg	1.5 mL	300 mg	1.5 mL
200 mg	1 mL	200 mg	1 mL
160 mg	0.8 mL	160 mg	0.8 mL

- f) Wipe the top of the vial of the reconstituted ABILIFY MAINTENA suspension with a sterile alcohol swab.
- g) Place and hold the vial of the reconstituted ABILIFY MAINTENA suspension on a hard surface. Attach the adapter-syringe assembly to the vial by holding the outside of the adapter and pushing the adapter's spike firmly through the rubber stopper, until the adapter snaps in place (see [Figure 16](#)).



**Figure 16**

- h) Slowly withdraw the recommended volume from the vial into the luer lock syringe to allow for injection (see [Figure 17](#)). A small amount of excess product will remain in the vial.



**Figure 17**

### **Injection Procedure**

- a) Detach the luer lock syringe containing the recommended volume of reconstituted ABILIFY MAINTENA suspension from the vial.
- b) Select the appropriate hypodermic safety needle and attach the needle to the luer lock syringe containing the suspension for injection. While holding the needle cap, ensure the

needle is firmly seated on the safety device with a push. Twist clockwise until snugly fitted and then pull the needle cap straight away from the needle (see [Figure 18](#)).

For deltoid administration:

- 23 gauge, 1 inch (25 mm) hypodermic safety needle with needle protection device for non-obese patients
- 22 gauge, 1.5 inch (38 mm) hypodermic safety needle with needle protection device for obese patients

For gluteal administration:

- 22 gauge, 1.5 inch (38 mm) hypodermic safety needle with needle protection device for non-obese patients
- 21 gauge, 2 inch (50 mm) hypodermic safety needle with needle protection device for obese patients



**Figure 18**

(c) Slowly inject the recommended volume as a single intramuscular injection into the deltoid or gluteal muscle. Do not massage the injection site.

### **Disposal Procedure**

- a) Engage the needle safety device as described in Section 2.6, Step (d) of Reconstitution of Lyophilized Powder in Vial and safely discard all kit components (see Figure 8). Dispose of the vials, adapter, needles, and syringe appropriately after injection. **The Sterile Water for Injection and ABILIFY MAINTENA vials are for single-use only.**
- b) Rotate sites of injections between the two deltoid or gluteal muscles.

## **3 DOSAGE FORMS AND STRENGTHS**

*For extended-release injectable suspension:* 300 mg and 400 mg of lyophilized powder for reconstitution in:

- single-dose pre-filled dual chamber syringe
- single-dose vial

The reconstituted extended-release injectable suspension is a uniform, homogeneous suspension that is opaque and milky-white in color.

## **4 CONTRAINDICATIONS**

ABILIFY MAINTENA is contraindicated in patients with a known hypersensitivity to aripiprazole. Hypersensitivity reactions ranging from pruritus/urticaria to anaphylaxis have been reported in patients receiving aripiprazole [see [ADVERSE REACTIONS \(6.1 and 6.2\)](#)].

## **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 MAINTENA is not approved for the treatment of patients with dementia-related psychosis.

### **5.2 Cerebrovascular Adverse Reactions, Including Stroke in Elderly Patients with Dementia-Related Psychosis**

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

### 5.3 Neuroleptic Malignant Syndrome

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

Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

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

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

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.

### 5.4 Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

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

There is no known treatment for established tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment,

itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and, thereby, may possibly mask the underlying process. The effect of symptomatic suppression on the long-term course of the syndrome is unknown.

Given these considerations, ABILIFY MAINTENA should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs and 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

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

## **5.5 Metabolic Changes**

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

### **Hyperglycemia/Diabetes Mellitus**

Hyperglycemia, in some cases extreme and associated with diabetic ketoacidosis, 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 \(6.1\)](#)]. 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 reactions 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 a short-term, placebo-controlled randomized trial in adults with schizophrenia, the mean change in fasting glucose was +9.8 mg/dL (N=88) in the ABILIFY MAINTENA- treated patients and +0.7 mg/dL (N=59) in the placebo-treated patients. Table 4 shows the proportion of ABILIFY MAINTENA-treated patients with normal and borderline fasting glucose at baseline and their changes in fasting glucose measurements.

**Table 4: Proportion of Patients with Potential Clinically Relevant Changes in Fasting Glucose from a 12-Week Placebo-Controlled Monotherapy Trial in Adult Patients with Schizophrenia**

	Category Change (at least once) from Baseline	Treatment Arm	n/N <sup>a</sup>	%
<b>Fasting Glucose</b>	Normal to High (<100 mg/dL to ≥126 mg/dL)	ABILIFY MAINTENA	7/88	8.0
		Placebo	0/75	0.0
	Borderline to High (≥100 mg/dL and <126 mg/dL to ≥126 mg/dL)	ABILIFY MAINTENA	1/33	3.0
		Placebo	3/33	9.1

<sup>a</sup> N = the total number of subjects who had a measurement at baseline and at least one post-baseline result. n = the number of subjects with a potentially clinically relevant shift.

## Dyslipidemia

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

Table 5 shows the proportion of adult patients from one short-term, placebo-controlled randomized trial in adults with schizophrenia taking ABILIFY MAINTENA, with changes in total cholesterol, fasting triglycerides, fasting LDL cholesterol and HDL cholesterol.

**Table 5: Proportion of Patients with Potential Clinically Relevant Changes in Blood Lipid Parameters From a 12-Week Placebo-Controlled Monotherapy Trial in Adults with Schizophrenia**

	<b>Treatment Arm</b>	<b>n/N<sup>a</sup></b>	<b>%</b>
<b>Total Cholesterol</b>	ABILIFY MAINTENA	3/83	3.6
Normal to High (<200 mg/dL to ≥240 mg/dL)	Placebo	2/73	2.7
Borderline to High (200~<240 mg/dL to ≥240 mg/dL)	ABILIFY MAINTENA	6/27	22.2
	Placebo	2/19	10.5
Any increase (≥40 mg/dL)	ABILIFY MAINTENA	15/122	12.3
	Placebo	6/110	5.5
<b>Fasting Triglycerides</b>	ABILIFY MAINTENA	7/98	7.1
Normal to High (<150 mg/dL to ≥200 mg/dL)	Placebo	4/78	5.1
Borderline to High (150~<200 mg/dL to ≥200 mg/dL)	ABILIFY MAINTENA	3/11	27.3
	Placebo	4/15	26.7
Any increase (≥ 50 mg/dL)	ABILIFY MAINTENA	24/122	19.7
	Placebo	20/110	18.2
<b>Fasting LDL Cholesterol</b>	ABILIFY MAINTENA	1/59	1.7
Normal to High (<100 mg/dL to ≥160 mg/dL)	Placebo	1/51	2.0
Borderline to High (100~<160 mg/dL to ≥160 mg/dL)	ABILIFY MAINTENA	5/52	9.6
	Placebo	1/41	2.4
Any increase (≥ 30 mg/dL)	ABILIFY MAINTENA	17/120	14.2
	Placebo	9/103	8.7
<b>HDL Cholesterol</b>	ABILIFY MAINTENA	14/104	13.5
Normal to Low (≥40 mg/dL to <40 mg/dL)	Placebo	11/87	12.6
Any decrease (≥ 20 mg/dL)	ABILIFY MAINTENA	7/122	5.7
	Placebo	12/110	10.9

<sup>a</sup> N = the total number of subjects who had a measurement at baseline and at least one post-baseline result. n = the number of subjects with a potentially clinically relevant shift.

## Weight Gain

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

In one short-term, placebo-controlled trial with ABILIFY MAINTENA, the mean change in body weight at Week 12 was +3.5 kg (N=99) in the ABILIFY MAINTENA-treated patients and +0.8 kg (N=66) in the placebo-treated patients.

Table 6 shows the percentage of adult patients with weight gain  $\geq 7\%$  of body weight in a short-term, placebo-controlled trial with ABILIFY MAINTENA.

**Table 6: Percentage of Patients From a 12-Week Placebo-Controlled Trial in Adult Patients with Schizophrenia with Weight Gain  $\geq 7\%$  of Body Weight**

	<b>Treatment Arm</b>	<b>N<sup>a</sup></b>	<b>Patients n (%)</b>
<b>Weight gain <math>\geq 7\%</math> of body weight</b>	ABILIFY MAINTENA	144	31 (21.5)
	Placebo	141	12 (8.5)

<sup>a</sup> N = the total number of subjects who had a measurement at baseline and at least one post-baseline result.

## 5.6 Pathological Gambling and Other Compulsive Behaviors

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

## 5.7 Orthostatic Hypotension

ABILIFY MAINTENA may cause orthostatic hypotension, perhaps due to its  $\alpha_1$ -adrenergic receptor antagonism. In the short-term, placebo-controlled trial in adults with schizophrenia, the adverse event of presyncope was reported in 1/167 (0.6%) of patients treated with ABILIFY MAINTENA, while syncope and orthostatic hypotension were each reported in 1/172 (0.6%) of patients treated with placebo. During the stabilization phase of the randomized-withdrawal (maintenance) study, orthostasis-related adverse events were reported in 4/576 (0.7%) of patients treated with ABILIFY MAINTENA, including abnormal orthostatic blood pressure (1/576, 0.2%), postural dizziness (1/576, 0.2%), presyncope (1/576, 0.2%) and orthostatic hypotension (1/576, 0.2%).

In the short-term placebo-controlled trial, there were no patients in either treatment group with a significant orthostatic change in blood pressure (defined as a decrease in systolic blood pressure  $\geq 20$  mmHg accompanied by an increase in heart rate  $\geq 25$  when comparing standing to supine values). During the stabilization phase of the randomized-withdrawal (maintenance) study, the incidence of significant orthostatic change in blood pressure was 0.2% (1/575).

## 5.8 Leukopenia, Neutropenia, and Agranulocytosis

In clinical trials and post-marketing experience, leukopenia and neutropenia have been reported temporally related to antipsychotic agents, including ABILIFY MAINTENA. Agranulocytosis has also been reported [see [ADVERSE REACTIONS \(6.1\)](#)].

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC)/absolute neutrophil count (ANC) and a 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 MAINTENA 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 MAINTENA in patients with severe neutropenia (absolute neutrophil count  $< 1000/\text{mm}^3$ ) and follow their WBC counts until recovery.

## 5.9 Seizures

As with other antipsychotic drugs, use ABILIFY MAINTENA cautiously in patients with a history of seizures or with conditions that lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

## 5.10 Potential for Cognitive and Motor Impairment

ABILIFY MAINTENA, like other antipsychotics, may impair judgment, thinking, or motor skills. Instruct patients to avoid operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with ABILIFY MAINTENA does not affect them adversely.

## 5.11 Body Temperature Regulation

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

## 5.12 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use, including ABILIFY MAINTENA. ABILIFY MAINTENA and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia [see [WARNINGS AND PRECAUTIONS \(5.1\)](#)].

## 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 Use [see [BOXED WARNING](#) and [WARNINGS AND PRECAUTIONS \(5.1\)](#)]
- Cerebrovascular Adverse Reactions, Including Stroke in Elderly Patients with Dementia-Related Psychosis [see [BOXED WARNING](#) and [WARNINGS AND PRECAUTIONS \(5.2\)](#)]
- Neuroleptic Malignant Syndrome [see [WARNINGS AND PRECAUTIONS \(5.3\)](#)]
- Tardive Dyskinesia [see [WARNINGS AND PRECAUTIONS \(5.4\)](#)]
- Metabolic Changes [see [WARNINGS AND PRECAUTIONS \(5.5\)](#)]
- Pathological Gambling and Other Compulsive Behaviors [see [WARNINGS AND PRECAUTIONS \(5.6\)](#)]
- Orthostatic Hypotension [see [WARNINGS AND PRECAUTIONS \(5.7\)](#)]
- Leukopenia, Neutropenia, and Agranulocytosis [see [WARNINGS AND PRECAUTIONS \(5.8\)](#)]
- Seizures [see [WARNINGS AND PRECAUTIONS \(5.9\)](#)]
- Potential for Cognitive and Motor Impairment [see [WARNINGS AND PRECAUTIONS \(5.10\)](#)]
- Body Temperature Regulation [see [WARNINGS AND PRECAUTIONS \(5.11\)](#)]
- Dysphagia [see [WARNINGS AND PRECAUTIONS \(5.12\)](#)]

## 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.

### Safety Database of ABILIFY MAINTENA and Oral Aripiprazole

Oral aripiprazole has been evaluated for safety in 16,114 adult patients who participated in multiple-dose, clinical trials in schizophrenia and other indications, and who had approximately 8,578 patient-years of exposure to oral aripiprazole. A total of 3,901 patients were treated with oral aripiprazole for at least 180 days, 2,259 patients were treated with oral aripiprazole for at least 360 days, and 933 patients continuing aripiprazole treatment for at least 720 days.

ABILIFY MAINTENA has been evaluated for safety in 2,188 adult patients in clinical trials in schizophrenia, with approximately 2,646 patient-years of exposure to ABILIFY MAINTENA. A total of 1,230 patients were treated with ABILIFY MAINTENA for at least 180 days (at least 7 consecutive injections) and 935 patients treated with ABILIFY MAINTENA had at least 1 year of exposure (at least 13 consecutive injections).

The conditions and duration of treatment with ABILIFY MAINTENA included double-blind and open-label studies. The safety data presented below are derived from the 12-week double-blind placebo-controlled study of ABILIFY MAINTENA in adult patients with schizophrenia.

### Adverse Reactions with ABILIFY MAINTENA

#### *Most Commonly Observed Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials in Schizophrenia*

Based on the placebo-controlled trial of ABILIFY MAINTENA in schizophrenia, the most commonly observed adverse reactions associated with the use of ABILIFY MAINTENA in patients (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) were increased weight (16.8% vs 7.0%), akathisia (11.4% vs 3.5%), injection site pain (5.4% vs 0.6%) and sedation (5.4% vs 1.2%).

#### *Commonly Reported Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials in Schizophrenia*

The following findings are based on the double-blind, placebo-controlled trial that compared ABILIFY MAINTENA 400 mg or 300 mg to placebo in patients with schizophrenia. Table 7 lists the adverse reactions reported in 2% or more of ABILIFY MAINTENA-treated subjects and at a greater proportion than in the placebo group.

**Table 7: Adverse Reactions in  $\geq 2\%$  of ABILIFY MAINTENA-Treated Adult Patients with Schizophrenia in a 12-Week Double-Blind, Placebo-Controlled Trial<sup>a</sup>**

System Organ Class Preferred Term	Percentage of Patients Reporting Reaction <sup>a</sup>	
	ABILIFY MAINTENA (n=167)	Placebo (n=172)
<b>Gastrointestinal Disorders</b>		
Constipation	10	7
Dry Mouth	4	2
Diarrhea	3	2
Vomiting	3	1
Abdominal Discomfort	2	1
<b>General Disorders and Administration Site Conditions</b>		
Injection Site Pain	5	1

<b>Infections and Infestations</b>		
Upper Respiratory Tract Infection	4	2
<b>Investigations</b>		
Increased Weight	17	7
Decreased Weight	4	2
<b>Musculoskeletal And Connective Tissue Disorders</b>		
Arthralgia	4	1
Back Pain	4	2
Myalgia	4	2
Musculoskeletal Pain	3	1
<b>Nervous System Disorders</b>		
Akathisia	11	4
Sedation	5	1
Dizziness	4	2
Tremor	3	1
<b>Respiratory, Thoracic And Mediastinal</b>		
Nasal Congestion	2	1

<sup>a</sup> This table does not include adverse reactions which had an incidence equal to or less than placebo.

#### *Other Adverse Reactions Observed During the Clinical Trial Evaluation of ABILIFY MAINTENA*

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

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

*Blood and Lymphatic System Disorders: rare* - thrombocytopenia

*Cardiac Disorders: infrequent* - tachycardia, *rare* - bradycardia, sinus tachycardia

*Endocrine Disorders: rare* - hypoprolactinemia

*Eye Disorders: infrequent* - vision blurred, oculogyric crisis

*Gastrointestinal Disorders: infrequent* - abdominal pain upper, dyspepsia, nausea, *rare* -swollen tongue

*General Disorders and Administration Site Conditions:* frequent - fatigue, injection site reactions (including erythema, induration, pruritus, injection site reaction, swelling, rash, inflammation, hemorrhage), infrequent - chest discomfort, gait disturbance, rare-irritability, pyrexia

*Hepatobiliary Disorders:* rare - drug induced liver injury

*Immune System Disorders:* rare - drug hypersensitivity

*Infections and Infestations:* rare - nasopharyngitis

*Investigations:* infrequent - blood creatine phosphokinase increased, blood pressure decreased, hepatic enzyme increased, liver function test abnormal, electrocardiogram QT-prolonged, rare - blood triglycerides decreased, blood cholesterol decreased, electrocardiogram T-wave abnormal

*Metabolism and Nutrition Disorders:* infrequent - decreased appetite, obesity, hyperinsulinemia

*Musculoskeletal and Connective Tissue Disorders:* infrequent - joint stiffness, muscle twitching, rare - rhabdomyolysis

*Nervous System Disorders:* infrequent - cogwheel rigidity, extrapyramidal disorder, hypersomnia, lethargy, rare- bradykinesia, convulsion, dysgeusia, memory impairment, oromandibular dystonia

*Psychiatric Disorders:* frequent - anxiety, insomnia restlessness, infrequent- agitation, bruxism, depression, psychotic disorder, suicidal ideation, rare - aggression, hypersexuality, panic attack

*Renal and Urinary Disorders:* rare - glycosuria, pollakiuria, urinary incontinence

*Vascular Disorders:* infrequent - hypertension

### *Demographic Differences*

An examination of population subgroups was performed across demographic subgroup categories for adverse reactions experienced by at least 5% of ABILIFY MAINTENA subjects at least twice rate of the placebo (i.e., increased weight, akathisia, injection site pain, and sedation) in the double-blind placebo-controlled trial. This analysis did not reveal evidence of differences in safety differential adverse reaction incidence on the basis of age, gender, or race alone; however, there were few subjects  $\geq 65$  years of age.

### *Injection Site Reactions of ABILIFY MAINTENA*

In the data from the short-term, double-blind, placebo-controlled trial with ABILIFY MAINTENA in patients with schizophrenia, the percent of patients reporting any injection site-related adverse reaction (all reported as injection site pain) was 5.4% for patients treated with gluteal administered ABILIFY MAINTENA and 0.6% for placebo. The mean intensity of injection pain reported by subjects using a visual analog scale (0=no pain to 100=unbearably

painful) approximately one hour after injection was 7.1 (SD 14.5) for the first injection and 4.8 (SD 12.4) at the last visit in the double-blind, placebo-controlled phase.

In an open-label study comparing bioavailability of ABILIFY MAINTENA administered in the deltoid or gluteal muscle, injection site pain was observed in both groups at approximately equal rates.

#### *Extrapyramidal Symptoms (EPS)*

In the short-term, placebo-controlled trial of ABILIFY MAINTENA in adults with schizophrenia, the incidence of reported EPS-related events, excluding events related to akathisia, for ABILIFY MAINTENA-treated patients was 9.6% vs. 5.2% for placebo. The incidence of akathisia-related events for ABILIFY MAINTENA-treated patients was 11.5% vs. 3.5% for placebo.

#### *Dystonia*

Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups. In the short-term, placebo-controlled trial of ABILIFY MAINTENA in adults with schizophrenia, the incidence of dystonia was 1.8% for ABILIFY MAINTENA vs. 0.6% for placebo.

#### *Neutropenia*

In the short-term, placebo-controlled trial of ABILIFY MAINTENA in adults with schizophrenia, the incidence of neutropenia (absolute neutrophil count  $\leq 1.5$  thous/ $\mu$ L) for ABILIFY MAINTENA-treated patients was 5.7% vs. 2.1% for placebo. An absolute neutrophil count of  $<1$  thous/ $\mu$ L (i.e. 0.95 thous/ $\mu$ L) was observed in only one patient on ABILIFY MAINTENA and resolved spontaneously without any associated adverse events [[\*see WARNINGS AND PRECAUTIONS \(5.8\)\*](#)]

#### *Adverse Reactions Reported in Clinical Trials with Oral Aripiprazole*

The following is a list of additional adverse reactions that have been reported in clinical trials with oral aripiprazole and not reported above for ABILIFY MAINTENA:

*Cardiac Disorders:* palpitations, cardiopulmonary failure, myocardial infarction, cardio-respiratory arrest, atrioventricular block, extrasystoles, angina pectoris, myocardial ischemia, atrial flutter, supraventricular tachycardia, ventricular tachycardia

*Eye Disorders:* photophobia, diplopia, eyelid edema, photopsia

*Gastrointestinal Disorders:* gastroesophageal reflux disease, swollen tongue, esophagitis, pancreatitis, stomach discomfort, toothache

*General Disorders and Administration Site Conditions:* asthenia, peripheral edema, chest pain, face edema, angioedema, hypothermia, pain

*Hepatobiliary Disorders:* hepatitis, jaundice

*Immune System Disorders:* hypersensitivity

*Injury, Poisoning, and Procedural Complications:* heat stroke

*Investigations:* blood prolactin increased, blood urea increased, blood creatinine increased, blood bilirubin increased, blood lactate dehydrogenase increased, glycosylated hemoglobin increased

*Metabolism and Nutrition Disorders:* anorexia, hyponatremia, hypoglycemia, polydipsia, diabetic ketoacidosis

*Musculoskeletal and Connective Tissue Disorders:* muscle rigidity, muscular weakness, muscle tightness, decreased mobility, rhabdomyolysis, musculoskeletal stiffness, pain in extremity, muscle spasms

*Nervous System Disorders:* coordination abnormal, speech disorder, hypokinesia, hypotonia, myoclonus, akinesia, bradykinesia, choreoathetosis

*Psychiatric Disorders:* loss of libido, suicide attempt, hostility, libido increased, anger, anorgasmia, delirium, intentional self injury, completed suicide, tic, homicidal ideation, catatonia, sleep walking

*Renal and Urinary Disorders:* urinary retention, polyuria, nocturia

*Reproductive System and Breast Disorders:* menstruation irregular, erectile dysfunction, amenorrhea, breast pain, gynecomastia, priapism

*Respiratory, Thoracic, and Mediastinal Disorders:* nasal congestion, dyspnea, pharyngolaryngeal pain, cough

*Skin and Subcutaneous Tissue Disorders:* rash (including erythematous, exfoliative, generalized, macular, maculopapular, papular rash; acneiform, allergic, contact, exfoliative, seborrheic dermatitis, neurodermatitis, and drug eruption), hyperhidrosis, pruritus, photosensitivity reaction, alopecia, urticaria

## 6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of oral aripiprazole or ABILIFY MAINTENA. 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), pathological gambling, hiccups and blood glucose fluctuation.

## 7 DRUG INTERACTIONS

### 7.1 Drugs Having Clinically Important Interactions with ABILIFY MAINTENA

Table 8: Clinically Important Drug Interactions with ABILIFY MAINTENA:

Concomitant Drug Name or Drug Class	Clinical Rationale	Clinical Recommendation
Strong CYP3A4 Inhibitors (e.g., ketoconazole) or strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine)	The concomitant use of oral aripiprazole with strong CYP 3A4 or CYP2D6 inhibitors increased the exposure of aripiprazole [see <a href="#">CLINICAL PHARMACOLOGY (12.3)</a> ].	With concomitant use of ABILIFY MAINTENA with a strong CYP3A4 inhibitor or CYP2D6 inhibitor for more than 14 days, reduce the ABILIFY MAINTENA dosage [see <a href="#">DOSAGE AND ADMINISTRATION (2.3)</a> ].
Strong CYP3A4 Inducers (e.g., carbamazepine)	The concomitant use of oral aripiprazole and carbamazepine decreased the exposure of aripiprazole [see <a href="#">CLINICAL PHARMACOLOGY (12.3)</a> ].	Avoid use of ABILIFY MAINTENA in combination with carbamazepine and other inducers of CYP3A4 for greater than 14 days [see <a href="#">DOSAGE AND ADMINISTRATION (2.3)</a> ].
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 <a href="#">WARNINGS AND PRECAUTIONS (5.7)</a> ].
Benzodiazepines (e.g., lorazepam)	The intensity of sedation was greater with the combination of	Monitor sedation and blood pressure. Adjust dose

	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 <a href="#">WARNINGS AND PRECAUTIONS (5.7)</a> ].	accordingly.
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## 7.2 Drugs Having No Clinically Important Interactions with ABILIFY MAINTENA

Based on pharmacokinetic studies with oral aripiprazole, no dosage adjustment of ABILIFY MAINTENA is required when administered concomitantly with famotidine, valproate, lithium, lorazepam [see [CLINICAL PHARMACOLOGY \(12.3\)](#)].

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), or CYP3A4 (e.g., dextromethorphan) when co-administered with ABILIFY MAINTENA. Additionally, no dosage adjustment is necessary for valproate, lithium, lamotrigine, lorazepam, or sertraline when co-administered with ABILIFY MAINTENA. [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 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 MAINTENA, during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms. There are insufficient data with ABILIFY MAINTENA use in pregnant women to inform a drug-associated risk. In animal reproduction studies, oral and intravenous aripiprazole administration during organogenesis in rats and/or rabbits at doses 10 and 11 times, respectively, 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 10 times the maximum recommended human dose (MRHD) produced prolonged gestation, stillbirths, decreased pup weight, and decreased pup survival. Consider the benefits and risks of ABILIFY MAINTENA and possible risks to the fetus when prescribing ABILIFY MAINTENA 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 2-4% and 15-20%, 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 oral 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 exhibiting extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately.

### **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 which are approximately 1 to 10 times the maximum recommended human dose [MRHD] of 30 mg/day on mg/m<sup>2</sup> basis of aripiprazole during the period of organogenesis. Treatment at the highest dose caused a slight prolongation of gestation and delay in fetal development, as evidenced by decreased fetal weight and undescended testes. Delayed skeletal ossification was observed at 3 and 10 times the oral MRHD on mg/m<sup>2</sup> basis.

At 3 and 10 times the oral MRHD on mg/m<sup>2</sup> basis, delivered offspring had decreased body weights. Increased incidences of hepatodiaphragmatic nodules and diaphragmatic hernia were observed in offspring from the highest dose group (the other dose groups were not examined for these findings). Postnatally, delayed vaginal opening was seen at 3 and 10 times the oral MRHD on mg/m<sup>2</sup> basis and impaired reproductive performance (decreased fertility rate, corpora lutea, implants, live fetuses, and increased post-implantation loss, likely mediated through effects on female offspring) along with some maternal toxicity were seen at the highest dose; however, there was no evidence to suggest that these developmental effects were secondary to maternal toxicity.

In pregnant rats treated with aripiprazole intravenously at doses of 3, 9, and 27 mg/kg/day, which are 1 to 9 times the oral MRHD on mg/m<sup>2</sup> basis, during the period of organogenesis, decreased fetal weight and delayed skeletal ossification were seen at the highest dose which also caused maternal toxicity.

In pregnant rabbits treated with oral doses of 10, 30, and 100 mg/kg/day which are 2 to 11 times human exposure at the oral MRHD based on AUC and 6 to 65 times the oral MRHD of aripiprazole on mg/m<sup>2</sup> basis during the period of organogenesis, decreased maternal food consumption and increased abortions were seen at the highest dose as well as increased fetal mortality. Decreased fetal weight and increased incidence of fused sternebrae were observed at 3 and 11 times the MRHD based on AUC.

In pregnant rabbits receiving aripiprazole injection intravenously at doses of 3, 10, and 30 mg/kg/day, which are 2 to 19 times the oral MRHD on mg/m<sup>2</sup> basis during the period of organogenesis, the highest dose caused pronounced maternal toxicity that resulted in decreased fetal weight, increased fetal abnormalities (primarily skeletal), and decreased fetal skeletal ossification. The fetal no-effect dose was 5 times the human exposure at the oral MRHD based on AUC and is 6 times the oral MRHD on mg/m<sup>2</sup> basis.

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

In rats treated with aripiprazole intravenously at doses of 3, 8, and 20 mg/kg/day which are 1 to 6 times the oral MRHD on mg/m<sup>2</sup> basis from day 6 of gestation through day 20 postpartum, increased stillbirths were seen at 3 and 6 times the MRHD on mg/m<sup>2</sup> basis, and decreases in early postnatal pup weight and survival were seen at the highest dose; these doses produced some maternal toxicity. There were no effects on postnatal behavioral and reproductive development.

## **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 MAINTENA and any potential adverse effects on the breastfed infant from ABILIFY MAINTENA or from the underlying maternal condition.

## 8.4 Pediatric Use

ABILIFY MAINTENA has not been studied in children 18 years of age or younger. However, juvenile animal studies have been conducted in rats and dogs.

### Juvenile Animal Studies

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

Aripiprazole in juvenile dogs (2 months old) caused CNS clinical signs of tremors, hypoactivity, ataxia, recumbency and limited use of hind limbs when administered orally for 6 months at 3, 10, 30 mg/kg/day. Mean body weight and weight gain were decreased up to 18% in females in all drug groups relative to control values. A NOAEL could not be determined and, at the lowest tested dose of 3mg/kg/day, there is no safety margin relative to the systemic exposures (AUC<sub>0-24</sub>) for aripiprazole or its major active metabolite in adolescents at the maximum recommended pediatric dose of 15 mg/day. All drug-related effects were reversible after a 2-month recovery period.

## 8.5 Geriatric Use

Clinical studies of oral aripiprazole did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience and pharmacokinetic data [*see* [CLINICAL PHARMACOLOGY \(12.3\)](#)] have not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing

range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

In single-dose and multiple-dose pharmacokinetic studies, there was no detectable age effect in the population pharmacokinetic analysis of oral aripiprazole in schizophrenia patients [*see [CLINICAL PHARMACOLOGY \(12.3\)](#)*]. No dosage adjustments are recommended based on age alone. ABILIFY MAINTENA is not approved for the treatment of patients with dementia-related psychosis [*see also [BOXED WARNING](#) and [WARNINGS AND PRECAUTIONS \(5.1\)](#)*].

## 8.6 CYP2D6 Poor Metabolizers

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

## 8.7 Hepatic and Renal Impairment

No dosage adjustment for ABILIFY MAINTENA 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 MAINTENA is required on the basis of a patient's sex, race, or smoking status [*see [CLINICAL PHARMACOLOGY \(12.3\)](#)*].

# 10 OVERDOSAGE

## 10.1 Human Experience

The largest known case of acute ingestion with a known outcome involved 1260 mg of oral aripiprazole (42 times the maximum recommended daily dose) in a patient who fully recovered.

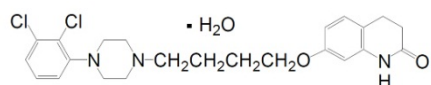
Common adverse reactions (reported in at least 5% of all overdose cases) reported with oral aripiprazole overdose (alone or in combination with other substances) include vomiting, somnolence, and tremor. Other clinically important signs and symptoms observed in one or more patients with aripiprazole 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

In case of overdosage, call the Poison Control Center immediately at 1-800-222-1222.

## 11 DESCRIPTION

Aripiprazole is an atypical antipsychotic which is present in ABILIFY MAINTENA as its monohydrate polymorphic form. Aripiprazole monohydrate is 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl] butoxy]-3,4 dihydrocarbostyryl monohydrate. The empirical formula is  $C_{23}H_{27}Cl_2N_3O_2 \cdot H_2O$  and its molecular weight is 466.40. The chemical structure is:



ABILIFY MAINTENA (aripiprazole) is an extended-release injectable suspension available in 400-mg or 300-mg strength pre-filled dual chamber syringes and 400-mg or 300-mg strength vials. The labeled strengths are calculated based on the anhydrous form (aripiprazole). Inactive ingredients (per administered dose) for 400 mg and 300 mg strength products, respectively, include carboxymethyl cellulose sodium (16.64 mg and 12.48 mg), mannitol (83.2 mg and 62.4 mg), sodium phosphate monobasic monohydrate (1.48 mg and 1.11 mg) and sodium hydroxide (pH adjuster).

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The mechanism of action of aripiprazole in the treatment of schizophrenia is unknown.

However, the efficacy of aripiprazole may be mediated through a combination of partial agonist activity at  $D_2$  and  $5-HT_{1A}$  receptors and antagonist activity at  $5-HT_{2A}$  receptors. Actions at receptors other than  $D_2$ ,  $5-HT_{1A}$ , and  $5-HT_{2A}$  may explain some of the other adverse reactions of aripiprazole (e.g., the orthostatic hypotension observed with aripiprazole may be explained by its antagonist activity at adrenergic  $\alpha_1$  receptors).

### 12.2 Pharmacodynamics

Aripiprazole exhibits high affinity for dopamine  $D_2$  and  $D_3$ , serotonin  $5-HT_{1A}$  and  $5-HT_{2A}$  receptors ( $K_i$  values of 0.34 nM, 0.8 nM, 1.7 nM, and 3.4 nM, respectively), moderate affinity for dopamine  $D_4$ , serotonin  $5-HT_{2C}$  and  $5-HT_7$ ,  $\alpha_1$ -adrenergic and histamine  $H_1$  receptors ( $K_i$  values of 44 nM, 15 nM, 39 nM, 57 nM, and 61 nM, respectively), and moderate affinity for the serotonin reuptake site ( $K_i=98$  nM). Aripiprazole has no appreciable affinity for cholinergic muscarinic receptors ( $IC_{50}>1000$  nM). Aripiprazole functions as a partial agonist at the dopamine  $D_2$  and the serotonin  $5-HT_{1A}$  receptors, and as an antagonist at serotonin  $5-HT_{2A}$  receptor.

### *Alcohol*

There was no significant difference between oral aripiprazole co-administered with ethanol and placebo co-administered with ethanol on performance of gross motor skills or stimulus response in healthy subjects. As with most psychoactive medications, patients should be advised to avoid alcohol while taking ABILIFY MAINTENA.

## **12.3 Pharmacokinetics**

ABILIFY MAINTENA 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<sub>2</sub> receptors similar to the parent drug and represents about 29% of the parent drug exposure in plasma.

Aripiprazole absorption into the systemic circulation is slow and prolonged following intramuscular injection due to low solubility of aripiprazole particles. Following a single dose administration of ABILIFY MAINTENA in the deltoid and gluteal muscle, the extent of absorption (AUC<sub>t</sub>, AUC<sub>∞</sub>) of aripiprazole was similar for both injection sites, but the rate of absorption (C<sub>max</sub>) was 31% higher following administration to the deltoid compared to the gluteal site. However, at steady state, AUC and C<sub>max</sub> were similar for both sites of injection. Following multiple intramuscular doses, the plasma concentrations of aripiprazole gradually rise to maximum plasma concentrations at a median T<sub>max</sub> of 5 - 7 days for the gluteal muscle and 4 days for the deltoid muscle. After gluteal administration, the mean apparent aripiprazole terminal elimination half-life was 29.9 days and 46.5 days after multiple injections for every 4-week injection of ABILIFY MAINTENA 300 mg and 400 mg, respectively. Steady state concentrations for the typical subject were attained by the fourth dose for both sites of administration. Approximate dose-proportional increases in aripiprazole and dehydro-aripiprazole exposure were observed after every four week ABILIFY MAINTENA injections of 300 mg and 400 mg.

Elimination of aripiprazole is mainly through hepatic metabolism involving two P450 isozymes, CYP2D6 and CYP3A4. Aripiprazole is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2E1 enzymes. Aripiprazole also does not undergo direct glucuronidation.

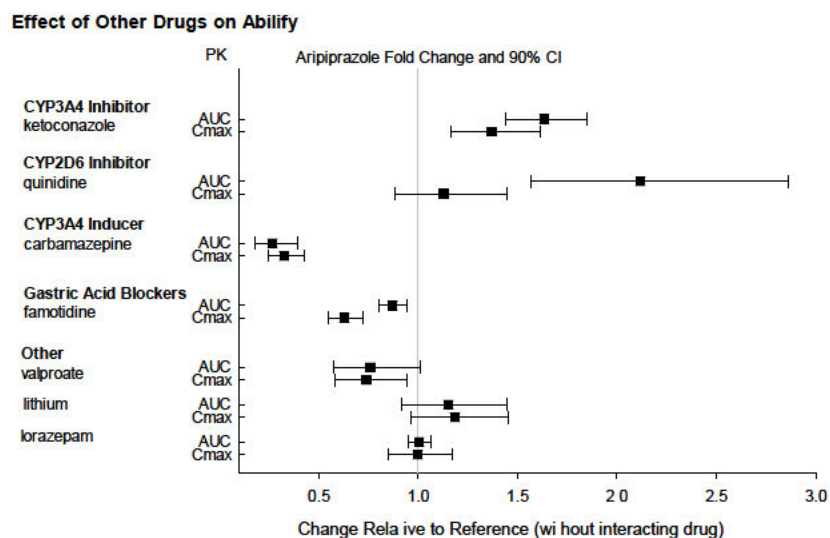
### **Drug Interaction Studies**

No specific drug interaction studies have been performed with ABILIFY MAINTENA. The information below is obtained from studies with oral aripiprazole.

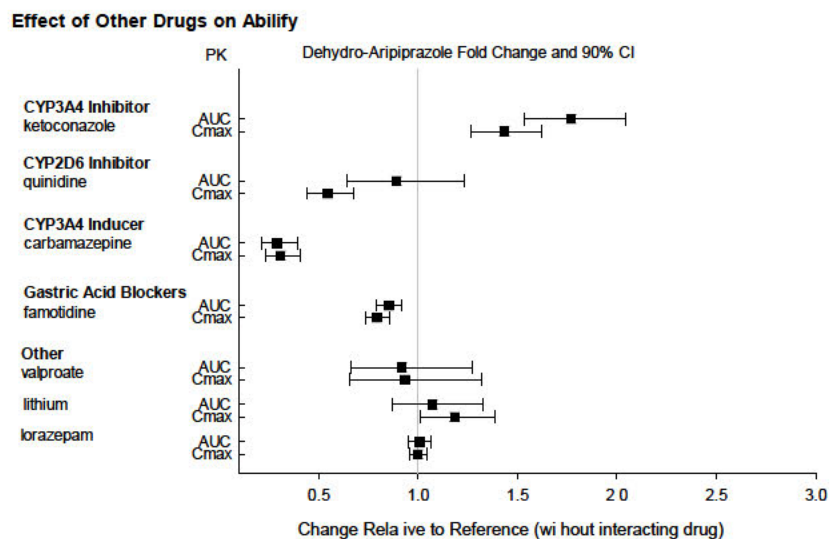
Effects of other drugs on the exposures of aripiprazole and dehydro-aripiprazole are summarized in Figure 19 and Figure 20, respectively. Based on simulation, a 4.5-fold increase in mean C<sub>max</sub> and AUC values at steady-state is expected when extensive metabolizers of CYP2D6 are

administered with both strong CYP2D6 and CYP3A4 inhibitors. After oral administration, a 3-fold increase in mean C<sub>max</sub> and AUC values at steady-state is expected in poor metabolizers of CYP2D6 administered with strong CYP3A4 inhibitors.

**Figure 19: The effects of other drugs on aripiprazole pharmacokinetics**



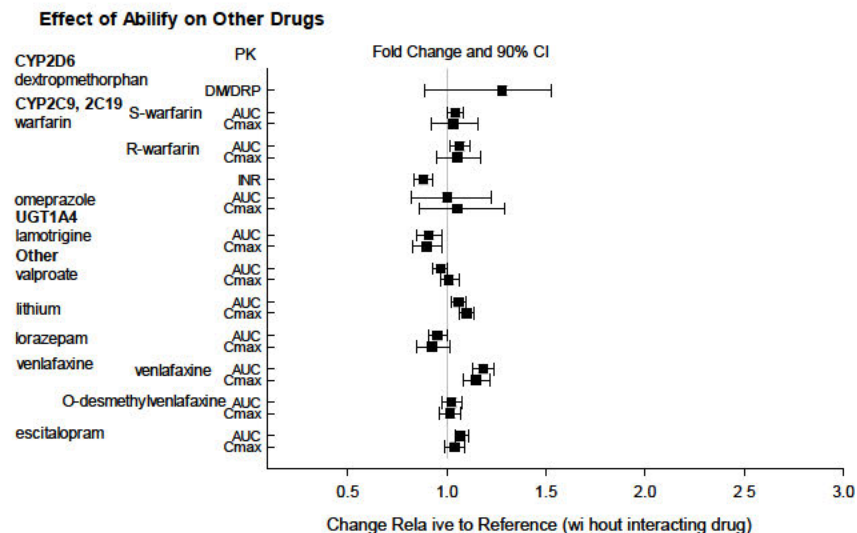
**Figure 20: The effects of other drugs on dehydro-aripiprazole pharmacokinetics**



The effects of ABILIFY on the exposures of other drugs are summarized in Figure 21. A population PK analysis in patients with major depressive disorder showed no substantial change in plasma concentrations of fluoxetine (20 mg/day or 40 mg/day), paroxetine CR (37.5 mg/day or 50 mg/day), or sertraline (100 mg/day 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 21: The effects of oral aripiprazole on pharmacokinetics of other drugs**

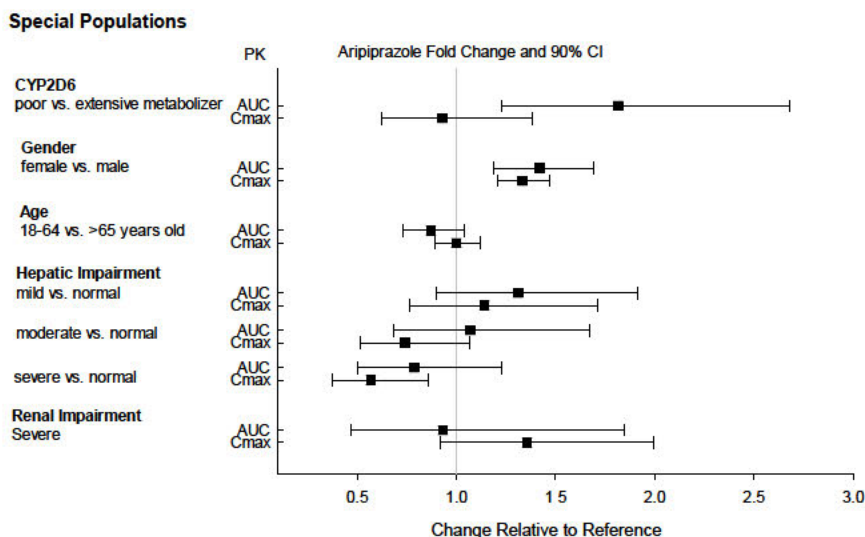


### Studies in Specific Populations

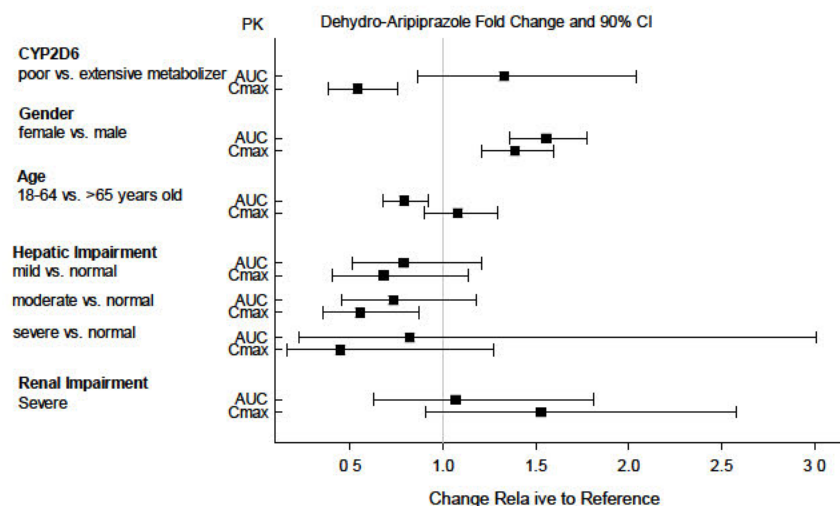
No specific pharmacokinetic studies have been performed with ABILIFY MAINTENA in specific populations. All the information is obtained from studies with oral aripiprazole.

Exposures of aripiprazole and dehydro-aripiprazole in specific populations are summarized in Figure 22 and Figure 23, respectively. In addition, in pediatric patients (10 to 17 years of age) administered with oral aripiprazole (20 mg to 30 mg), the body weight corrected aripiprazole clearance was similar to the adults.

**Figure 22 Effects of intrinsic factors on aripiprazole pharmacokinetics**



**Figure 23: Effects of intrinsic factors on dehydro-aripiprazole pharmacokinetics:**



## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

#### *Carcinogenesis*

Lifetime carcinogenicity studies were conducted in ICR mice, 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<sup>2</sup>, 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<sup>2</sup>). 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<sup>2</sup>). 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<sup>2</sup>); 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<sup>2</sup>).

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

### *Mutagenesis*

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

### *Impairment of Fertility*

Female rats were treated with oral doses of 2, 6, and 20 mg/kg/day (0.6, 2, and 6 times the maximum recommended human dose [MRHD] on a mg/m<sup>2</sup> 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<sup>2</sup> 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

### *Oral Aripiprazole*

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  $\text{mg}/\text{m}^2$  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.

### *Intramuscular Aripiprazole*

The toxicological profile for aripiprazole administered to experimental animals by intramuscular injection is generally similar to that seen following oral administration at comparable plasma levels of the drug. With intramuscular injection, however, injection-site tissue reactions are observed that consist of localized inflammation, swelling, scabbing and foreign-body reactions to deposited drug. These effects gradually resolved with discontinuation of dosing.

After 26 weeks of treatment in rats, the no-observed-adverse-effect level (NOAEL) was 50 mg/kg in male rats and 100 mg/kg in female rats, which are approximately 1 and 2 times, respectively, the maximum recommended human 400 mg dose of aripiprazole extended-release injectable suspension on a  $\text{mg}/\text{m}^2$  body surface area. At the NOAEL in rats, the  $\text{AUC}_{7\text{d}}$  values were  $14.4 \mu\text{g}\cdot\text{h}/\text{mL}$  in males and  $104.1 \mu\text{g}\cdot\text{h}/\text{mL}$  in females. In dogs at 52 weeks of treatment at the NOAEL of 40 mg/kg, which is approximately 3 times the MRHD (400 mg) on a  $\text{mg}/\text{m}^2$  body surface area, the  $\text{AUC}_{7\text{d}}$  values were approximately  $59 \mu\text{g}\cdot\text{h}/\text{mL}$  in males and  $44 \mu\text{g}\cdot\text{h}/\text{mL}$  in females. In patients at the MRHD of 400 mg, the  $\text{AUC}_\tau$  (0-28 days) was  $163 \mu\text{g}\cdot\text{h}/\text{mL}$ . For comparison to this human AUC, extrapolating the animal  $\text{AUC}_{7\text{d}}$  values to an  $\text{AUC}_{28\text{d}}$  results in  $\text{AUC}_{28\text{d}}$  values of approximately 58 and  $416 \mu\text{g}\cdot\text{h}/\text{mL}$  for male and female rats, respectively, and 236 and  $175 \mu\text{g}\cdot\text{h}/\text{mL}$  for male and female dogs, respectively.

## 14 CLINICAL STUDIES

The efficacy of ABILIFY MAINTENA for treatment of schizophrenia was established in:

- One short-term (12-week), randomized, double-blind, placebo-controlled trial in acutely relapsed adults, Protocol 31-12-291 (Study 1)
- One longer-term, double-blind, placebo-controlled, randomized-withdrawal (maintenance) trial in adults, Protocol 31-07-246 (Study 2).

### Short-Term Efficacy

In the short-term (12-week), randomized, double-blind, placebo-controlled trial in acutely relapsed adults (Study 1), the primary measure used for assessing psychiatric signs and symptoms was 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 primary endpoint was the change from baseline in PANSS total score to week 10.

The inclusion criteria for this short-term trial included adult inpatients who met DSM-IV-TR criteria for schizophrenia. In addition, all patients entering the trial must have experienced an acute psychotic episode as defined by both PANSS Total Score  $\geq 80$  and a PANSS score of  $> 4$  on each of four specific psychotic symptoms (conceptual disorganization, hallucinatory behavior, suspiciousness/persecution, unusual thought content) at screening and baseline. The key secondary endpoint was the change from baseline in Clinical Global Impression-Severity (CGI-S) assessment scale to week 10. The CGI-S rates the severity of mental illness on a scale of 1 (normal) to 7 (among the most extremely ill) based on the total clinical experience of the rater in treating patients with schizophrenia. Patients had a mean PANSS total score of 103 (range 82 to 144) and a CGI-S score of 5.2 (markedly ill) at entry.

In this 12-week study (n=339) comparing ABILIFY MAINTENA (n=167) to placebo (n=172), patients were administered 400 mg ABILIFY MAINTENA or placebo on days 0, 28, and 56. The dose could be adjusted down and up within the range of 400 to 300 mg on a one time basis. ABILIFY MAINTENA was superior to placebo in improving the PANSS total score at the end of week 10 (see Table 9).

**Table 9: Schizophrenia Short-term Study**

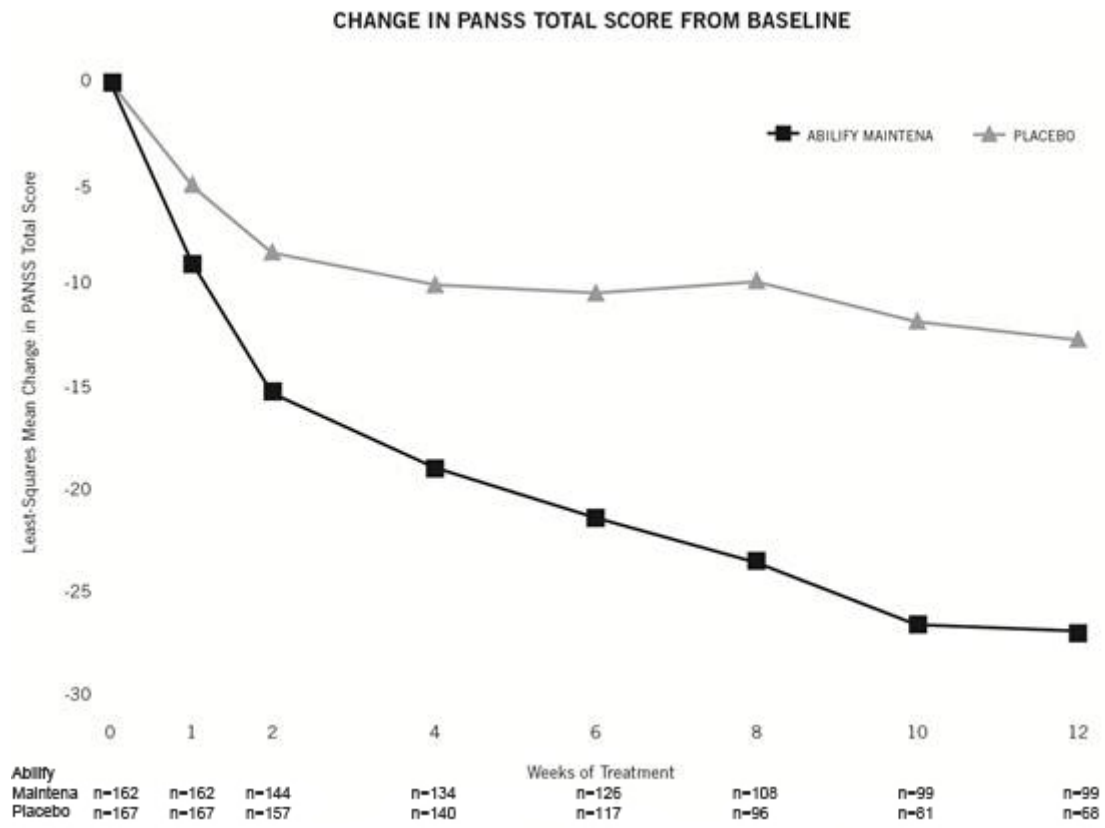
Study Number	Treatment Group	Primary Efficacy Measure: PANSS Total Score		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference <sup>a</sup> (95% CI)
Study 1	ABILIFY MAINTENA (400 to 300 mg)	102.4 (11.4)	-26.8 (1.6)	-15.1 (-19.4, -10.8)
	Placebo	103.4 (11.1)	-11.7 (1.6)	--

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

<sup>a</sup> Difference (drug minus placebo) in least-squares mean change from baseline.

The change in PANSS total score by week is shown in Figure 24. ABILIFY MAINTENA also showed improvement in symptoms represented by CGI-S score mean change from baseline to week 10. The results of exploratory subgroup analyses by gender, race, age, ethnicity, and BMI were similar to the results of the overall population.

**Figure 24: Weekly PANSS Total Score-Change in the 12-Week, Placebo-Controlled Study with ABILIFY MAINTENA**



**n = the number of patients remaining in the respective study arm at each time point**

### *Longer-Term Efficacy*

The efficacy of ABILIFY MAINTENA in maintaining symptomatic control in schizophrenia was established in a double-blind, placebo-controlled, randomized-withdrawal trial in adult patients (Study 2) who met DSM-IV-TR criteria for schizophrenia and who were being treated with at least one antipsychotic medication. Patients had at least a 3-year history of illness and a history of relapse or symptom exacerbation when not receiving antipsychotic treatment.

In addition to the PANSS and CGI-S, clinical ratings during this trial included the:

- Clinical Global Impression-Improvement (CGI-I) scale, a scale of 1 (very much improved) to 7 (very much worse) based on the change from baseline in clinical condition and
- Clinical Global Impression-Severity of Suicide (CGI-SS) scale, which is comprised of 2 parts: Part 1 rates the severity of suicidal thoughts and behavior on a scale of 1 (not at all suicidal) to 5 (attempted suicide) based on the most severe level in the last 7 days from all information available to the rater and Part 2 rates the change from baseline in suicidal thoughts and behavior on a scale of 1 (very much improved) to 7 (very much worse).

This trial included:

- A 4 to 6 week open-label, oral conversion phase for patients on antipsychotic medications other than aripiprazole. A total of 633 patients entered this phase.
- An open-label, oral aripiprazole stabilization phase (target dose of 10 mg to 30 mg once daily). A total of 710 patients entered this phase. Patients were 18 to 60 years old (mean 40 years) and 60% were male. The mean PANSS total score was 66 (range 33 to 124). The mean CGI-S score was 3.5 (mildly to moderately ill). Prior to the next phase, stabilization was required. Stabilization was defined as having all of the following for four consecutive weeks: an outpatient status, PANSS total score  $\leq 80$ , CGI-S  $\leq 4$  (moderately ill), and CGI-SS score  $\leq 2$  (mildly suicidal) on Part 1 and  $\leq 5$  (minimally worsened) on Part 2; and a score of  $\leq 4$  on each of the following PANSS items: conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content.
- A minimum 12-week uncontrolled, single-blind ABILIFY MAINTENA stabilization phase (treatment with 400 mg of ABILIFY MAINTENA given every 4 weeks in conjunction with oral aripiprazole [10 mg to 20 mg/day] for the first 2 weeks). The dose of ABILIFY MAINTENA may have been decreased to 300 mg due to adverse reactions. A total of 576 patients entered this phase. The mean PANSS total score was 59 (range 30 to 80) and the mean CGI-S score was 3.2 (mildly ill). Prior to the next phase, stabilization was required (see above for the definition of stabilization) for 12 consecutive weeks.

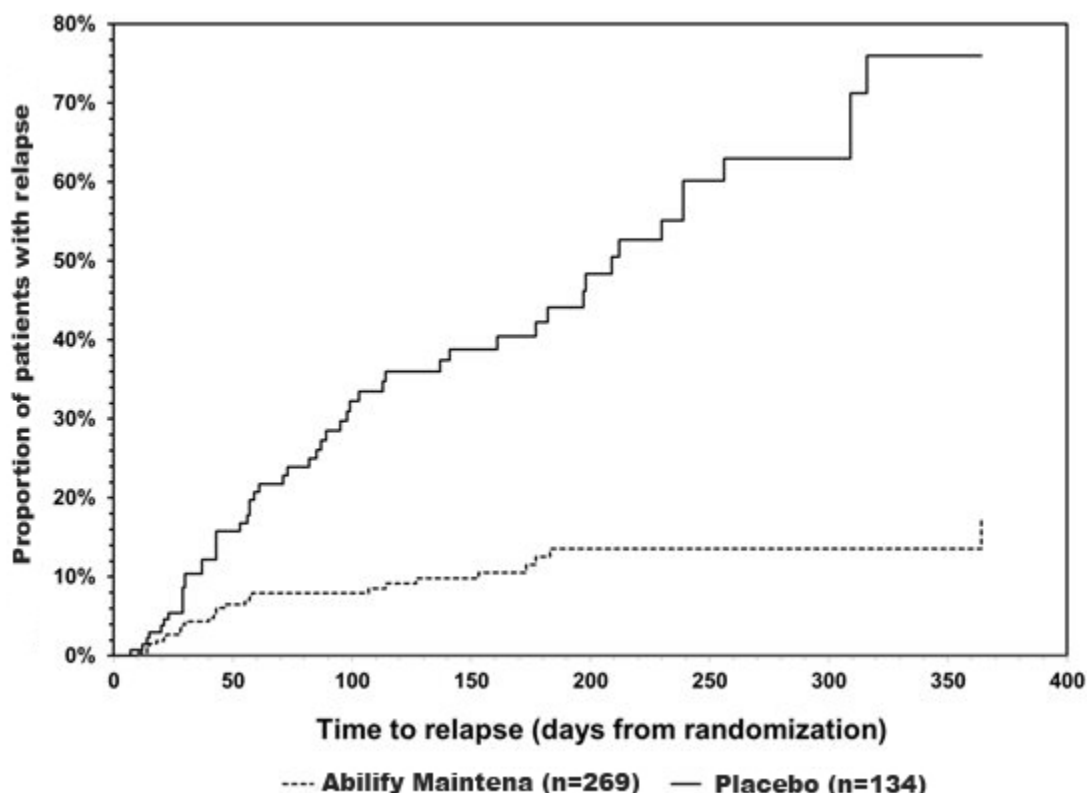
- A double-blind, placebo-controlled randomized-withdrawal phase to observe for relapse (defined below). A total of 403 patients were randomized 2:1 to the same dose of ABILIFY MAINTENA they were receiving at the end of the stabilization phase, (400 mg or 300 mg administered once every 4 weeks) or placebo. Patients had a mean PANSS total score of 55 (range 31 to 80) and a CGI-S score of 2.9 (mildly ill) at entry. The dose could be adjusted up and down or down and up within the range of 300 to 400 mg on a one time basis.

The primary efficacy endpoint was time from randomization to relapse. Relapse was defined as the first occurrence of one or more of the following criteria:

- CGI-I of  $\geq 5$  (minimally worse) and
  1. an increase on any of the following individual PANSS items (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content) to a score  $>4$  with an absolute increase of  $\geq 2$  on that specific item since randomization or
  2. an increase on any of the following individual PANSS items (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content) to a score  $>4$  and an absolute increase  $\geq 4$  on the combined four PANSS items (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content) since randomization
- Hospitalization due to worsening of psychotic symptoms (including partial hospitalization), but excluding hospitalization for psychosocial reasons
- CGI-SS of 4 (severely suicidal) or 5 (attempted suicide) on Part 1 and/or 6 (much worse) or 7 (very much worse) on Part 2, or
- Violent behavior resulting in clinically significant self-injury, injury to another person, or property damage.

A pre-planned interim analysis demonstrated a statistically significantly longer time to relapse in patients randomized to the ABILIFY MAINTENA group compared to placebo-treated patients and the trial was subsequently terminated early because maintenance of efficacy was demonstrated. The final analysis demonstrated a statistically significantly longer time to relapse in patients randomized to the ABILIFY MAINTENA group than compared to placebo-treated patients. The Kaplan-Meier curves of the cumulative proportion of patients with relapse during the double-blind treatment phase for ABILIFY MAINTENA and placebo groups are shown in Figure 25.

**Figure 25: Kaplan-Meier Estimation of Cumulative Proportion of Patients with Relapse<sup>1</sup>**



<sup>1</sup>This figure is based on a total of 80 relapse events

The key secondary efficacy endpoint, percentage of subjects meeting the relapse criteria, was statistically significantly lower in patients randomized to the ABILIFY MAINTENA group (10%) than in the placebo group (40%).

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

### **16.1 How Supplied**

#### **Pre-filled Dual Chamber Syringe:**

ABILIFY MAINTENA (aripiprazole) pre-filled dual chamber syringe for extended-release injectable suspension in single-use syringes is available in 300 mg or 400 mg strength syringes. The pre-filled dual chamber syringe consists of a front chamber that contains the lyophilized powder of aripiprazole monohydrate and a rear chamber that contains sterile water for injection.

The 300 mg kit includes (NDC 59148-045-80):

- 300 mg single-dose pre-filled dual chamber syringe containing ABILIFY MAINTENA (aripiprazole) for extended-release injectable suspension lyophilized powder and Sterile Water for Injection
- One 23 gauge, 1 inch (25 mm) hypodermic safety needle with needle protection device for deltoid administration in non-obese patients
- One 22 gauge, 1.5 inch (38 mm) hypodermic safety needle with needle protection device for gluteal administration in non-obese patients or deltoid administration in obese patients
- One 21 gauge, 2 inch (50 mm) hypodermic safety needle with needle protection device for gluteal administration in obese patients

The 400 mg kit includes (NDC 59148-072-80):

- 400 mg single-dose pre-filled dual chamber syringe containing ABILIFY MAINTENA (aripiprazole) for extended-release injectable suspension lyophilized powder and Sterile Water for Injection
- One 23 gauge, 1 inch (25 mm) hypodermic safety needle with needle protection device for deltoid administration in non-obese patients
- One 22 gauge, 1.5 inch (38 mm) hypodermic safety needle with needle protection device for gluteal administration in non-obese patients or deltoid administration in obese patients
- One 21 gauge, 2 inch (50 mm) hypodermic safety needle with needle protection device for gluteal administration in obese patients

### **Single-Use Vial:**

ABILIFY MAINTENA (aripiprazole) extended-release injectable suspension in single-use vials is available in 300 mg or 400 mg strength vials.

The 300 mg kit includes (NDC 59148-018-71):

- 300 mg single-use vial of ABILIFY MAINTENA (aripiprazole) extended-release injectable suspension lyophilized powder
- 5 mL single-use vial of Sterile Water for Injection, USP
- One 3 mL luer lock syringe with pre-attached 21 gauge, 1.5 inch hypodermic safety needle with needle protection device
- One 3 mL luer lock disposable syringe with luer lock tip
- One vial adapter
- One 23 gauge, 1 inch (25 mm) hypodermic safety needle with needle protection device for deltoid administration in non-obese patients
- One 22 gauge, 1.5 inch (38 mm) hypodermic safety needle with needle protection device for gluteal administration in non-obese patients or deltoid administration in obese patients

- One 21 gauge, 2 inch (50 mm) hypodermic safety needle with needle protection device for gluteal administration in obese patients

The 400 mg kit includes (NDC 59148-019-71):

- 400 mg single-use vial of ABILIFY MAINTENA (aripiprazole) extended-release injectable suspension lyophilized powder
- 5 mL single-use vial of Sterile Water for Injection, USP
- One 3 mL luer lock syringe with pre-attached 21 gauge, 1.5 inch hypodermic safety needle with needle protection device
- One 3 mL luer lock disposable syringe with luer lock tip
- One vial adapter
- One 23 gauge, 1 inch (25 mm) hypodermic safety needle with needle protection device for deltoid administration in non-obese patients
- One 22 gauge, 1.5 inch (38 mm) hypodermic safety needle with needle protection device for gluteal administration in non-obese patients or deltoid administration in obese patients
- One 21 gauge, 2 inch (50 mm) hypodermic safety needle with needle protection device for gluteal administration in obese patients

## 16.2 Storage

### Pre-filled dual chamber syringe:

Store below 30°C [86°F]. Do not freeze. Protect the syringe from light by storing in the original package until time of use.

### Vial:

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

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling ([MEDICATION GUIDE](#))

### 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 \(5.6\)](#)].

### Neuroleptic Malignant Syndrome

Counsel patients about a potentially fatal adverse reaction referred to as NMS that has been reported in association with administration of antipsychotic drugs. Advise patients, family members, or caregivers to contact a health care provider or report to the emergency room if they experience signs and symptoms of NMS [see [WARNINGS AND PRECAUTIONS \(5.3\)](#)].

### **Tardive Dyskinesia**

Advise patients that abnormal involuntary movements have been associated with the administration of antipsychotic drugs. Counsel patients to notify their health care provider if they notice any movements which they cannot control in their face, tongue, or other body part [see [WARNINGS AND PRECAUTIONS \(5.4\)](#)].

### **Metabolic Changes (Hyperglycemia and Diabetes Mellitus, Dyslipidemia, and Weight Gain)**

Educate patients about the risk of metabolic changes, how to recognize symptoms of hyperglycemia and diabetes mellitus, and the need for specific monitoring, including blood glucose, lipids, and weight [see [WARNINGS AND PRECAUTIONS \(5.5\)](#)].

### **Orthostatic Hypotension**

Educate patients about the risk of orthostatic hypotension and syncope especially early in treatment, and also at times of re-initiating treatment or increases in dosage [see [WARNINGS AND PRECAUTIONS \(5.7\)](#)].

### **Leukopenia/Neutropenia**

Advise patients with a pre-existing low WBC count or a history of drug-induced leucopenia/neutropenia that they should have their CBC monitored while receiving ABILIFY MAINTENA [see [WARNINGS AND PRECAUTIONS \(5.8\)](#)].

### **Interference with Cognitive and Motor Performance**

Because ABILIFY MAINTENA may have the potential to impair judgment, thinking, or motor skills, instruct patients to be cautious about operating hazardous machinery, including automobiles, until they are reasonably certain that ABILIFY MAINTENA therapy does not affect them adversely [see [WARNINGS AND PRECAUTIONS \(5.10\)](#)].

### **Heat Exposure and Dehydration**

Advise patients regarding appropriate care in avoiding overheating and dehydration [see [WARNINGS AND PRECAUTIONS \(5.11\)](#)].

### **Concomitant Medication**

Advise patients to inform their health care providers of any changes to their current prescription or over-the-counter medications since there is a potential for clinically significant interactions [see [DRUG INTERACTIONS \(7\)](#)].

### **Pregnancy**

Advise patients that ABILIFY MAINTENA 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 MAINTENA during pregnancy [see [USE IN SPECIFIC POPULATIONS \(8.1\)](#)].

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## MEDICATION GUIDE

ABILIFY MAINTENA® (a-BIL-i-fy main-TEN-a)  
(aripiprazole) for extended-release injectable suspension, for intramuscular use

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

Each injection of ABILIFY MAINTENA must be administered by a healthcare professional only.

#### **ABILIFY MAINTENA may cause serious side effects, including:**

- **Increased risk of death in elderly people with dementia-related psychosis.** ABILIFY MAINTENA is not for the treatment of people who have lost touch with reality (psychosis) due to confusion and memory loss (dementia).
- **Neuroleptic malignant syndrome (NMS) a serious condition that can lead to death.** Tell your healthcare provider right away if you have some or all of the following symptoms of NMS:
  - high fever
  - confusion
  - changes in pulse, heart rate, and blood pressure
  - stiff muscles
  - sweating

**Call your healthcare provider or go to the nearest emergency room right away if you have any of these symptoms.**

### What is ABILIFY MAINTENA?

ABILIFY MAINTENA is a prescription medicine given by injection by a healthcare professional and used to treat schizophrenia.

It is not known if ABILIFY MAINTENA is safe and effective in children under 18 years of age.

**Do not receive ABILIFY MAINTENA if you** are allergic to aripiprazole or any of the ingredients in ABILIFY MAINTENA. See the end of this leaflet for a complete list of ingredients in ABILIFY MAINTENA.

#### **Before receiving ABILIFY MAINTENA, tell your healthcare provider** about all your medical conditions, including if you:

- have never taken ABILIFY (aripiprazole) before
- have diabetes or high blood sugar or a family history of diabetes or high blood sugar. Your healthcare provider should check your blood sugar before you start receiving ABILIFY MAINTENA and during your treatment.
- have or had seizures (convulsions)
- have or had low or high blood pressure
- have or had heart problems or a stroke
- have or had a low white blood cell count
- have any other medical problems including problems that may affect you receiving an injection in your arm or buttocks
- are pregnant or plan to become pregnant. It is not known if ABILIFY MAINTENA will harm your unborn baby.
- If you become pregnant while taking ABILIFY MAINTENA, 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 visit <http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/>
- are breastfeeding or plan to breastfeed. ABILIFY MAINTENA can pass into your milk and may harm your baby. Talk to your healthcare provider about the best way to feed your baby if you receive ABILIFY MAINTENA.

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

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

Your healthcare provider can tell you if it is safe to take ABILIFY MAINTENA with your other medicines. Do not start or stop any medicines while taking ABILIFY MAINTENA without talking to your healthcare provider first. Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

### How should I receive ABILIFY MAINTENA?

- Follow your ABILIFY MAINTENA treatment schedule exactly as your healthcare provider tells you to.
- ABILIFY MAINTENA is an injection given in your arm or buttock by your healthcare provider 1 time every month. You may feel a little pain in your arm or buttock during your injection.
- After your first injection of ABILIFY MAINTENA you should continue your current antipsychotic medicine for 2 weeks.
- You should not miss a dose of ABILIFY MAINTENA. If you miss a dose for some reason, call your healthcare provider right away to discuss what you should do next.

### What should I avoid while taking ABILIFY MAINTENA?

- Do not drive, operate machinery, or do other dangerous activities until you know how ABILIFY MAINTENA affects you. ABILIFY MAINTENA may make you feel drowsy.
- Do not drink alcohol while you receive ABILIFY MAINTENA.
- Do not become too hot or dehydrated while you receive ABILIFY MAINTENA.
  - 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 MAINTENA?

**ABILIFY MAINTENA may cause serious side effects, including:**

- **See "What is the most important information I should know about ABILIFY MAINTENA?"**
- **Uncontrolled body movements (tardive dyskinesia).** ABILIFY MAINTENA may cause movements that you cannot control in your face, tongue, or other body parts. Tardive dyskinesia may not go away, even if you stop receiving ABILIFY MAINTENA. Tardive dyskinesia may also start after you stop receiving ABILIFY MAINTENA.
- **Problems with your metabolism such as:**
  - **High blood sugar (hyperglycemia):** Increases in blood sugar can happen in some people who take ABILIFY MAINTENA. 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 receiving ABILIFY MAINTENA and during your treatment.

**Call your healthcare provider if you have any of these symptoms of high blood sugar while receiving ABILIFY MAINTENA:**

- 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 MAINTENA 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.
- **Low white blood cell count**
- **Seizures (convulsions)**
- **Problems controlling your body temperature so that you feel too warm. See "What should I avoid while receiving ABILIFY MAINTENA?"**
- **Difficulty swallowing**

**The most common side effect of ABILIFY MAINTENA includes** feeling like you need to move to stop unpleasant feelings in your legs (restless leg syndrome or akathisia), injection site pain, or sleepiness (sedation).

Tell your healthcare provider if you have any side effect that bothers you or does not go away.

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

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

### General information about the safe and effective use of ABILIFY MAINTENA.

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

### What are the ingredients in ABILIFY MAINTENA?

**Active ingredient:** aripiprazole monohydrate

**Inactive ingredients:** carboxymethyl cellulose sodium, mannitol, sodium phosphate monobasic monohydrate and sodium hydroxide

ABILIFY MAINTENA is a trademark of Otsuka Pharmaceutical Company.

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For more information, [www.ABILIFYMAINTENA.com](http://www.ABILIFYMAINTENA.com) or call 1-800-441-6763.

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**021436Orig1s041**

**OTHER REVIEW(S)**

# REGULATORY PROJECT MANAGER LABELING REVIEW

Date: July 26, 2016

DRUG/NDA: Abilify (aripiprazole) 2 mg, 5 mg, 10 mg, 15mg, 20mg, 30 mg tablets (NDA 021436)

Abilify (aripiprazole) 1 mg/mL oral solution (NDA 021713)

Abilify (aripiprazole) 10 mg and 15 mg orally disintegrating tablets (NDA 021729)

Abilify (aripiprazole) 9.75 mg/1.3 mL injection for IM use (NDA 021866)

Abilify Maintena (aripiprazole) 300 mg/vial and 400 mg/vial extended-release injectable suspension for intramuscular injection (NDA 202971)

Sponsor: Otsuka Pharmaceutical Co Ltd

C/O Otsuka Pharmaceutical Development and Communications Inc.

Indication: NDAs 021436, 021713, 021729, and 021866: Schizophrenia, acute treatment of manic and mixed episodes associated with Bipolar I, treatment of irritability associated with autistic disorder in pediatric patients (aged 6-17 years), Maintenance adjunctive treatment of Bipolar I disorder with lithium or valproate, Tourette's disorder. Injection form (NDA 021866) is indicated for agitation associated with schizophrenia or bipolar mania.  
NDA 202971: Treatment of schizophrenia

Supplements under review:

NDA	Supplement	Dated	Provides for	Status
<b>Abilify (aripiprazole) Tablets (NDA 021436)</b>				
021436	S-040	1/8/16	Add pathological gambling and hiccups to 6.2 Postmarketing Experience	Approved on 1/15/16
021436	S-041	5/31/16	Adding Pathological Gambling and Impulse-control Problems under Warnings and Precaution as requested in 5/3/16 SLC letter	Pending
<b>Abilify (aripiprazole) Oral Solution (NDA 021713)</b>				
021713	S-031	1/8/16	Add pathological gambling and hiccups to 6.2 Postmarketing Experience	Approved on 1/15/16
021713	S-032	5/31/16	Adding Pathological Gambling and Impulse-control Problems under Warnings and Precaution as requested in 5/3/16 SLC letter	Pending
<b>Abilify (aripiprazole) ODT (NDA 021729)</b>				
021729	S-023	1/8/16	Add pathological gambling and hiccups to 6.2 Postmarketing Experience	Approved on 1/15/16

021729	S-024	5/31/16	Adding Pathological Gambling and Impulse-control Problems under Warnings and Precaution as requested in 5/3/16 SLC letter	Pending
<b>Abilify (aripiprazole) Injection for IM (NDA 021866)</b>				
021866	S-025	1/8/16	Add pathological gambling and hiccups to 6.2 Postmarketing Experience	Approved on 1/15/16
021866	S-026	5/31/16	Adding Pathological Gambling and Impulse-control Problems under Warnings and Precaution as requested in 5/3/16 SLC letter	Pending
<b>Abilify (aripiprazole) Extended-release injectable suspension for IM (NDA 202971)</b>				
202971	S-008	1/8/16	Add pathological gambling and hiccups to 6.2 Postmarketing Experience	Approved on 1/15/16
202971	S-009	5/31/16	Adding Pathological Gambling and Impulse-control Problems under Warnings and Precaution as requested in 5/3/16 SLC letter	Pending

**NOTES**

- The last approved labeling, for comparison purposes, was the labeling attached to the 1/15/16 approval letter for NDAs 021436/S-040, 021713/S-031, 021729/s-023, 021866/s-025, and 202971/S-008.
- The Agency issued a Section 901 Safety Labeling Change letter dated 5/3/16, requiring labeling revisions to address the risk of Pathological Gambling and Impulse-Control Problems and add this information under Warnings and Precautions immediately following the subsection titled “Metabolic Changes:”
- The Sponsor responded with revisions to the Agency’s requested language. They also proposed revisions to the Highlights, Patient Counseling Information section (17), and Medication Guide. Given these changes, the Agency issued an Extension Letter dated 6/22/16, informing the sponsor of the revised discussion period ending on August 4, 2016.
- Sponsor specifically proposed to replace the terms “uncontrolled spending” and “uncontrolled sexual urges” by more specific terms, “compulsive shopping” and “compulsive sexual urges”, to which the Agency agreed.
- NDAs 021436, 021713, 021729 and 021866 share the same labeling. 202971 for Abilify Maintena has separate labeling.
- There was TSI opened for this SLC. The TSI number is 001645.

## **REVIEW**

**021436/S-041**  
**021713/S-032**  
**021729/S-024**  
**021866/S-026**  
**202971/S-009**

**Date: 5/3/16**

**PAS: Yes**

**Reviewed by Medical Officer: No formal review. Labeling input from the safety team completed via e-mail.**

These PAS labeling supplements provide for the following revisions to labeling:

1. Administrative and editorial changes throughout labeling.
2. Add "Pathological Gambling and Other Compulsive Behaviors" under Recent Major Changes in the Highlights section and corresponding sections in PI (section 5.7).
3. Add corollary changes to the Patient Counseling Information section (17)
4. Medication Guide was also revised to reduce redundancy to make patient information more consistent and concise.

## **DISCUSSION**

1. Given the sponsor's added revisions to the Medication Guide, the Patient Labeling Team (PLT) was consulted. In addition to content, PLT made significant revisions to the format in their review of patient labeling. In lieu of attaching annotated Medication Guide, a marked-up version with PLT's comment is attached, the Sponsor agreed to all of the revisions.
2. The sponsor agreed, with minor revisions, to the Agency's labeling counterproposal in an e-mail dated 7/13/16 and 7/25/16. These minor revisions were found to be acceptable to the review team

## **CONCLUSIONS**

1. A side by side review found no changes other than those specified above when compared to the last approved labeling.
2. The sponsor has agreed to the revisions proposed by the Agency and submitted labeling changes with minor language proposal which was also accepted by the Agency. Therefore, I recommend that this review, alone, be sufficient to take a regulatory action.
3. I recommend that an approval letter issue for these 5 pending supplemental applications.

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*{See appended electronic signature page}*

Danbi Lee, Pharm.D., Regulatory Project Manager

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*{See appended electronic signature page}*

Paul David, R.Ph., CPMS

Enclosure:

1. Labeling agreement e-mail dated 7/13 and 7/25/16 from Sponsor
2. Annotated labeling changes – Full Prescribing Information and Medication Guide

**Lee, Danbi**

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**From:** Cahill, Dana <Dana.Cahill@otsuka-us.com>  
**Sent:** Monday, July 25, 2016 2:57 PM  
**To:** Lee, Danbi  
**Cc:** David, Paul A; Hardeman, Steven D; Patel, Hiren; Tran, Mariana; Cahill, Dana; TC-Jiang, Julia  
**Subject:** RE: Labeling Supplements for NDAs 021436, 021713, 021729, 021866, and 202971  
**Attachments:** aripiprazole (Abilify Maintena) 202971 009 DMPP MG JUL 2016 clean.docx; aripiprazole (Abilify Maintena) 202971 009 DMPP MG JUL 2016 marked.docx; aripiprazole (Abilify Maintena) 202971 009 DMPP MG JUL 2016 marked.pdf; aripiprazole (Abilify Maintena) 202971 009 DMPP MG JUL 2016 clean.pdf

Dear Danbi,

We have reviewed and accepted all proposed changes to the Medication Guide (MG) for NDA 202971, Abilify Maintena. Clean and marked versions are attached.

Let me know if a formal submission of the updated MG to NDA 202971 via ESG is required. Otherwise, I plan to submit the complete USPI/MG for Maintena and Abilify once we receive FDA comments from our 14 Jul 2016 submission.

Kindest regards,  
Dana

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**From:** Lee, Danbi [<mailto:Danbi.Lee@fda.hhs.gov>]  
**Sent:** Friday, July 22, 2016 10:09 AM  
**To:** Cahill, Dana  
**Cc:** David, Paul A; Hardeman, Steven D; Patel, Hiren; Tran, Mariana  
**Subject:** RE: Labeling Supplements for NDAs 021436, 021713, 021729, 021866, and 202971

Good morning Dr. Cahill,  
Attached is an updated Medication Guide (MG) for NDA 202971, Abilify Maintena. Your July 14, 2016 submission of the Abilify Maintena's MG was not submitted in table format. We, with input from Division of Medical Policy Program (DMPP), are sending you the updated version to be used as base document for comments or changes. Other than the table format, the revisions made by the Agency are very similar if not the same as the MG for other Abilify applications. Please respond by COB, Monday, July 25, 2016.

Thank you,  
Danbi

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**From:** Cahill, Dana [<mailto:Dana.Cahill@otsuka-us.com>]  
**Sent:** Wednesday, July 13, 2016 11:14 PM  
**To:** Lee, Danbi  
**Cc:** David, Paul A; Hardeman, Steven D; Patel, Hiren; Cahill, Dana; Tran, Mariana  
**Subject:** RE: Labeling Supplements for NDAs 021436, 021713, 021729, 021866, and 202971

Dear Danbi,

Enclosed please find Otsuka's response to the agencies proposed labeling changes from 07July2016 for NDAs 021436, 021713, 021729, 021866, and 202971.

We have accepted the FDA text with minor revisions. Briefly:

- Sponsor accepts the term “other compulsive behaviors” and proposes to revise headings throughout label with FDA’s proposed text for consistency
- Replace the terms “uncontrolled spending” and “uncontrolled sexual urges” with the more specific terms, “compulsive shopping” and “compulsive sexual urges”
- Our proposed revisions are also reflected in the Patient Counseling Information sections, as well as in the Medication Guide

As instructed, all labeling changes are shown using the Abilify label document received on Jul 7 as the base document. For ease of review, all comments and responses relevant to the July 7, 2016 communication have been highlighted in yellow. In addition, the Medication Guide has been incorporated back into the PI.

A formal submission will be made to all NDAs via ESG by COB July 15, 2016.

Kindest regards,  
Dana

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**From:** Lee, Danbi [<mailto:Danbi.Lee@fda.hhs.gov>]

**Sent:** Thursday, July 07, 2016 8:43 AM

**To:** Cahill, Dana

**Cc:** David, Paul A; Hardeman, Steven D; Patel, Hiren; Lee, Danbi

**Subject:** Labeling Supplements for NDAs 021436, 021713, 021729, 021866, and 202971

Dr. Cahill,

Reference is made to labeling supplements submitted on May 31, 2016 for NDAs 021436, 021713, 021729, 021866, and 202971.

Here are our revisions to your proposed labeling changes. Use these documents as the base documents for any further comments or changes. Please note that Med Guide is included as a separate document but needs to be incorporated into your PI submission.

Please respond by COB Friday, July 15, 2016.

Thank you,  
Danbi

148 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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DANBI LEE  
07/29/2016

PAUL A DAVID  
07/29/2016

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy Initiatives  
Division of Medical Policy Programs**

**PATIENT LABELING REVIEW**

Date: June 16, 2016

To: Mitchell Mathis, MD  
Director  
**Division of Psychiatry Products (DPP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

Marcia Williams, PhD  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Shawna Hutchins, MPH, BSN, RN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

Subject: Focused Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): ABILIFY (aripiprazole)

Dosage Form and Route: 

- Tablets
- Oral Solution
- DISCMELT
- Injection, for intramuscular use
- For extended-release injectable suspension, for intramuscular use

Application Type/Number: NDA:

- 021436 S-041
- 021713
- 021729
- 021866
- 202971

Applicant: Otsuka

## **1 INTRODUCTION**

On May 31, 2016, Otsuka submitted for the Agency's review revised labeling for Abilify (aripiprazole) in response to a Safety Labeling Change Notification Letter issued by the Agency on May 03, 2016, pertaining to adverse event reports of impulse-control problems including compulsive gambling, binge or compulsive eating and increased sexual urges.

This focused review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Psychiatry Products (DPP) on June 14, 2016, for DMPP to provide a focused review of the Applicant's proposed Medication Guide (MG) for Abilify (aripiprazole).

## **2 MATERIAL REVIEWED**

- Draft Abilify (aripiprazole) MG received on May 31, 2016, and received by DMPP on June 14, 2016.
- Draft Abilify (aripiprazole) Prescribing Information (PI) received on May 31, 2016, revised by the Review Division throughout the review cycle, and received by DMPP on June 14, 2016.

## **3 REVIEW METHODS**

In our focused review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)

## **4 CONCLUSIONS**

The MG is acceptable with our recommended changes.

## **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Consult DMPP during the next review cycle for a comprehensive review of the Patient Labeling to bring it up to current Patient Labeling standards.
- Our focused review of the MG is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/  
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SHAWNA L HUTCHINS  
06/16/2016

MARCIA B WILLIAMS  
06/16/2016

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**021436Orig1s041**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**



NDA 021436  
NDA 021713  
NDA 021729  
NDA 021866  
NDA 202971

## **LABELING DISCUSSION EXTENSION**

OTSUKA PHARMACEUTICAL CO LTD  
C/O OTSUKA PHARMACEUTICAL DEVELOPMENT AND COMMUNICATIONS INC  
Attention: Dana Cahill, PhD  
Associate Director, Global Regulatory Affairs  
2440 Research Blvd.  
Rockville, MD 20850

Dear Dr. Cahill:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Abilify (aripiprazole) 2, 5, 10, 15, 20, 30 mg tablets (NDA 21436); Abilify (aripiprazole) 1mg/mL oral solution (NDA 21713); Abilify (aripiprazole) 10 and 15 mg Orally Disintegrating Tablets (NDA 21729); Abilify (aripiprazole) 9.75 mg/1.3 mL injection for IM use (NDA 21866); and Abilify Maintena (aripiprazole) for extended-release injectable suspension, for intramuscular injection 300 mg/vial and 400 mg/vial (NDA 202971).

On May 3, 2016, we sent a letter invoking our authority under section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (FDCA) to require safety related label changes to the labeling of aripiprazole to address the risk of Pathological Gambling and Impulse-Control Problems, based on new safety information about this risk identified since the product was approved. You were directed to submit a supplement proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a statement detailing the reasons why such a change is not warranted.

On May 31, 2016, we received your prior approval supplement containing your proposed safety related labeling changes, including changes to the Medication Guide. Section 505(o) requires FDA to promptly review the supplement/rebuttal statement and, if we disagree with the proposed changes/reasons why the required labeling changes are not warranted, to initiate discussions with you. These discussions were to be completed within 30 days, unless FDA determined that an extension was warranted.

NDA 021436  
NDA 021713  
NDA 021729  
NDA 021866  
NDA 202971  
Page 2

This letter is to inform you that we have determined that an additional 60-day extension of the discussion period is warranted to allow us to complete our review and reach agreement on the content of the labeling/reasons why the required labeling changes are not warranted. Therefore, the discussion period for this supplement/rebuttal statement ends on August 4, 2016.

If you have any questions, call Sharon Sagoo, Regulatory Project Manager, at (301) 796-0431.

Sincerely,

*{See appended electronic signature page}*

Marc Stone, M.D.  
Deputy Director for Safety (Acting)  
Division of Psychiatry Products  
Center for Drug Evaluation and Research

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/s/  
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MARC B STONE  
06/22/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR PATIENT LABELING REVIEW CONSULTATION</b>				
TO:  <b>CDER-DMPP-PatientLabelingTeam</b>		FROM: (Name/Title, Office/Division/Phone number of requestor) Ermias Zerislassie, Safety Regulatory Project Manager, DPP (301)796-2770 Ermias.Zerislassie@fda.hhs.gov				
REQUEST DATE: 6/14/16	NDA/BLA NO.: NDA 21436	TYPE OF DOCUMENTS: Med Guide				
NAME OF DRUG: Abilify (aripiprazole)	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG: Antipsychotic	DESIRED COMPLETION DATE June 28, 2016			
SPONSOR: Otsuka						
<b>TYPE OF LABEL TO REVIEW</b>						
<table style="width: 100%; border: none;"> <tr> <td style="width: 33%; vertical-align: top;"> <b>TYPE OF LABELING:</b>            (Check all that apply)  <input checked="" type="checkbox"/> PATIENT PACKAGE INSERT (PPI)  <input checked="" type="checkbox"/> MEDICATION GUIDE            INSTRUCTIONS FOR USE(IFU)         </td> <td style="width: 33%; vertical-align: top;"> <b>TYPE OF APPLICATION/SUBMISSION</b>  <input type="checkbox"/> ORIGINAL NDA/BLA  <input type="checkbox"/> EFFICACY SUPPLEMENT  <input checked="" type="checkbox"/> SAFETY SUPPLEMENT  <input type="checkbox"/> LABELING SUPPLEMENT  <input type="checkbox"/> MANUFACTURING (CMC) SUPPLEMENT  <input type="checkbox"/> PLR CONVERSION         </td> <td style="width: 34%; vertical-align: top;"> <b>REASON FOR LABELING CONSULT</b>  <input type="checkbox"/> INITIAL PROPOSED LABELING  <input checked="" type="checkbox"/> LABELING REVISION         </td> </tr> </table>				<b>TYPE OF LABELING:</b> (Check all that apply) <input checked="" type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> MEDICATION GUIDE INSTRUCTIONS FOR USE(IFU)	<b>TYPE OF APPLICATION/SUBMISSION</b> <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> EFFICACY SUPPLEMENT <input checked="" type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> MANUFACTURING (CMC) SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	<b>REASON FOR LABELING CONSULT</b> <input type="checkbox"/> INITIAL PROPOSED LABELING <input checked="" type="checkbox"/> LABELING REVISION
<b>TYPE OF LABELING:</b> (Check all that apply) <input checked="" type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> MEDICATION GUIDE INSTRUCTIONS FOR USE(IFU)	<b>TYPE OF APPLICATION/SUBMISSION</b> <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> EFFICACY SUPPLEMENT <input checked="" type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> MANUFACTURING (CMC) SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	<b>REASON FOR LABELING CONSULT</b> <input type="checkbox"/> INITIAL PROPOSED LABELING <input checked="" type="checkbox"/> LABELING REVISION				
<b>EDR link to submission:</b> <a href="..\Desktop\abilifydraft-labeling-text-marked-pas-may2016.doc">..\Desktop\abilifydraft-labeling-text-marked-pas-may2016.doc</a>						
<b>Paste EDR link to relevant documents</b>						
<b>Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.</b>						
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b> DPP requests review of the proposed Med Guide (word document above). Sponsor was told to make changes in SLC to include the language below:						
<p>The addition of the following language under Warnings and Precautions: Pathological Gambling and (b) (4)</p> <p>Post-marketing case reports suggest that patients can experience intense urges, particularly for gambling, and the inability to control these urges while taking aripiprazole. Other urges, reported less frequently (b) (4), include: (b) (4) sexual urges (b) (4) (b) (4), binge (b) (4) eating, and other (b) (4) compulsive (b) (4) (b) (4). 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 increased gambling urges, (b) (4) sexual urges, (b) (4) binge or compulsive eating, or other urges while being treated with aripiprazole. (b) (4) (b) (4) urges may result in harm to the patient and to others. Consider dose reduction or stopping the medication if a patient develops such urges (b) (4)</p> <p>In addition, add the following language to the Patient Counseling Information:</p> <p>(b) (4) (b) (4) patients and their caregivers to the possibility that they may experience (b) (4) urges to gamble, (b) (4) sexual urges, binge eating and/or other (b) (4) urges and the inability to control these urges while taking aripiprazole.</p>						

The Medication Guides for the drug products were also revised to be consistent with the proposed package insert.

Please let me know if you have any questions

SIGNATURE OF REQUESTER  
Ermias Zerislassie

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)

☒ eMAIL

(BLAs Only)

☐

DARRTS

Version: 12/9/2011

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/s/  
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ERMIAS ZERISLASSIE

06/14/2016