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) 09/2014

----------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 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)
- Dosage adjustments for patients who are CYP2D6 poor metabolizers and for patients taking CYP2D6 inhibitors, CYP3A4 inhibitors, or CYP3A4 inducers for greater than 14 days (2.3):

	Adjusted Dose
CYP2D6 Poor Metabolizers	
CYP2D6 Poor Metabolizers	300 mg
CYP2D6 Poor Metabolizers taking concomitant CYP3A4 inhibitors	200 mg*
Patients Taking 400 mg of ABILIFY MAINTENA	
Strong CYP2D6 **or** CYP3A4 inhibitors	300 mg
CYP2D6 **and** CYP3A4 inhibitors	200 mg*
CYP3A4 inducers	Avoid use
Patients Taking 300 mg of ABILIFY MAINTENA	
Strong CYP2D6 **or** CYP3A4 inhibitors	200 mg*
CYP2D6 **and** CYP3A4 inhibitors	160 mg*
CYP3A4 inducers	Avoid use

*200 mg and 160 mg dose 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).

----------DOSAGE FORMS AND STRENGTHS----------
- *For extended-release injectable suspension in single-use pre-filled dual chamber syringe*: 400 mg/syringe and 300 mg/syringe of lyophilized powder for reconstitution (3)
- *For extended-release injectable suspension in single-use vials*: 400 mg/vial and 300 mg/vial of lyophilized powder for reconstitution (3)

----------CONTRAINDICATIONS----------
Known hypersensitivity to aripiprazole (4)

----------WARNINGS/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)
- *Orthostatic Hypotension:* Use with caution in patients with known cardiovascular or cerebrovascular disease (5.6)
- *Leukopenia, Neutropenia, and Agranulocytosis:* Perform complete blood counts in patients with a history of a clinically significant low white blood cell count (WBC). Consider discontinuation if clinically significant decline in WBC in the absence of other causative factors (5.7)
- *Seizures:* Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold (5.8)
- *Potential for Cognitive and Motor Impairment:* Use caution when operating machinery (5.9)

----------ADVERSE REACTIONS----------
Most commonly observed adverse reaction with oral aripiprazole (incidence ≥5% and at least twice that for placebo) was akathisia (6.1)

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

----------USE IN SPECIFIC POPULATIONS----------
- *Pregnancy:* Based on animal data, may cause fetal harm (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

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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. Efficacy was demonstrated in a placebo-controlled, randomized-withdrawal maintenance trial in patients with schizophrenia and additional support for efficacy was derived from oral aripiprazole trials *[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. For patients who have never taken aripiprazole, establish tolerability with oral aripiprazole prior to initiating treatment with ABILIFY MAINTENA. The recommended starting and maintenance dose of ABILIFY MAINTENA is 400 mg monthly (no sooner than 26 days after the previous injection).

After the first ABILIFY MAINTENA injection, continue treatment with oral aripiprazole (10 mg to 20 mg) or other oral 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**.**

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- **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 CYP450 Interactions

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 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 CYP2D6 Poor Metabolizers and Patients Taking Concomitant CYP2D6 Inhibitors, 3A4 Inhibitors, and/or CYP3A4 Inducers for Greater than 14 days

	Adjusted Dose
CYP2D6 Poor Metabolizers	
CYP2D6 Poor Metabolizers	300 mg
CYP2D6 Poor Metabolizers taking concomitant CYP3A4 inhibitors	200 mg*
Patients Taking 400 mg of ABILIFY MAINTENA	
Strong CYP2D6 **or** CYP3A4 inhibitors	300 mg
CYP2D6 **and** CYP3A4 inhibitors	200 mg*

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CYP3A4 inducers	Avoid use
Patients Taking 300 mg of ABILIFY MAINTENA	
Strong CYP2D6 **or** CYP3A4 inhibitors	200 mg*
CYP2D6 **and** CYP3A4 inhibitors	160 mg*
CYP3A4 inducers	Avoid use

*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 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:

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

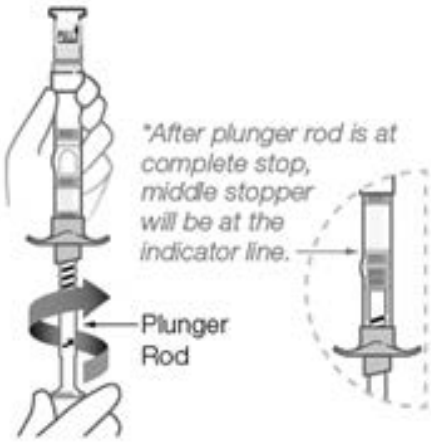

Figure 1

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

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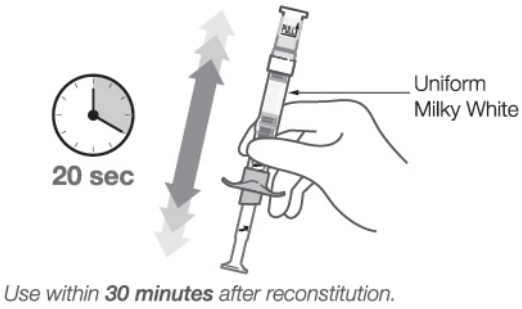

Figure 2

(c) Visually inspect the syringe for particulate matter and discoloration prior to administration. The reconstituted product 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. Do not administer intravenously or subcutaneously.

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

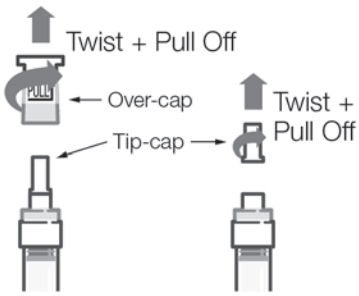

Figure 3

(b) Select appropriate needle (See Figure 4).

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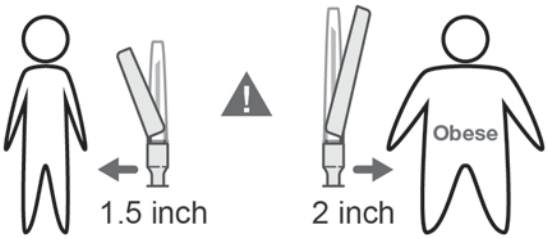

Figure 4

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

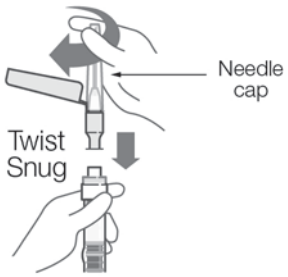

Figure 5

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

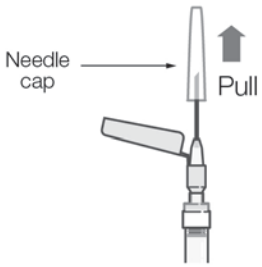

Figure 6

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(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 plunder rod is rotated to a complete stop (See Figure 7).

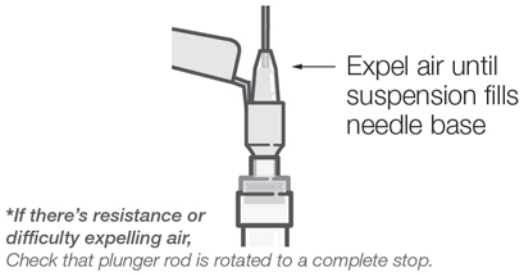

Figure 7

(f) **Inject slowly** into **the gluteal muscle.** Do **not** massage the injection site. Do not administer intravenously or subcutaneously

Disposal Procedure

(a) Engage the needle safety device as described in Section 2.5, Step (d) of Reconstitution of the Lyophilized Powder and safely discard all kit components (See Figure 8). **ABILIFY MAINTENA pre-filled dual chamber syringe is for single-use only.**

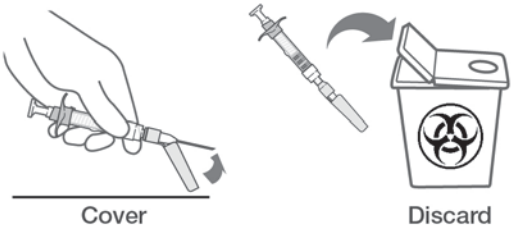

Figure 8

(b) Rotate sites of injections between the two gluteal muscles.

2.6 Vial: Preparation and Administration Instructions

Preparation Prior to Reconstitution

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For deep intramuscular gluteal 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 21 gauge, 1.5 inch (38 mm) hypodermic safety needle with needle protection device for non-obese patients
- One 21 gauge, 2 inch (50 mm) hypodermic safety needle with needle protection device for 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

400 mg Vial		**300 mg Vial**	
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.

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Reconstitution of Lyophilized Powder in Vial

(a) 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.

(b) 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

(c) 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.

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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.

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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	---	---

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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). <u>A small amount of excess product will remain in the vial.</u>

Figure 17

Injection Procedure

(a) Detach the luer lock syringe containing the recommended volume of reconstituted ABILIFY MAINTENA suspension from the vial.

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(b) Select one of the following hypodermic safety needles and attach the needle to the luer lock syringe containing the suspension for injection. While holding the needle, 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).

- 21 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 gluteal muscle. Do not massage the injection site. Do not administer intravenously or subcutaneously.

Disposal Procedure

(a) Engage the needle safety device as described in Section 2.5, Step (d) of Reconstitution of the Lyophilized Powder. 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 gluteal muscles.

3 DOSAGE FORMS AND STRENGTHS

- ***Pre-filled dual chamber syringe*** *with lyophilized powder for intramuscular gluteal injection for extended-release injectable suspension:* 300 mg and 400 mg in a single-use pre-filled dual chamber syringe.

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- ***Vials*** *with lyophilized powder for intramuscular gluteal injection for extended-release injectable suspension:* 300 mg and 400 mg in a single-use 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 (6.2)]*.

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-

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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

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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. Although the following metabolic data were collected in patients treated with oral formulations of aripiprazole, the findings pertain to patients receiving ABILIFY MAINTENA as well.

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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. Because aripiprazole was not marketed at the time these studies were performed, it is not known if aripiprazole is associated with this increased risk. Precise risk estimates for hyperglycemia-related adverse 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 atypical antipsychotic drug.

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

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

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

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

Dyslipidemia

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

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

Table 5 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 5: Changes in Blood Lipid Parameters From Placebo-Controlled Monotherapy Trials in Adults

	Treatment Arm	n/N	%
Total Cholesterol Normal to High (<200 mg/dL to ≥240 mg/dL)	Aripiprazole	34/1357	2.5
	Placebo	27/973	2.8
Fasting Triglycerides	Aripiprazole	40/539	7.4

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Table 5: Changes in Blood Lipid Parameters From Placebo-Controlled Monotherapy Trials in Adults

	Treatment Arm	n/N	%
Normal to High (<150 mg/dL to ≥200 mg/dL)	Placebo	30/431	7.0
Fasting LDL Cholesterol Normal to High (<100 mg/dL to ≥160 mg/dL)	Aripiprazole	2/332	0.6
	Placebo	2/268	0.7
HDL Cholesterol Normal to Low (≥40 mg/dL to <40 mg/dL)	Aripiprazole	121/1066	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 aripiprazole- and placebo-treated patients: at 12 weeks, Total Cholesterol (fasting/nonfasting), 1/71 (1.4%) vs. 3/74 (4.1%); Fasting Triglycerides, 8/62 (12.9%) vs. 5/37 (13.5%); Fasting LDL Cholesterol, 0/34 (0%) vs. 1/25 (4.0%), respectively; and at 24 weeks, Total Cholesterol (fasting/nonfasting), 1/42 (2.4%) vs. 3/37 (8.1%); Fasting Triglycerides, 5/34 (14.7%) vs. 5/20 (25%); Fasting LDL Cholesterol, 0/22 (0%) vs. 1/18 (5.6%), respectively.

Weight Gain

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

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

Table 6 shows the percentage of adult patients with weight gain ≥7% of body weight in the 13 pooled placebo-controlled monotherapy trials.

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Table 6: Percentage of Patients From Placebo-Controlled Trials in Adult Patients with Weight Gain ≥7% of Body Weight

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

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

5.6 Orthostatic Hypotension

Aripiprazole may cause orthostatic hypotension, perhaps due to its α_1-adrenergic receptor antagonism. Orthostasis occurred in 4/576 (0.7%) patients treated with ABILIFY MAINTENA during the stabilization phase, 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 stabilization phase, the incidence of significant orthostatic change in blood pressure (defined as a decrease in systolic blood pressure ≥20 mmHg accompanied by an increase in heart rate ≥25 when comparing standing to supine values) was 0.2% (1/575).

5.7 Leukopenia, Neutropenia, and Agranulocytosis

Class Effect: In clinical trials and post-marketing experience, leukopenia and neutropenia have been reported temporally related to antipsychotic agents, including oral aripiprazole. Agranulocytosis has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug-induced leukopenia/neutropenia. In patients with a history of a clinically significant low WBC 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

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ABILIFY MAINTENA in patients with severe neutropenia (absolute neutrophil count <1000/mm^3) and follow their WBC counts until recovery.

5.8 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.

5.9 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.

5.10 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).

5.11 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)]*

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- 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)]*
- Orthostatic Hypotension *[see Warnings and Precautions (5.6)]*
- Leukopenia, Neutropenia, and Agranulocytosis *[see Warnings and Precautions (5.7)]*
- Seizures *[see Warnings and Precautions (5.8)]*
- Potential for Cognitive and Motor Impairment *[see Warnings and Precautions (5.9)]*
- Body Temperature Regulation *[see Warnings and Precautions (5.10)]*
- Dysphagia *[see Warnings and Precautions (5.11)]*

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

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 300-400 mg every 4 weeks has been evaluated for safety in 1,287 adult patients in clinical trials in schizophrenia, with approximately 1,281 patient-years of exposure to ABILIFY MAINTENA. A total of 832 patients were treated with ABILIFY MAINTENA for at least 180 days (at least 7 consecutive injections) and 630 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 profile of ABILIFY MAINTENA is expected to be similar to that of oral aripiprazole. Therefore, most of the safety data presented below

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are derived from trials with the oral formulation. In patients who tolerated and responded to treatment with oral aripiprazole and single-blind ABILIFY MAINTENA and were then randomized to receive ABILIFY MAINTENA or placebo injections under double-blind conditions, the incidence of adverse reactions was similar between the two treatment groups.

Adverse Reactions of ABILIFY MAINTENA and Oral Aripiprazole

Adverse Reactions Associated with Discontinuation of Oral Aripiprazole

Based on a pool of five placebo-controlled trials (four 4-week and one 6-week) in which oral aripiprazole was administered to adults with schizophrenia in doses ranging from 2 mg/day to 30 mg/day, the incidence of discontinuation due to adverse reactions was 7% in oral aripiprazole-treated and 9% in placebo-treated patients. The types of adverse reactions that led to discontinuation were similar for the aripiprazole-treated and placebo-treated patients.

Commonly Observed Adverse Reactions of Oral Aripiprazole

Based on a pool of five placebo-controlled trials (four 4-week and one 6-week) in which oral aripiprazole was administered to adults with schizophrenia in doses ranging from 2 mg/day to 30 mg/day, the only commonly observed adverse reaction associated with the use of oral aripiprazole in patients with schizophrenia (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) was akathisia (aripiprazole 8%; placebo 4%).

Less Common Adverse Reactions in Adults Treated with Oral Aripiprazole

Table 7 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 oral aripiprazole (doses ≥2 mg/day) and for which the incidence in patients treated with aripiprazole was greater than the incidence in patients treated with placebo in the combined dataset.

Table 7: Adverse Reactions in Short-Term, Placebo-Controlled Trials in Adult Patients Treated with Oral Aripiprazole

	Percentage of Patients Reporting Reaction[a]	
System Organ Class **Preferred Term**	**Oral Aripiprazole** **(n=1843)**	**Placebo** **(n=1166)**
Eye Disorders		
Blurred Vision	3	1

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Table 7: Adverse Reactions in Short-Term, Placebo-Controlled Trials in Adult Patients Treated with Oral Aripiprazole

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

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

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

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Dose-Related Adverse Reactions of Oral Aripiprazole

Dose response relationships for the incidence of treatment-emergent adverse events were evaluated from four trials in adult patients with schizophrenia comparing various fixed oral doses of aripiprazole (2 mg/day, 5 mg/day, 10 mg/day, 15 mg/day, 20 mg/day, and 30 mg/day) 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%).

Injection Site Reactions of ABILIFY MAINTENA

In the open-label, stabilization phase of a study with ABILIFY MAINTENA in patients with schizophrenia, the percent of patients reporting any injection site-related adverse reaction was 6.3% for ABILIFY MAINTENA-treated patients. The mean intensity of injection pain reported by subjects using a visual analog scale (0=no pain to 100=unbearably painful) was minimal and improved in subjects receiving ABILIFY MAINTENA from the first to the last injection in the open-label, stabilization phase (6.1 to 4.9).

Investigator evaluation of the injection site for pain, swelling, redness and induration following injections of ABILIFY MAINTENA in the open-label, stabilization phase were rated as absent for 74%-96% of subjects following the first injection and 77%-96% of subjects following the last injection.

Extrapyramidal Symptoms of Oral Aripiprazole

In short-term, placebo-controlled trials in schizophrenia, the incidence of reported EPS-related events, excluding events related to akathisia, for oral aripiprazole-treated patients was 13% vs. 12% for placebo; and the incidence of akathisia-related events for aripiprazole-treated patients was 8% vs. 4% for placebo.

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

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 Abnormal Involuntary Movement Scale (for dyskinesias) did not show a difference between aripiprazole and placebo.

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Dystonia

Class Effect: 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.

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

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

Other Adverse Reactions Observed During the Premarketing Evaluation of Oral Aripiprazole

Following is a list of MedDRA terms that reflect adverse reactions reported by patients treated with oral aripiprazole at multiple doses ≥2 mg/day during any phase of a trial within the database of 13,543 adult patients. All events assessed as possible adverse drug reactions have been included with the exception of more commonly occurring events. In addition, medically/clinically meaningful adverse reactions, particularly those that are likely to be useful to the prescriber or that have pharmacologic plausibility, have been included. Events already listed in other parts of *Adverse Reactions (6),* or those considered in *Warnings and Precautions (5)* or *Overdosage (10)* have been excluded. Although the reactions reported occurred during treatment with aripiprazole, they were not necessarily caused by it.

Events are further categorized by MedDRA system organ class and listed in order of decreasing frequency according to the following definitions: those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-

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controlled trials appear in this listing); those occurring in 1/100 to 1/1000 patients; and those occurring in fewer than 1/1000 patients.

Blood and Lymphatic System Disorders:

≥1/1000 patients and <1/100 patients - thrombocytopenia

Cardiac Disorders:

≥1/1000 patients and <1/100 patients - palpitations, cardiopulmonary failure, myocardial infarction, cardio-respiratory arrest, atrioventricular block, extrasystoles, angina pectoris, myocardial ischemia; *<1/1000 patients* - atrial flutter, supraventricular tachycardia, ventricular tachycardia

Eye Disorders:

≥1/1000 patients and <1/100 patients - photophobia, diplopia, eyelid edema, photopsia

Gastrointestinal Disorders:

≥1/1000 patients and <1/100 patients - gastroesophageal reflux disease, swollen tongue, esophagitis; *<1/1000 patients* - pancreatitis

General Disorders and Administration Site Conditions:

≥1/100 patients - asthenia, peripheral edema, chest pain; *≥1/1000 patients and <1/100 patients* - face edema, angioedema; *<1/1000 patients* - hypothermia

Hepatobiliary Disorders:

<1/1000 patients - hepatitis, jaundice

Immune System Disorders:

≥1/1000 patients and <1/100 patients - hypersensitivity

Injury, Poisoning, and Procedural Complications:

≥1/100 patients - fall; *<1/1000 patients* - heat stroke

Investigations:

≥1/1000 patients and <1/100 patients - blood prolactin increased, blood urea increased, blood creatinine increased, blood bilirubin increased; *<1/1000 patients* - blood lactate dehydrogenase increased, glycosylated hemoglobin increased

Metabolism and Nutrition Disorders:

≥1/1000 patients and <1/100 patients - anorexia, hyponatremia, hypoglycemia, polydipsia; *<1/1000 patients* - diabetic ketoacidosis

Musculoskeletal and Connective Tissue Disorders:

≥1/1000 patients and <1/100 patients - muscle rigidity, muscular weakness, muscle tightness, mobility decreased; *<1/1000 patients* - rhabdomyolysis

Nervous System Disorders:

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≥1/100 patients - coordination abnormal; *≥1/1000 patients and <1/100 patients* - speech disorder, hypokinesia, hypotonia, myoclonus, akinesia, bradykinesia; *<1/1000 patients* - choreoathetosis

Psychiatric Disorders:

≥1/100 patients - suicidal ideation; *≥1/1000 patients and <1/100 patients* - loss of libido, suicide attempt, hostility, libido increased, anger, anorgasmia, delirium, intentional self injury, completed suicide, tic, homicidal ideation; *<1/1000 patients* - catatonia, sleep walking

Renal and Urinary Disorders:

≥1/1000 patients and <1/100 patients - urinary retention, polyuria, nocturia

Reproductive System and Breast Disorders:

≥1/1000 patients and <1/100 patients - menstruation irregular, erectile dysfunction, amenorrhea, breast pain; *<1/1000 patients* - gynecomastia, priapism

Respiratory, Thoracic, and Mediastinal Disorders:

≥1/100 patients - nasal congestion, dyspnea

Skin and Subcutaneous Tissue Disorders:

≥1/100 patients - rash (including erythematous, exfoliative, generalized, macular, maculopapular, papular rash; acneiform, allergic, contact, exfoliative, seborrheic dermatitis, neurodermatitis, and drug eruption), hyperhydrosis; *≥1/1000 patients and <1/100 patients* - pruritus, photosensitivity reaction, alopecia, urticaria

6.2 Postmarketing Experience

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

7 DRUG INTERACTIONS

7.1 Carbamazepine or Other CYP3A4 Inducers

Concomitant use of ABILIFY MAINTENA with carbamazepine or other CYP3A4 inducers decreases the concentrations of aripiprazole. Avoid use of ABILIFY MAINTENA in combination with carbamazepine and other inducers of CYP3A4 for greater than 14 days *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

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7.2 Ketoconazole or Other Strong CYP3A4 Inhibitors

Concomitant use of ABILIFY MAINTENA with ketoconazole or other CYP3A4 inhibitors for more than 14 days increases the concentrations of aripiprazole and reduction of the ABILIFY MAINTENA dose is recommended *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*. Due to prolonged-release characteristics of ABILIFY MAINTENA, short-term co-administration of ketoconazole or other inhibitors of CYP3A4 with ABILIFY MAINTENA does not require a dose adjustment.

7.3 Quinidine or Other Strong CYP2D6 Inhibitors

Concomitant use of ABILIFY MAINTENA with quinidine or other CYP2D6 inhibitors increases the concentrations of aripiprazole after longer-term use (i.e., over 14 days) and reduction of the ABILIFY MAINTENA is recommended *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*. Due to prolonged-release characteristics of ABILIFY MAINTENA, short-term co-administration of quinidine or other CYP2D6 inhibitors with ABILIFY MAINTENA does not require a dose adjustment.

7.4 CNS Depressants

Given the CNS depressant effects of aripiprazole, use caution when ABILIFY MAINTENA is taken in combination with other centrally-acting drugs or alcohol.

7.5 Anti-Hypertensive Agents

Due to its alpha adrenergic antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C:

Risk Summary

Adequate and well controlled studies with aripiprazole have not been conducted in pregnant women. Neonates exposed to antipsychotic drugs (including MAINTENA)

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during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. In animal studies, aripiprazole demonstrated developmental toxicity, including possible teratogenic effects in rats and rabbits at doses 1 - 10 times the oral maximum recommended human dose [MRHD] of 30 mg/day based on a mg/m^2 body surface area. ABILIFY MAINTENA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Monitor neonates exhibiting extrapyramidal or withdrawal symptoms. Some neonates recover within hours or days without specific treatment; others may require prolonged hospitalization.

Animal Data

Pregnant rats were treated with oral doses of 3 mg/kg/day, 10 mg/kg/day, and 30 mg/kg/day (1 times, 3 times, and 10 times the oral maximum recommended human dose [MRHD] of 30 mg/day on a mg/m^2 body surface area) of aripiprazole during the period of organogenesis. Gestation was slightly prolonged at 30 mg/kg. Treatment caused a slight delay in fetal development, as evidenced by decreased fetal weight (30 mg/kg), undescended testes (30 mg/kg), and delayed skeletal ossification (10 mg/kg and 30 mg/kg). There were no adverse effects on embryofetal or pup survival. Delivered offspring had decreased body weights (10 mg/kg and 30 mg/kg), and increased incidences of hepatodiaphragmatic nodules and diaphragmatic hernia at 30 mg/kg (the other dose groups were not examined for these findings). A low incidence of diaphragmatic hernia was also seen in the fetuses exposed to 30 mg/kg. Postnatally, delayed vaginal opening was seen at 10 mg/kg and 30 mg/kg 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. Some maternal toxicity was seen at 30 mg/kg; however, there was no evidence to suggest that these developmental effects were secondary to maternal toxicity.

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

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

In pregnant rabbits receiving aripiprazole injection intravenously (3 mg/kg/day, 10 mg/kg/day, 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, which produced 5 times the human exposure at the oral MRHD based on AUC and is 6 times the oral MRHD of 30 mg/day based on mg/m^2 body surface area.

In a study in which rats were treated with oral doses of 3 mg/kg/day, 10 mg/kg/day, and 30 mg/kg/day (1 times, 3 times, and 10 times the oral MRHD of 30 mg/day on a mg/m^2 body surface area) of aripiprazole perinatally and postnatally (from day 17 of gestation through day 21 postpartum), slight maternal toxicity and slightly prolonged gestation were seen at 30 mg/kg. An increase in stillbirths and decreases in pup weight (persisting into adulthood) and survival were seen at this dose.

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

8.3 Nursing Mothers

Aripiprazole is excreted in human breast milk. 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.

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8.4 Pediatric Use

Safety and effectiveness of ABILIFY MAINTENA in patients <18 years of age have not been evaluated.

8.5 Geriatric Use

Safety and effectiveness of ABILIFY MAINTENA in patients >60 years of age have not been evaluated.

In oral single-dose pharmacokinetic studies (with aripiprazole given in a single oral dose of 15 mg), aripiprazole clearance was 20% lower in elderly (≥65 years) subjects compared to younger adult subjects (18 to 64 years). There was no detectable age effect, however, in the population pharmacokinetic analysis of oral aripiprazole in schizophrenia patients. Also, the pharmacokinetics of oral aripiprazole after multiple doses in elderly patients appeared similar to that observed in young, healthy subjects. No dosage adjustment of ABILIFY MAINTENA is recommended for elderly patients *[see Boxed Warning and Warnings and Precautions (5.1)]*.

8.6 CYP2D6 Poor Metabolizers

Approximately 8% of Caucasians and 3–8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers (PM). Dosage adjustment is recommended in CYP2D6 poor metabolizers due to high aripiprazole concentrations *[see Dosage and Administration (2.3) and 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 overdosage (alone or in combination with other substances) include vomiting, somnolence, and tremor. Other clinically important signs and symptoms observed in one or more patients with aripiprazole overdoses (alone or with other substances) include acidosis, aggression, aspartate aminotransferase increased, atrial

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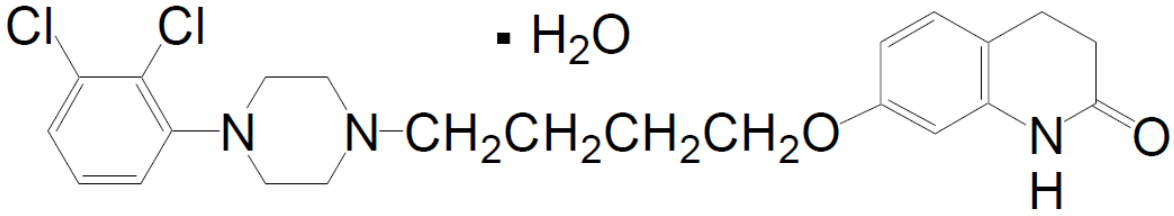
fibrillation, bradycardia, coma, confusional state, convulsion, blood creatine phosphokinase increased, depressed level of consciousness, hypertension, hypokalemia, hypotension, lethargy, loss of consciousness, QRS complex prolonged, QT prolonged, pneumonia aspiration, respiratory arrest, status epilepticus, 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 dihydrocarbostyril monohydrate. The empirical formula is $C_{23}H_{27}Cl_2N_3O_2.H_2O$ 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.

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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_2 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 intramuscular dose, the plasma concentrations of aripiprazole gradually rise to reach maximum plasma concentrations at a median T_{max} of 5-7 days. The mean aripiprazole terminal elimination half-life was 29.9 days and 46.5 days after every 4-week injection of ABILIFY MAINTENA 300 mg and 400 mg, respectively, and steady state concentrations were attained by the fourth dose. Approximate dose-proportional increases in aripiprazole and dehydro-aripiprazole concentrations and AUC parameters were observed after every four week ABILIFY MAINTENA injections of 300 mg and 400 mg.

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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.

Potential for Other Drugs to Affect ABILIFY MAINTENA

Ketoconazole and Other Strong CYP3A4 Inhibitors

Co-administration of ketoconazole (200 mg/day for 14 days) with a 15 mg single oral dose of aripiprazole increased the AUC of aripiprazole and its active metabolite by 63% and 77%, respectively. The effect of a higher ketoconazole dose (400 mg/day) has not been studied.

Other strong inhibitors of CYP3A4 (itraconazole) would be expected to have similar effects and need similar dose reductions; moderate inhibitors (erythromycin, grapefruit juice) have not been studied *[see Dosage and Administration (2.3) and Drug Interactions (7.2)]*.

Quinidine and Other Strong CYP2D6 Inhibitors

Co-administration of a 10 mg single oral dose of aripiprazole with quinidine (166 mg/day for 13 days), a potent inhibitor of CYP2D6, increased the AUC of aripiprazole by 112% but decreased the AUC of its active metabolite, dehydro-aripiprazole, by 35%. Other significant inhibitors of CYP2D6, such as fluoxetine or paroxetine, would be expected to have similar effects *[see Dosage and Administration (2.3) and Drug Interactions (7.3)]*.

Carbamazepine and Other CYP3A4 Inducers

Co-administration of carbamazepine (200 mg twice daily), a potent CYP3A4 inducer, with oral aripiprazole (30 mg/day) resulted in an approximate 70% decrease in C_{max} and AUC values of both aripiprazole and its active metabolite, dehydro-aripiprazole *[see Dosage and Administration (2.3) and Drug Interactions (7.1)]*.

Valproate

When valproate (500 mg/day-1500 mg/day) and oral aripiprazole (30 mg/day) were co-administered, at steady-state the C_{max} and AUC of aripiprazole were decreased by 25%. No dosage adjustment of ABILIFY MAINTENA is required when administered concomitantly with valproate.

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Lithium

A pharmacokinetic interaction of ABILIFY MAINTENA with lithium is unlikely because lithium is not bound to plasma proteins, is not metabolized, and is almost entirely excreted unchanged in urine. Co-administration of therapeutic doses of lithium (1200 mg/day-1800 mg/day) for 21 days with oral aripiprazole (30 mg/day) did not result in clinically significant changes in the pharmacokinetics of aripiprazole or its active metabolite, dehydro-aripiprazole (C_{max} and AUC increased by less than 20%). No dosage adjustment of ABILIFY MAINTENA is required when administered concomitantly with lithium.

Potential for ABILIFY MAINTENA to Affect Other Drugs

Aripiprazole is unlikely to cause clinically important pharmacokinetic interactions with drugs metabolized by cytochrome P450 enzymes. *In vivo* studies, 10 mg/day to 30 mg/day doses of oral aripiprazole had no significant effect on metabolism by CYP2D6 (dextromethorphan), CYP2C9 (warfarin), CYP2C19 (omeprazole, warfarin), and CYP3A4 (dextromethorphan) substrates. Additionally, aripiprazole and dehydro-aripiprazole did not show potential for altering CYP1A2-mediated metabolism *in vitro*.

No effect of oral aripiprazole was seen on the pharmacokinetics of lithium or valproate.

***V**alproate*

When oral aripiprazole (30 mg/day) and valproate (1000 mg/day) were co-administered, at steady state there were no clinically significant changes in the C_{max} or AUC of valproate. No dosage adjustment of valproate is required when administered concomitantly with ABILIFY MAINTENA.

Lithium

Co-administration of oral aripiprazole (30 mg/day) with lithium (900 mg/day) did not result in clinically significant changes in the pharmacokinetics of lithium. No dosage adjustment of lithium is required when administered concomitantly with ABILIFY MAINTENA.

Dextromethorphan

Oral aripiprazole at doses of 10 mg/day to 30 mg/day for 14 days had no effect on dextromethorphan's O-dealkylation to its major metabolite, dextrorphan, a pathway dependent on CYP2D6 activity. Oral aripiprazole also had no effect on dextromethorphan's N-demethylation to its metabolite 3-methoxymorphinan, a pathway

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dependent on CYP3A4 activity. No dosage adjustment of dextromethorphan is required when administered concomitantly with ABILIFY MAINTENA.

Warfarin

Oral aripiprazole 10 mg/day for 14 days had no effect on the pharmacokinetics of R-warfarin and S-warfarin or on the pharmacodynamic end-point of International Normalized Ratio, indicating the lack of a clinically relevant effect of aripiprazole on CYP2C9 and CYP2C19 metabolism or the binding of highly protein-bound warfarin. No dosage adjustment of warfarin is required when administered concomitantly with ABILIFY MAINTENA.

Omeprazole

Oral aripiprazole 10 mg/day for 15 days had no effect on the pharmacokinetics of a single 20 mg dose of omeprazole, a CYP2C19 substrate, in healthy subjects. No dosage adjustment of omeprazole is required when administered concomitantly with ABILIFY MAINTENA.

Escitalopram

Co-administration of 10 mg/day doses of oral aripiprazole for 14 days to healthy subjects had no effect on the steady-state pharmacokinetics of 10 mg/day escitalopram, a substrate of CYP2C19 and CYP3A4. No dosage adjustment of escitalopram is required when ABILIFY MAINTENA is added to escitalopram.

Venlafaxine

Co-administration of 10 mg/day to 20 mg/day doses of oral aripiprazole for 14 days to healthy subjects had no effect on the steady-state pharmacokinetics of venlafaxine and O-desmethylvenlafaxine following 75 mg/day venlafaxine XR, a CYP2D6 substrate. No dosage adjustment of venlafaxine is required when ABILIFY MAINTENA is added to venlafaxine.

Specific Population Studies

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

CYP2D6 Poor Metabolizers

Approximately 8% of Caucasians and 3–8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers (PMs). People who are not PMs are classified as extensive metabolizers (EMs). Laboratory tests are available to identify CYP2D6 PMs. PMs have about an 80% increase in aripiprazole

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exposure and about a 30% decrease in exposure to the active metabolite compared to EMs, resulting in about a 60% higher exposure to the total active moieties from a given dose of aripiprazole compared to EMs. The mean elimination half-lives for aripiprazole are about 75 and 146 hours in EMs and PMs, respectively. Hence, the recommended dosage of ABILIFY MAINTENA is lower *[see Dosage and Administration (2.3) and Use in Specific Populations (8.6)]*.

Aripiprazole does not inhibit or induce the CYP2D6 pathway.

Gender

C_{max} and AUC of aripiprazole and its active metabolite, dehydro-aripiprazole, are 30% to 40% higher in women than in men, and correspondingly, the apparent oral clearance of aripiprazole is lower in women. These differences, however, are largely explained by differences in body weight (25%) between men and women. No dosage adjustment of ABILIFY MAINTENA is recommended based on gender.

Race

Although no specific pharmacokinetic study was conducted to investigate the effects of race on the disposition of aripiprazole, population pharmacokinetic evaluation revealed no evidence of clinically significant race-related differences in the pharmacokinetics of aripiprazole. No dosage adjustment of ABILIFY MAINTENA is recommended based on race.

Smoking

Based on studies utilizing human liver enzymes *in vitro*, aripiprazole is not a substrate for CYP1A2 and also does not undergo direct glucuronidation. Smoking should, therefore, not have an effect on the pharmacokinetics of aripiprazole. Consistent with these *in vitro* results, population pharmacokinetic evaluation did not reveal any significant pharmacokinetic differences between smokers and nonsmokers. No dosage adjustment of ABILIFY MAINTENA is recommended based on smoking status.

Renal Impairment

In patients with severe renal impairment (creatinine clearance <30 mL/min), C_{max} of oral aripiprazole (given in a single dose of oral 15 mg) and dehydro-aripiprazole increased by 36% and 53%, respectively, but AUC was 15% lower for aripiprazole and 7% higher for dehydro-aripiprazole. Renal excretion of both unchanged aripiprazole and dehydro-aripiprazole is less than 1% of the dose. No dosage adjustment of ABILIFY MAINTENA is required for doses in subjects with renal impairment.

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Hepatic Impairment

In a single-dose trial (15 mg of oral aripiprazole) in subjects with varying degrees of liver cirrhosis (Child-Pugh Classes A, B, and C), the AUC of aripiprazole, compared to healthy subjects, increased 31% in mild hepatic impairment, increased 8% in moderate hepatic impairment, and decreased 20% in severe hepatic impairment. None of these differences would require dose adjustment of ABILIFY MAINTENA.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

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

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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

Aripiprazole was not mutagenic when tested in the *in vitro* bacterial mutation assay, the *in vitro* bacterial DNA repair assay, and the *in vitro* mouse lymphoma gene mutation assay. The clastogenic potential of aripiprazole was tested in 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 its metabolite (2,3-DCPP) were clastogenic in the *in vitro* chromosomal aberration assay in CHL cells both in the presence and absence of 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 oral *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 mg/kg/day, 6 mg/kg/day, and 20 mg/kg/day (0.6 times, 2 times, and 6 times the oral maximum recommended human dose [MRHD] of 30 mg/day on a mg/m^2 body surface area) 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 mg/kg and 20 mg/kg and decreased fetal weight was seen at 20 mg/kg.

Male rats were treated with oral doses of 20 mg/kg/day, 40 mg/kg/day, and 60 mg/kg/day (6 times, 13 times, and 19 times the oral MRHD of 30 mg/day on a mg/m^2 body surface area) 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 mg/kg and 60 mg/kg, but no impairment of fertility was seen.

13.2 Animal Toxicity 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 mg/kg

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and 60 mg/kg. The 40 mg/kg and 60 mg/kg doses are 13 times and 19 times the oral maximum recommended human dose (MRHD) of 30 mg/day based on mg/m^2 body surface area and 7 times to 14 times human exposure at the oral 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 mg/m^2 body surface area. At the NOAEL in rats, the AUC_{7d} values were 14.4 μg·h/mL in males and 104.1 μg·h/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 mg/m^2 body surface area, the AUC_{7d} values were approximately 59 μg·h/mL in males and 44 μg·h/mL in females. In patients at the MRHD of 400 mg, the AUCτ (0-28 days) was 163 μg·h/mL. For comparison to this human AUC, extrapolating the animal AUC_{7d} values to an AUC_{28d} results in AUC_{28d} values of approximately 58 and 416 μg·h/mL for male and female rats, respectively, and 236 and 175 μg·h/mL for male and female dogs, respectively.

14 CLINICAL STUDIES

The efficacy of ABILIFY MAINTENA in the treatment of patients with schizophrenia was established, in part, on the basis of efficacy data from trials with the oral formulation of aripiprazole. In addition, the efficacy of ABILIFY MAINTENA in maintaining symptomatic control in schizophrenia was established in a randomized-withdrawal, double-blind, placebo-controlled, trial in adult patients 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.

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Clinical ratings during this trial included:

• 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-Severity (CGI-S) scale. 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.

• The Clinical Global Impression-Improvement (CGI-I) scale. The CGI-I rates improvement in mental illness on a scale of 1 (very much improved) to 7 (very much worse) based on the change from baseline in clinical condition.

• The 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 4-6 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 ≤80, CGI-S ≤4 (moderately ill), and CGI-SS score ≤2 (mildly suicidal) on Part 1 and ≤5 (minimally worsened) on Part 2; and a score of ≤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

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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:

1) CGI-I of ≥5 (minimally worse) and

   a) 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 ≥2 on that specific item since randomization or

   b) 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 ≥4 on the combined four PANSS items (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content) since randomization

2) Hospitalization due to worsening of psychotic symptoms (including partial hospitalization), but excluding hospitalization for psychosocial reasons

3) 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

4) Violent behavior resulting in clinically significant self-injury, injury to another person, or property damage.

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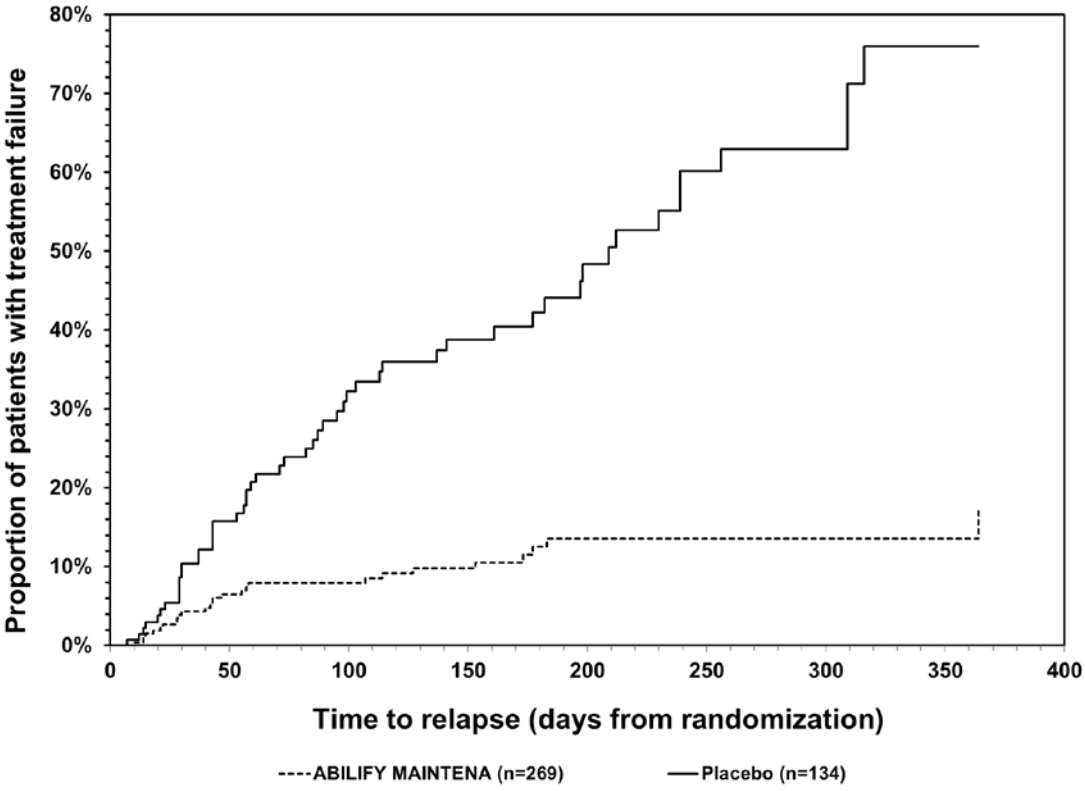
A pre-planned interim analysis demonstrated a statistically significantly longer time to relapse in patients randomized to the ABILIFY MAINTENA group compared to placebo-treated patients and the trial was subsequently terminated early because maintenance of efficacy was demonstrated. The final analysis demonstrated a statistically significantly longer time to relapse in patients randomized to the ABILIFY MAINTENA group than compared to placebo-treated patients (log-rank test $p<0.0001$). The Kaplan-Meier curves of the time from randomization to relapse during the double-blind treatment phase for ABILIFY MAINTENA and placebo groups are shown in Figure 19.

Figure 19: Time to Relapse [1]



[1] This figure is based on a total of 80 relapse events

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

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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-use pre-filled dual chamber syringe containing ABILIFY MAINTENA (aripiprazole) and Sterile Water for Injection for extended-release injectable suspension lyophilized powder
- One 21 gauge, 1.5 inch (38 mm) hypodermic safety needle with needle protection device for non-obese patients
- One 21 gauge, 2 inch (50 mm) hypodermic safety needle with needle protection device for obese patients

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

- 400 mg single-use pre-filled dual chamber syringe containing ABILIFY MAINTENA (aripiprazole) and Sterile Water for Injection for extended-release injectable suspension lyophilized powder
- One 21 gauge, 1.5 inch (38 mm) hypodermic safety needle with needle protection device for non-obese patients
- One 21 gauge, 2 inch (50 mm) hypodermic safety needle with needle protection device for 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.

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

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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

See FDA-approved patient labeling (Medication Guide)

Discuss the following issues with patients for whom they prescribe ABILIFY MAINTENA**.**

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Advise patients and caregivers that elderly patients with dementia-related psychoses treated with antipsychotic drugs are at increased risk of death. Aripiprazole is not approved for elderly patients with dementia-related psychosis *[see Warning and Precautions (5.1)]*.

Neuroleptic Malignant Syndrome

Counsel patients and caregivers that a potentially fatal symptom complex sometimes referred to as NMS has been reported in association with administration of antipsychotic drugs. Signs and symptoms of NMS include hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia) *[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 physician if they

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notice any movements which they cannot control in their face, tongue, or other body part *[see Warnings and Precautions (5.4)]*.

Hyperglycemia and Diabetes mellitus

Advise patients of the symptoms of hyperglycemia and diabetes mellitus. Patients who are diagnosed with diabetes, those with risk factors for diabetes, or those that develop these symptoms during treatment should have their blood glucose monitored at the beginning of and periodically during treatment *[see Warnings and Precautions (5.5)]*.

Orthostatic Hypotension

Advise patients of the risk of orthostatic hypotension, particularly at the time of initiating treatment, re-initiating treatment, or increasing the dose *[see Warnings and Precautions (5.6)]*.

Leukopenia/Neutropenia

Advise patients with a pre-existing low WBC count or a history of drug-induced leukopenia/neutropenia that they should have their CBC monitored while receiving ABILIFY MAINTENA *[see Warnings and Precautions (5.7)]*.

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 (5.9)]*.

Heat Exposure and Dehydration

Advise patients regarding appropriate care in avoiding overheating and dehydration *[see Warnings and Precautions (5.10)]*.

Concomitant Medication

Advise patients 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)]*.

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Pregnancy

Advise patients to notify their physician if they become pregnant or intend to become pregnant during therapy with ABILIFY MAINTENA *[see Use in Specific Populations (8.1)]*.

Nursing

Aripiprazole is excreted in human breast milk. A decision should be made whether to discontinue nursing or to discontinue ABILIFY MAINTENA, taking into account the importance of the drug to the mother *[see Use in Specific Populations (8.3)]*.

Alcohol

Advise patients to avoid alcohol while taking ABILIFY MAINTENA *[see Clinical Pharmacology (12.2)]*.

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MEDICATION GUIDE

ABILIFY MAINTENA®(a-BIL-i-fy main-TEN-a**)**

(aripiprazole)

for extended-release injectable suspension, for intramuscular use

Read this Medication Guide before you receive your first injection of ABILIFY MAINTENA and before each injection. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

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

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
    - stiff muscles
    - confusion
    - sweating
    - changes in pulse, heart rate, and blood pressure

Call your healthcare provider right away if you have any of these symptoms.

What is ABILIFY MAINTENA?

ABILIFY MAINTENA is a prescription medicine used to treat schizophrenia.

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

Who should not receive ABILIFY MAINTENA?

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.

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What should I tell my healthcare provider before receiving ABILIFY MAINTENA?

Before you receive ABILIFY MAINTENA, tell your healthcare provider 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 buttocks
- are pregnant or plan to become pregnant. It is not known if ABILIFY MAINTENA will harm your unborn baby.
- 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, non-prescription 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.

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How should I receive ABILIFY MAINTENA?

- ABILIFY MAINTENA is an injection given in your buttock by your healthcare provider 1 time a month. You may feel a little pain in your 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 receiving 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

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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.

- **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).

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. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of ABILIFY MAINTENA

This Medication Guide summarizes the most important information about ABILIFY MAINTENA. If you would like more information, talk with your healthcare provider.

You can ask your healthcare provider or pharmacist for information about ABILIFY MAINTENA. If you would like more information, talk with your healthcare provider. You can

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ask your pharmacist or healthcare provider for information about ABILIFY MAINTENA that is written for healthcare professionals.

For more information about ABILIFY MAINTENA, go to www.ABILIFYMAINTENA.com or call 1-800-441-6763.

What are the ingredients in ABILIFY MAINTENA?

Active ingredient: aripiprazole monohydrate

Inactive ingredients: carboxymethyl cellulose sodium, mannitol, sodium phosphate monobasic monohydrate and sodium hydroxide

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

ABILIFY MAINTENA is a trademark of Otsuka Pharmaceutical Company.

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