Fax

To: John McCall, RPh  From: OPDC MedInfo 240-683-3235
Fax: 1-888-656-6822  Pages: 22
Phone:  Date: October 14, 2016

ABILIFY MAINTENA® (aripiprazole)
Re: Submission Request Forms

☐ Urgent  ☑ For Review  ☐ Please Comment  ☐ Please Reply  ☐ Please Recycle

Please find attached the submission request forms for ABILIFY MAINTENA.

If you have further questions or require additional information, please feel free to contact your Managed Market Liaison, Dr. Samantha Sweeney at 619-518-0757.

Otsuka Pharmaceutical Development & Commercialization, Inc.
Members of the Pharmacy and Therapeutics (P&T) Committee have requested that all clinical information, questions, or comments about the Preferred Drug List (PDL) be sent directly to Magellan Medicaid Administration. Manufacturers and other interested parties have been requested not to contact the members directly. Written comments on the PDL from all interested parties should be submitted to Erin Narus, PharmD, R.Ph. at the State of Alaska.

Note: Manufacturers submitting comments are requested to do so through their Product Manager using this form. This form constitutes a request for NEW information pertaining to peer-reviewed literature including off-label peer-reviewed studies.

---

**Contact Information**

**MANUFACTURER NAME:**
Otsuka Pharmaceutical Development & Commercialization, Inc.

**PRODUCT MANAGER'S NAME:**
Samantha Sweeney, PharmD, MBA

**ADDRESS:**
508 Carnegie Center Drive

**CITY:**
Princeton

**STATE:**
NJ

**ZIP CODE:**
08540

**PHONE NUMBER:**
619-518-0757

**PRODUCT:**
ABILIFY MAINTENA® (aripiprazole)

---

**Clinical Rationale Request for Consideration (If additional space is required, use Clinical Rationale Continuation Page).**

**ABILIFY MAINTENA**

**QUALIFY Study:** ABILIFY MAINTENA versus Paliperidone Palmitate Long Acting Injectable (PLAI) (Naber, 2015; Potkin 2016)

Naber et al., published a head-to-head, randomized, noninferiority, open label, rater blinded study (n=295) to evaluate the efficacy and safety of ABILIFY MAINTENA to PLAI in adult patients with schizophrenia. The primary efficacy endpoint using the Heinrichs-Carpenter Quality of Life Scale (QLS) showed a statistically significant improvement on total scores from baseline to Week 28 with ABILIFY MAINTENA compared to PLAI. The difference in least squares mean (LSM) change from baseline to week 28 on QLS total scores between treatments was 4.67 (95% CI: [0.32; 9.02], P=0.036). Non-inferiority was confirmed and subsequently demonstrated the superiority of ABILIFY MAINTENA 400 mg over PLAI. Additionally Clinical Global Impression-Severity scale (CGI-S), key secondary endpoint showed significant improvements in LSM change from baseline to week 28 after ABILIFY MAINTENA 400 mg (-0.75±0.07) compared to PLAI (-0.46±0.07). Adverse events were the most frequent reason for discontinuation; ABILIFY MAINTENA: 11.1% and PLAI: 19.7%. In the 20 week continuation phase, the incidence of treatment emergent adverse events (TEAEs) occurring in ≥5% of the ABILIFY MAINTENA treatment group was weight gain and in the PLAI group was weight gain, insomnia and psychotic disorder.

A post-hoc analysis of QUALIFY by Potkin et al., investigated the association between the QLS and measures of patient functioning/work readiness. The Readiness for Work Questionnaire (WoRQ) was included as an additional endpoint in the QUALIFY study and may reflect broader functioning in patients with schizophrenia. QLS instrumental role domain scores improved significantly only in patients shifting from No to Yes in work readiness vs patients not ready to work at Week 28. At Week 28, the odds of being rated ready for work were higher for the ABILIFY MAINTENA 400 mg vs the PLAI group (adjusted odds ratio: 2.67, 95% CI: [1.39; 5.14], P=0.003). Of the patients not ready for work at baseline, 29/74 (39.2%) in the ABILIFY MAINTENA 400 mg group changed to Yes in work readiness vs 12/69 (17.4%) in the PLAI group.
Clinical Rationale Request for Consideration (If additional space is required, use Clinical Rationale Continuation Page).

COST EFFECTIVENESS DATA (Citrome, 2016)
Citrome et al, a cost-effectiveness model that evaluated incremental cost per schizophrenia hospitalization averted was developed to compare ABILIFY MAINTENA and PLAI. Rates of relapse, adverse events, and direct medical costs were estimated for 1 year. The model used data from placebo-controlled, pivotal trials and product prescribing information to estimate efficacy and adverse events over a one year time horizon. Due to the variation of dosing strategies used in clinical practice, four different dosing scenarios were evaluated: dosing observed in the clinical trials for each product, real-world dosing, dosing based on package insert, and highest dose available. ABILIFY MAINTENA was the dominant strategy compared with PLAI when real-world dosing and highest available dosing with equivalent treatment efficacy were assumed. ABILIFY MAINTENA remained a cost-effective treatment option compared with PLAI when more conservative dosing strategies were considered.

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

Fax this request to: 1-888-656-6822   ATTN: John McCall, R.Ph.

Note: Processing May be Delayed if Information Submitted is Illegible or Incomplete

Clinical Rationale Continuation Page (Use only if needed).
State of Alaska Department of Health and Social Services, Division of Health Care Services
Submission Request Form for Pharmaceutical Manufacturers
Fax this request to: 1-888-656-6822   ATTN: John McCall, R.Ph.
Note: Processing may be delayed if information submitted is illegible or incomplete

Published Citations (If additional space is required, use Published Citations Continuation Page).

References:
State of Alaska Department of Health and Social Services, Division of Health Care Services
Submission Request Form for Pharmaceutical Manufacturers
Fax this request to: 1-888-656-6822    ATTN: John McCall, R.Ph.
Note: Processing may be delayed if information submitted is illegible or incomplete

Public Citations Continuation Page (Use only if needed).
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 complete boxed warning.

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 (6.1)

- ABILIFY MAINTENA is not approved for the treatment of patients with dementia-related psychosis (5.1)

RECENT MAJOR CHANGES

Warnings and Precautions, Pathological Gambling and Other Compulsive Behaviors (5.6)

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

INDICATIONS AND USAGE

- Only to be administered by intramuscular injection in the deltoid or gluteal muscle by a healthcare professional (2.1)

- For patients naïve to aripiprazole, establish tolerability with oral aripiprazole prior to initiating ABILIFY MAINTENA (2.1)

- Recommended starting and maintenance dose is 400 mg administered monthly as a single injection. Dose can be reduced to 300 mg in patients with adverse reactions (2.1)

- In conjunction with first dose, take 14 consecutive days of concurrent oral aripiprazole (10 mg to 20 mg) or current oral antipsychotic (2.2)

- Dosage adjustments are required for missed doses (2.2)

- Known CYP2D6 poor metabolizers; Recommended starting and maintenance dose is 300 mg administered monthly as a single injection (2.3)

- ABILIFY MAINTENA comes in two types of vials. See instructions for reconstitution/dosage procedures for (1) Pre-filled Dual Chamber Syringe (2.3, 2.5) and (2) Vials (2.6)

- DOSAGE FORMS AND STRENGTHS

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

- single-dose pre-filled dual chamber syringe

- single-dose vial

- CONTRAINDICATIONS

- Known hypersensitivity to aripiprazole (4)

- WARNINGS AND PRECAUTIONS

- Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis: Increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack, including fatalities) (5.2)

- Neuroleptic Malignant Syndrome: Manage with Immediate discontinuation and close monitoring (5.3)

- Tardive Dyskinesia: Discontinue if clinically appropriate (5.4)

- Metabolic Changes: Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and weight gain (5.5)

- Hyperglycemia and Diabetes Mellitus: Monitor patients for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Monitor glucose regularly in patients with and at risk for diabetes (5.5)

- Dystonia: Undesirable alterations have been observed in patients treated with antipsychotic medications (5.5)

- Weight Gain: Gain in body weight has been observed; clinical monitoring of weight is recommended (5.5)

- Pathological Gambling and Other Compulsive Behaviors: Consider dose reduction or discontinuation (5.5)

- Orthostatic Hypotension: Use with caution in patients with known cardiovascular or cerebrovascular disease (5.7)

- Leukopenia, Neutropenia, and Agranulocytosis: Perform complete blood counts in patients with a history of a clinically significant low white blood cell count (WBC)/absolute neutrophil count (ANC). Consider discontinuation if clinically significant decline in WBC/ANC in the absence of other causative factors (5.8)

- Seizures: Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold (5.9)

- Potential for Cognitive and Motor Impairment: Use caution when operating machinery (5.10)

- ADVERSE REACTIONS

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

- To report SUSPECTED ADVERSE REACTIONS, contact Otsuka America Pharmaceutical, Inc. at 1-888-438-9927 or FDA at 1-888-FDA-1088 or www.fda.gov/medwatch.

- DRUG INTERACTIONS

- Dosage adjustments for patients taking CYP2D6 Inhibitors, CYP3A4 Inhibitors, or CYP3A4 Inducers for greater than 14 days (2.3):

- Full Prescribing Information: Contents

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Dosage Overview for the Treatment of Schizophrenia

2.2 Dosage Adjustments for Missed Doses

2.3 Dosage Adjustments for Cytomegalovirus (CMV) Considerations

2.4 Different Aripiprazole Formulations and Kits

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

2.6 Vial: Preparation and Administration Instructions

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

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

5.3 Neuroleptic Malignant Syndrome

5.4 Tardive Dyskinesia

5.5 Metabolic Changes

5.6 Pathological Gambling and Other Compulsive Behaviors

5.7 Orthostatic Hypotension

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with ABILIFY MAINTENA

7.2 Drugs Having No Clinically Important Interactions with ABILIFY MAINTENA

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation

8.4 Pediatric Use

8.5 Geriatric Use

8.6 CYP2D6 Poor Metabolizers

8.7 Hepatic and Renal Impairment

8.8 Other Specific Populations

9 OVERDOSAGE

9.1 Management of Overdose

10.1 Human Experience

10.2 Management of Overdose

10.4 Management of Overdose
ABILIFY MAINTENA* (aripiprazole)

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

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 psychoses [see WARNINGS AND PRECAUTIONS (5.1)].

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Dosage Overview for the Treatment of Schizophrenia

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

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

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

2.2 Dosage Adjustments for Missed Doses

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

2.3 Dosage Adjustments for Cytochrome P450 Considerations

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

If the CYP3A4 inhibitor or CYP2D6 inhibitor is withdrawn, the ABILIFY MAINTENA dosage may need to be increased [see DOSAGE AND ADMINISTRATION (2.1)]. Avoid the concomitant use of CYP3A4 inducers with ABILIFY MAINTENA for greater than 14 days because the blood levels of aripiprazole are decreased and may be below the effective levels.

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

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

<table>
<thead>
<tr>
<th>Factors</th>
<th>Adjusted Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6 Poor Metabolizers</td>
<td>300 mg</td>
</tr>
<tr>
<td>Known CYP2D6 Poor Metabolizers Taking Concomitant CYP3A4 Inhibitors</td>
<td>200 mg</td>
</tr>
<tr>
<td>Patients Taking 400 mg of ABILIFY MAINTENA</td>
<td>Avoid use</td>
</tr>
<tr>
<td>Patients Taking 300 mg of ABILIFY MAINTENA</td>
<td>200 mg</td>
</tr>
<tr>
<td>CYP2D6 and CYP3A4 Inhibitors</td>
<td>300 mg</td>
</tr>
<tr>
<td>CYP3A4 Inducers</td>
<td>Avoid use</td>
</tr>
<tr>
<td>CYP2D6 and CYP3A4 Inducers</td>
<td>300 mg</td>
</tr>
<tr>
<td>CYP3A4 Inducers</td>
<td>Avoid use</td>
</tr>
</tbody>
</table>

*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 Syringes (2.5), and 2) Vials (2.4).

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 (5.75 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 Syringes (2.5), and 2) Single-use vials available in 300 mg or 400 mg strength vials [see DOSAGE AND ADMINISTRATION (2.6)].

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

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

Preparation Prior to Reconstitution

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

Lay out and confirm that components listed below are provided in the kit:
- One ABILIFY MAINTENA (aripiprazole), pre-filled dual chamber syringes (400 mg or 300 mg as appropriate) for extended release injectable suspension containing hypotonic sodium chloride and Sterile Water for Injection
- One 23 gauge, 1 inch (25 mm) hypodermic needle with needle protection device for depot administration in non-obese patients
- One 23 gauge, 1.5 inch (38 mm) hypodermic needle with needle protection device for depot administration in obese patients
- One 23 gauge, 2 inch (50 mm) hypodermic needle with needle protection device for depot administration in obese patients

Reconstitution of Lyophilized Powder in Pre-filled Dual Chamber Syringe

Reconstitute at room temperature:
- Push plunger rod slightly to engage threads. And then, rotate plunger rod until rod stops rotating to release plunger. After plunger rod is at complete stop, middle stopper will be at the indicator line (See Figure 1).

14 CLINICAL STUDIES

14.1 How Supplied/Storage and Handling

14.2 Storage

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.
After plunger rod is at complete stop, plunger stopper will be at the indicator line.

*Figure 1*

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

![Uniform Milky White](image)

Use within 30 minutes after reconstitution.

*Figure 2*

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

Injection Procedure

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

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

![Twist + Pull Off](image)

b) Select appropriate needle (See Figure 4).

<table>
<thead>
<tr>
<th>Body Type</th>
<th>Injection Site</th>
<th>Needle Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-obese</td>
<td>Deltoid</td>
<td>1 inch (25 mm) hypodermic safety needle with needle protection device for non-obese patients</td>
</tr>
<tr>
<td></td>
<td>Gluteal</td>
<td>1.5 inch (38 mm) hypodermic safety needle with needle protection device for non-obese patients</td>
</tr>
<tr>
<td>Obese</td>
<td>Deltoid</td>
<td>1.5 inch (38 mm) hypodermic safety needle with needle protection device for obese patients</td>
</tr>
<tr>
<td></td>
<td>Gluteal</td>
<td>2 inch (50 mm) hypodermic safety needle with needle protection device for obese patients</td>
</tr>
</tbody>
</table>

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).

![Twist Snug](image)

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

![Pull](image)

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

![Expel air until suspension fills needle base](image)

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

Disposal Procedure

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

![Cover Discard](image)

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

2.6 Vial: Preparation and Administration Instructions

Preparation Prior to Reconstitution

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

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

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

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

<table>
<thead>
<tr>
<th>Dose</th>
<th>Sterile Water for Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 mg</td>
<td>1.0 mL</td>
</tr>
<tr>
<td>160 mg</td>
<td>0.8 mL</td>
</tr>
<tr>
<td>120 mg</td>
<td>0.6 mL</td>
</tr>
<tr>
<td>100 mg</td>
<td>0.5 mL</td>
</tr>
<tr>
<td>80 mg</td>
<td>0.4 mL</td>
</tr>
<tr>
<td>60 mg</td>
<td>0.3 mL</td>
</tr>
<tr>
<td>40 mg</td>
<td>0.2 mL</td>
</tr>
<tr>
<td>20 mg</td>
<td>0.1 mL</td>
</tr>
</tbody>
</table>

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

Reconstitution of Lyophilized Powder in Vial

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.

c) Slowly inject the Sterile Water for Injection into the vial containing the ABILIFY MAINTENA lyophilized powder (see 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.

e) Shake the vial vigorously for 30 seconds until the reconstituted suspension appears uniform (see 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.

c) Using the vial adapter package to handle the vial adapter, attach the prepackaged luer lock syringe to the vial adapter (see 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.

e) Determine the recommended volume for injection (Table 3).

Table 3: ABILIFY MAINTENA Reconstituted Suspension Volume to Inject

<table>
<thead>
<tr>
<th>Dose</th>
<th>Volume to Inject</th>
</tr>
</thead>
<tbody>
<tr>
<td>400 mg</td>
<td>2 mL</td>
</tr>
<tr>
<td>300 mg</td>
<td>1.5 mL</td>
</tr>
<tr>
<td>200 mg</td>
<td>1 mL</td>
</tr>
<tr>
<td>100 mg</td>
<td>0.5 mL</td>
</tr>
</tbody>
</table>

Figure 9

Figure 10

Figure 11

Figure 12

Figure 13

Figure 14

Figure 15
ABILIFY MAINTENA* (aripiprazole)

1) Wipe the top of the vial of the reconstituted ABILIFY MAINTENA suspension with a sterile alcohol swab.
2) 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](image)

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

![Figure 17](image)

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

**Dosage Procedure**

a) Engage the needle safety device as described in Section 2.6, Step (c) of Reconstitution of Lyophilized Powder in Vial and safely discard all kit components (see Figure 6). Dispose of the vials, adapters, needles, and syringe appropriately after injection. The Starlite Water for Injection and ABILIFY MAINTENA vials are for single-use only.
b) Rotate sites of injections between the two deltoid or gluteal muscles.

**Dosage Forms and Strengths**

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

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

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality In Elderly Patients With Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. A meta-analysis of 17 placebo-controlled trials (median duration of 10 weeks) of 1835 elderly patients with dementia-related psychosis, that included both atypical and typical antipsychotics, found that the risk of death was 1.6 times higher (95% CI: 1.1, 2.1) in patients treated with those agents compared to placebo. In one of the placebo-controlled trials (Tie et al., 1999), the risk of death in drug-treated patients was 2.5 times higher (95% CI: 1.1, 5.6) compared to placebo. It is unknown if mortality is higher with aripiprazole treatment compared to placebo or to other antipsychotics.

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 (cerebrovascular events, transient ischemic attack, stroke, transient ischemic attack) compared to placebo. The rate of cerebrovascular adverse reactions was higher in patients treated with aripiprazole compared to placebo. The rate of cerebrovascular adverse reactions among patients treated with aripiprazole was not different from placebo. [see ADVERSE REACTIONS (6.1)].

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. The overall incidence of NMS is unknown. However, case-control studies of atypical antipsychotics have shown a lower incidence of NMS compared to typical antipsychotics. The diagnosis of NMS requires a high index of suspicion. NMS must be considered in any abdomen serious medical illness for which specific treatment is available. In patients treated with antipsychotic drugs, NMS may be difficult to distinguish from the neuroleptic malignant syndrome syndrome (NMS). The syndrome, which can occur with aripiprazole, is characterized by hyperthermia, muscle rigidity, altered mental status, and autonomic instability (rigid pulse, diaphoresis, tachycardia). Additional symptoms may include elevations in creatine phosphokinase, myoglobinuria, rhabdomyolysis, and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In patients treated with antipsychotic drugs, NMS may be difficult to distinguish from the neuroleptic malignant syndrome syndrome (NMS). The syndrome, which can occur with aripiprazole, is characterized by hyperthermia, muscle rigidity, altered mental status, and autonomic instability (rigid pulse, diaphoresis, tachycardia). Additional symptoms may include elevations in creatine phosphokinase, myoglobinuria, rhabdomyolysis, and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In patients treated with antipsychotic drugs, NMS may be difficult to distinguish from the neuroleptic malignant syndrome syndrome (NMS). The syndrome, which can occur with aripiprazole, is characterized by hyperthermia, muscle rigidity, altered mental status, and autonomic instability (rigid pulse, diaphoresis, tachycardia). Additional symptoms may include elevations in creatine phosphokinase, myoglobinuria, rhabdomyolysis, and acute renal failure.

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 closely monitored, since recurrences of NMS have been reported.

5.4 Tardive Dyskinesia

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

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to be increased as the duration of treatment and the 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 not respond to chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

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

5.5 Metabolic Changes

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

Hyperglycemia/Diabetes Mellitus

Hyperglycemia, in some cases moderate 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 atypical antipsychotics (see ADVERSE REACTIONS (8.1)). 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 typical 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 atypical antipsychotics.

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

In a short-term, placebo-controlled randomized trial in adults with schizophrenia, the mean change in fasting glucose was +8.8 mg/dL (N=88) in the ABILIFY MAINTENA-treated patients and +0.7 mg/dL (N=59) in the placebo-treated patients. Table 4 shows the proportion of ABILIFY MAINTENA-treated patients with normal and borderline fasting glucose at baseline and their changes in fasting glucose measurements.

<table>
<thead>
<tr>
<th>Category Change</th>
<th>Treatment Arm</th>
<th>n/N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting Glucose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal to High</td>
<td>ABILIFY MAINTENA</td>
<td>7/88</td>
<td>8.0</td>
</tr>
<tr>
<td>Normal to High</td>
<td>Placebo</td>
<td>0/75</td>
<td>0.0</td>
</tr>
<tr>
<td>Borderline to High</td>
<td>ABILIFY MAINTENA</td>
<td>1/39</td>
<td>3.0</td>
</tr>
<tr>
<td>Borderline to High</td>
<td>Placebo</td>
<td>3/33</td>
<td>9.1</td>
</tr>
</tbody>
</table>

* N = the total number of subjects who had a measurement at baseline and at least one post-baseline visit.
** n = the number of subjects with a potentially clinically relevant shift.

Dyslipidemia

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

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

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>n/N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal to High</td>
<td>Placebo</td>
<td>2/73</td>
</tr>
<tr>
<td>Borderline to High</td>
<td>Placebo</td>
<td>2/19</td>
</tr>
<tr>
<td>Any increase</td>
<td>Placebo</td>
<td>5/52</td>
</tr>
<tr>
<td>Fasting Triglycerides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal to High</td>
<td>Placebo</td>
<td>7/79</td>
</tr>
<tr>
<td>Any increase</td>
<td>Placebo</td>
<td>4/78</td>
</tr>
<tr>
<td>Fasting LDL Cholesterol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal to High</td>
<td>Placebo</td>
<td>1/51</td>
</tr>
<tr>
<td>Any increase</td>
<td>Placebo</td>
<td>4/11</td>
</tr>
<tr>
<td>HDL Cholesterol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal to Low</td>
<td>Placebo</td>
<td>1/79</td>
</tr>
<tr>
<td>Any decrease</td>
<td>Placebo</td>
<td>12/101</td>
</tr>
</tbody>
</table>

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

5.6 Pathological Gambling and Other Compulsive Behaviors

Post-market case reports suggest that patients can experience intense urges, particularly for gambling, and the inability to control these urges while taking antipsychotics. Other compulsive urges, reported less frequently, include sexual urges, excessive appetite, and drug cravings or compulsive behaviors. Because patients may not recognize these behaviors as abnormal, it is important for prescribers to inquire about the development of new or increased gambling urges, compulsive sexual urges, compulsive eating, or drug cravings while being treated with atypical antipsychotics. It should be noted that impulse-control symptoms can be associated with the underlying disorder. In some cases, although not all, urges were reported to have stopped when the dose was reduced or the medication was discontinued. Compulsive behaviors may result in harm to the patient and others if not recognized. Consider dose reduction or stopping the medication if a patient develops such urges.
5.7 Orthostatic Hypotension

ABILIFY MAINTENA may cause orthostatic hypotension, possibly due to its α₂-adrenergic receptor antagonism. In the short-term, placebo-controlled trial in adults with schizophrenia, the adverse event of presyncope was reported in 0.177 (0.8%) of patients treated with ABILIFY MAINTENA, while syncope and orthostatic hypotension occurred in 0.017 (0.1%) of patients treated with placebo. During the stabilization phase of the randomized-withdrawal (maintenance) study, orthostasis-related adverse events were reported in 0.057 (0.3%) of patients treated with ABILIFY MAINTENA, including abdominal orthostatic blood pressure (0.057, 0.3%), postural dizziness (0.057, 0.3%), presyncope (0.057, 0.3%) and orthostatic hypotension (0.057, 0.3%).

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

5.8 Leukopenia, Neutropenia, and Agranulocytosis

In clinical trials and post-marketing experience, leukopenia and neutropenia have been reported temporally related to antipsychotic agents, including ABILIFY MAINTENA. Agranulocytosis has also been reported (see ADVERSE REACTIONS [5.1]). Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC)/absolute neutrophil count (ANC) and a history of drug-induced leukopenia/neutropenia. In patients with a history of clinically significant low WBCs 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 signal of a clinically significant decrease in WBC in the absence of other causes. Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue ABILIFY MAINTENA in patients with severe neutropenia (absolute neutrophil count <1000/mm³) and follow their WBC counts until recovery.

5.9 Sures

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

5.10 Potential for Cognitive and Motor Impairment

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

5.11 Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing ABILIFY MAINTENA for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, including heat, exercise, dehydration, or drug-induced. In patients with a history of clinically significant low WBCs 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 signal of a clinically significant decrease in WBC in the absence of other causes. Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue ABILIFY MAINTENA in patients with severe neutropenia (absolute neutrophil count <1000/mm³) and follow their WBC counts until recovery.

5.12 Dysphagia

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

6 ADVERSE REACTIONS

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

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

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

The following listing does not include reactions: 1) already listed in previous tables of adverse events, 2) for which the drug class was renal 3) which were not general as to be uninformative, 4) which were after 1 year of use and had not occurred or had not occurred at a rate equal to or less than placebo.
Reactions are categorized by body system according to the following definitions: frequent adverse reactions are those occurring in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients; rare reactions are those occurring in fewer than 1/1000 patients;

**Cardiovascular Disorders:**
- Hypotension
- Palpitations
- Cardiac arrhythmias
- Bradycardia
- Angina pectoris

**Respiratory Disorders:**
- Dyspnea
- Asthma
- Bronchitis

**Gastrointestinal Disorders:**
- Nausea
- Diarrhea
- Vomiting
- Constipation
- Flatulence

**Dermatological Disorders:**
- Rash
- Urticaria
- Pruritus
- Erythema

**Neurological Disorders:**
- Dizziness
- Headache
- Confusion

**Metabolism and Nutrition Disorders:**
- Weight gain
- Weight loss

**Musculoskeletal and Connective Tissue Disorders:**
- Myalgia
- Arthralgia

**Mental Health Disorders:**
- Anxiety
- Depression

**Hepatic Disorders:**
- Hepatitis

**Renal and Urinary Disorders:**
- Hematuria

**Skin and Subcutaneous Tissue Disorders:**
- Pruritus

**Other Disorders:**
- Hypersensitivity reactions

**Drug Interactions**
- Strong CYP3A4 inhibitors (e.g., ketoconazole or itraconazole) and CYP2D6 inhibitors (e.g., paroxetine)
- CYP3A4 inducers (e.g., carbamazepine)

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

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

**Cardiac Disorders:**
- Palpitations, cardiac dysrhythmia, cardiac arrhythmia, cardiac conduction disorder

**Respiratory Disorders:**
- Dyspnea, bronchitis, asthma

**Gastrointestinal Disorders:**
- Nausea, vomiting, diarrhea, constipation, flatulence

**Dermatological Disorders:**
- Rash, urticaria, pruritus, erythema

**Neurological Disorders:**
- Dizziness, headache, confusion

**Metabolism and Nutrition Disorders:**
- Weight gain, weight loss, nausea

**Musculoskeletal and Connective Tissue Disorders:**
- Myalgia, arthralgia

**Mental Health Disorders:**
- Anxiety, depression

**Hepatic Disorders:**
- Hepatitis

**Renal and Urinary Disorders:**
- Hematuria

**Skin and Subcutaneous Tissue Disorders:**
- Pruritus

**Other Disorders:**
- Hypersensitivity reactions
8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

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

Risk Summary

Neonates exposed to antipsychotic drugs, including ABILIFY MAINTENA, during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms. There are insufficient data with ABILIFY MAINTENA use in pregnant women to inform a drug-associated risk, in animal reproduction studies, oral and intravenous arlprazole administration during organogenesis in rats and/or rabbits at doses 10 and 11 times, respectively, the maximum recommended human dose (MRHD) produced fetal death, decreased fetal weight, undescended testes, delayed skeletal ossification, skeletal abnormalities, and diaphragmatic hernia. Oral and intravenous arlprazole administration during the pre- and post-natal period in rats at doses 10 times the maximum recommended human dose (MRHD) produced increased gestation length, stillbirths, decreased pup weight, and decreased pup survival. Consider the benefits and risks of ABILIFY MAINTENA and possible risks to the fetus when prescribing ABILIFY MAINTENA to a pregnant woman. Advise pregnant women of potential fetal risk.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects is 2.4% and 19-20%, respectively.

Clinical Considerations

Fetal/Newborn Adverse Reactions

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

Animal Data

In animal studies, arlprazole demonstrated developmental toxicity, including possible teratogenic effects in rats and rabbits. Pregnant rats were treated with oral doses of 3, 10, and 30 mg/kg/day which are approximately 1000, 30, and 100 times, respectively, the maximum recommended human dose (MRHD) on a mg/m² basis of arlprazole during the period of organogenesis. Treatment at the highest dose caused a slight prolongation of gestation and delay in fetal development as evidenced by decreased fetal weight and undescended testes. Delayed skeletal ossification was observed at 10 and 11 times the oral MRHD on mg/m² basis. At 3 and 10 times the oral MRHD on mg/m² basis, delivered offspring had decreased body weights. Increased incidences of hip dislocation, skeletal abnormalities, and diaphragmatic hernia were observed in offspring from the highest dose group (the other doses were not examined for these findings). Postnatal, delayed vaginal opening was seen at 3 and 10 times the oral MRHD on mg/m² basis and impaired reproductive performance (decreased fertility rate, corpora lutea, implants, live fetuses, and increased post-implantation loss, likely mediated through effects on female offspring) along with some maternal toxicity were seen at the highest dose. However, there was no evidence to suggest that these developmental effects were secondary to maternal toxicity.

In pregnant rats treated with arlprazole intraventricularly at doses of 3, 9, and 27 mg/kg/day, which are 10, 30, and 90 times, respectively, the oral MRHD on mg/m² basis, during the period of organogenesis, decreased fetal weight and delayed skeletal ossification were seen at the highest dose which also caused maternal toxicity.

In pregnant rabbits treated with arlprazole intravenously at doses of 3, 9, and 27 mg/kg/day, which are 10, 30, and 90 times, respectively, the oral MRHD on mg/m² basis during the period of organogenesis; decreased maternal food consumption and increased abortions were seen at the highest dose as well as decreased fetal body weights. Decreased fetal body weight and increased incidence of fused sternebrae were observed at 3 and 11 times the MRHD based on AUC.
11:1 Human Experience
The largest known case of acute ingestion with a known outcome involved 1260 mg of oral aripiprazole (42 times the maximum recommended daily dose) in a patient who fully recovered.

Common adverse reactions (reported in at least 5% of all overdose cases) reported with oral aripiprazole overdose (alone or in combination with other substances) include vomiting, somnolence, and tachycardia. Other clinically significant symptoms observed in one or more patients with aripiprazole overdose (alone or with other substances) include dizziness, nausea, tachycardia, coma, convulsions, and status epilepticus.

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

10.2 Management of Overdosage
In case of overdosage, call the Poison Control Center Immediately at 1-800-222-1222.

12.2 Pharmacodynamics
Aripiprazole exhibits high affinity for dopamine D2 and D3 receptors, serotonin 5-HT1A receptors, and 5-HT2A receptors (K values of 0.4 µM, 5 nM, and 5 nM, respectively), moderate affinity for dopamine D4, serotonin 5HT2A, and 5-HT2C receptors (K values of 44 nM, 15 nM, and 15 nM, respectively), and moderate affinity for the serotonin 5-HT2C receptor (K values of 44 nM, 15 nM, and 15 nM, respectively). Aripiprazole has no appreciable affinity for cholinergic muscarinic receptors (K values of 1000 nM). Aripiprazole functions as a partial agonist at the dopamine D3 and serotonin 5-HT2 receptors, and as an antagonist at serotonin 5-HT2A receptors.

There was no significant difference between oral aripiprazole co-administered with alcohol and placebo co-administered with alcohol 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 presumed 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 D2 receptors similar to the parent drug and represents about 25% of the parent drug in vivo in plasma.

Aripiprazole is slowly absorbed into the systemic circulation following a single dose administration of ABILIFY MAINTENA in the deltoid and gluteal muscle, the extent of absorption (AUC) of aripiprazole was similar for both injection sites. The relative systemic clearance following single intramuscular doses was 31% higher following administration to the deltoid compared to the gluteal site. However, at steady state, AUC and Cmax were similar for both sites of injection. Following multiple intramuscular doses, the plasma concentrations of aripiprazole gradually rise to maximum plasma concentrations at a median T max of 5-7 days for the deltoid muscle and 4 days for the gluteal muscle. After gluteal administration, the mean apparent aripiprazole terminal elimination half-life was 34.9 days and 45.8 days after multiple injections for every 4-week injection of ABILIFY MAINTENA 300 mg and 400 mg, respectively. Steady state concentrations for the typical subject were attained by the fourth dose for both sites of administration. Approximate dose-proportional increases in aripiprazole and dehydro-aripiprazole exposure were observed after every 4-week ABILIFY MAINTENA injections of 300 mg and 400 mg.

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

In the population PK analysis in patients with major depressive disorder showed no substantial change in plasma concentrations of fluoxetine (20 mg/day or 40 mg/day), paroxetine CR (25 mg/day or 50 mg/day), or sertraline (100 mg/day or 150 mg/day) dosed to steady-state. The steady-state plasma concentrations of fluoxetine and norfluoxetine increased by about 15% and 32%, respectively, and concentrations of paroxetine decreased by about 23%. The steady-state plasma concentrations of sertraline and desmethylsertraline were not substantially changed when these antidepressant therapies were coadministered with aripiprazole.

The effects of ABILIFY on the exposures of other drugs are summarized in Figure 19 and Figure 20, respectively. Based on simulation, a 4.5-fold increase in mean Cmax and AUC values at steady-state is expected when extensive metabolizers of CYP2D6 are administered with both strong CYP2D6 and CYP3A4 inhibitors. After oral administration, a 3-fold increase in mean Cmax and AUC values at steady-state is expected in poor metabolizers of CYP2D6 administered with strong CYP3A4 inhibitors.

Figure 19: The effects of other drugs on aripiprazole pharmacokinetics

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

Effect of Other Drugs on Ability

The effects of ABILIFY on the exposures of other drugs are summarized in Figure 19 and Figure 20, respectively. Based on simulation, a 4.5-fold increase in mean Cmax and AUC values at steady-state is expected when extensive metabolizers of CYP2D6 are administered with both strong CYP2D6 and CYP3A4 inhibitors. After oral administration, a 3-fold increase in mean Cmax and AUC values at steady-state is expected in poor metabolizers of CYP2D6 administered with strong CYP3A4 inhibitors.

The effects of ABILIFY on the exposures of other drugs are summarized in Figure 19 and Figure 20, respectively. Based on simulation, a 4.5-fold increase in mean Cmax and AUC values at steady-state is expected when extensive metabolizers of CYP2D6 are administered with both strong CYP2D6 and CYP3A4 inhibitors. After oral administration, a 3-fold increase in mean Cmax and AUC values at steady-state is expected in poor metabolizers of CYP2D6 administered with strong CYP3A4 inhibitors.

Figure 19: The effects of other drugs on aripiprazole pharmacokinetics

Figure 20: The effects of other drugs on dehydro-aripiprazole pharmacokinetics
Studies in Specific Populations

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

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

Figure 22: Effects of intrinsic factors on aripiprazole pharmacokinetics

Special Populations

- Younger vs. adult
- Age 18-45 vs. 65+ years old
- Male vs. female
- Anorexia vs. normal
- Obesity vs. normal
- Renal impairment: Severe

Figure 13: NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Lifetime carcinogenicity studies were conducted in ICR mice, Sprague-Dawley (SD) rats, and F344 rats. Aripiprazole was administered for 2 years to the diet at doses of 1, 3, 10, and 30 mg/kg/day in ICR mice and 1, 3, and 10 mg/kg/day in F344 rats. The maximum recommended human dose (MRHD) based on mg/m², respectively, in addition, SD rats were dosed orally for 2 years at 10, 25, 40, and 60 mg/kg/day (9 to 10 times the MRHD based on mg/m²). Aripiprazole did not induce tumors in male mice or male rats. In female mice, the incidence of pituitary gland adenomas and mammary gland adenocarcinomas and adenocarcinomas were increased at dietary doses of 3 to 30 mg/kg/day (0.1 to 0.9 times human exposure at MRHD based on AUC and 0.6 to 6 times the MRHD based on mg/m²). In rat females, the incidence of mammary gland fibroadenomas was increased at a dietary dose of 10 mg/kg/day (0.1 times human exposure at MRHD based on AUC and 3 times the MRHD based on mg/m²), and the incidences of adenocarcinomas and combined adenocarcinomas were increased at an oral dose of 60 mg/kg/day (14 times human exposure at MRHD based on AUC and 19 times the MRHD based on mg/m²).

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, serum prolactin levels were observed to be increased in female mice in a 13-week dietary study at the doses associated with mammary gland adenocarcinomas and adenocarcinomas. Serum prolactin was not increased in female rats in 4-week and 13-week dietary studies at the dose associated with mammary gland tumors. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown.

Mutagenesis

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

Impairment of Fertility

Female rats were treated with oral doses of 2, 5, and 20 mg/kg/day (0.6, 2, and 6 times the maximum recommended human dose (MRHD) on a mg/m² basis) of aripiprazole from 2 weeks prior to mating through day 7 of gestation. Estrous cycle irregularities and increased corpora lutea were seen at all doses, but no impairment of fertility was seen. Increased preimplantation loss was seen at 6 and 20 mg/kg/day and decreased fetal weight was seen at 20 mg/kg/day.

Male rats were treated with oral doses of 20, 40, and 60 mg/kg/day (6, 19, and 19 times the MRHD in a mg/m² basis) of aripiprazole from 3 weeks prior to mating through mating. Disturbances in spermatogenesis were seen at 60 mg/kg and prostate atrophy was seen at 40 and 60 mg/kg, but no impairment of fertility was seen.

13.2 Animal Toxicology and/or Pharmacology

Clearance of Aripiprazole

Aripiprazole produced retinal degeneration in albino rats in a 28-week chronic toxicity study at a dose of 60 mg/kg in 2-year carcinogenicity study at doses of 40 and 60 mg/kg. The 40 and 60 mg/kg/dose are 13 and 19 times the maximum recommended human dose (MRHD) based on mg/m² and 7 to 14 times human exposure at MRHD based on AUC. Evaluation of retinal toxicity and potential association with increased prolactin levels were not performed. Additional studies to further evaluate the mechanism have not been performed. The relevance of this finding to human risk is unknown.

Intramuscular Injection

The toxicological profile for aripiprazole administered via 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 localised inflammation, swelling, sebaceous and foreign-body reactions to the deposited drug. These effects gradually resolved with discontinuation of dosing.

14 CLINICAL STUDIES

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

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

Short-Term Efficacy}

A short-term (12-week), randomized, double-blind, placebo-controlled trial in acute relapsed adults (Study 1), the primary measures used for assessing psychiatric signs and symptoms were 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 (15 items), each rated on a scale of 1 (absent) to 7 (extreme); total PANSS scores range from 30 to 210. The primary endpoint was the change from baseline in PANSS total score to week 10.

The inclusion criteria for this short-term trial included adult inpatients who met DSM-IV-TR criteria for schizophrenia. In addition, all patients entering the trial must have experienced an acute psychotic episode as defined by both PANSS Total Score >50 and a PANSS score of >4 on each of four specific psychotic symptoms (conceptual disorganization, hallucinatory behavior, suspiciousness/paranoid ideation, unusual thought content) at screening and baseline. The key secondary endpoint was the change from baseline in Clinical Global Impression-Schizophrenia (CGI-S) assessment scale to week 10. The CGI-S rates the severity of illness on a scale of 1 (normal) to 7 (among the most extremely ill) based on the total clinical experience of the rater in treating patients with schizophrenia. Patients had a mean PANSS total score of 192 (range 52 to 144) and a CGI-S score of 6.2 (markedly ill) at entry.

In this 12-week study (n=339) comparing ABILIFY MAINTENA (n=167) to placebo (n=172), patients were administered 400 mg ABILIFY MAINTENA or placebo on days 0, 28, and 56. The dose could be adjusted up and down within the range of 400 to 1000 mg on a one-step basis. ABILIFY MAINTENA was superior to placebo in improving the PANSS total score at the end of week 10 (see Table 9).

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

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Treatment Group</th>
<th>Primary Efficacy Measure: PANSS Total Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean Baseline Score (SD)</td>
<td>LS Mean Change from Baseline (SE)</td>
</tr>
<tr>
<td>Study 1</td>
<td>ABILIFY MAINTENA (400 to 500 mg)</td>
<td>102.4 (11.4)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>103.4 (11.1)</td>
</tr>
</tbody>
</table>

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

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

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

This trial included:

- A 4 to 5 week open-label, oral conversion phase for patients on antipsychotic medications other than aripiprazole. A total of 693 patients entered this phase.
- An open-label, oral aripiprazole stabilization phase (target dose of 10 mg to 30 mg once daily). A total of 310 patients entered this phase. Patients were 18 to 56 years of age, and 60% were female. 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, no PANSS total score <20, CGI-S >4 (moderately ill), and CGI-S score <2 (mildly ill) 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 of 2 weeks, single-dose ABILIFY MAINTENA stabilization phase (treatment with 400 mg of ABILIFY MAINTENA given every 4 weeks in conjunction with oral aripiprazole 10 mg to 20 mg/day) for the first 2 weeks. The dose of ABILIFY MAINTENA may be decreased to 300 mg and 200 mg given every 4 weeks due to adverse reactions. A total of 675 patients entered this phase. The mean PANSS total score was 59 (range 30 to 60) 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 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 3.0 (mildly ill) at entry. The dose could be adjusted up and down down and up within the range of 300 to 400 mg on a one-step basis.

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

- CGI-I of <5 (minimally worse) and:
  1. an increase on any of the following individual PANSS items (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content) to a score ≥4 with an absolute increase of ≥2 on that specific item from stabilization or
  2. an increase on any of the remaining individual PANSS items (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content) to a score ≥4 and an absolute increase ≥3 on any of the combined four PANSS items (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content) since randomization
- Hospitalization due to worsening of psychotic symptoms (including partial hospitalization), but excluding hospitalization for patients with mental retardation
- CGI-S of 4 (severely suicidal) or 5 (attempted suicide) on Part 1 and/or 6 (very much worse) on Part 2, or
- Violent behavior resulting in clinically significant self-injury, injury to another person, or property damage.

A prespecified 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 compared to placebo-treated patients. The Kaplan-Meier curves of the cumulative proportion of patients with relapse during the double-blind treatment phase for ABILIFY MAINTENA and placebo groups are shown in Figure 25.

**Figure 25:** Kaplan-Meier Estimation of Cumulative Proportion of Patients with Relapse

\[\text{Time to relapse (days from randomization)}\]

- ABILIFY MAINTENA (n=149) — Placebo (n=134)

*This figure is based on a total of 80 relapse events*

The key secondary efficacy endpoint, percentage of subjects meeting the relapse criteria, was statistically significantly lower in patients randomized to the ABILIFY MAINTENA group (16%) than in the placebo group (40%).
15 HOW SUPPLIED/STORAGE AND HANDLING

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

The 300 mg kit includes (NDC 59148-045-80):
- 300 mg single-dose pre-filled dual chamber syringes containing ABILIFY MAINTENA (aripiprazole) for extended-release injectable suspension lyophilized powder and Sterile Water for Injection
- One 29 gauge, 1 inch (25 mm) hypodermic safety needle with needle protection device for deltoid administration in non-obese patients
- One 22 gauge, 1.5 inch (38 mm) hypodermic safety needle with needle protection device for gluteal administration in non-obese patients or deltoid administration in obese patients
- One 21 gauge, 2 inch (50 mm) hypodermic safety needle with needle protection device for gluteal administration in obese patients

The 400 mg kit includes (NDC 59148-072-80):
- 400 mg single-dose pre-filled dual chamber syringes containing ABILIFY MAINTENA (aripiprazole) for extended-release injectable suspension lyophilized powder and Sterile Water for Injection
- One 29 gauge, 1 inch (25 mm) hypodermic safety needle with needle protection device for deltoid administration in non-obese patients
- One 22 gauge, 1.5 inch (38 mm) hypodermic safety needle with needle protection device for deltoid administration in non-obese patients or deltoid administration in obese patients
- One 21 gauge, 2 inch (50 mm) hypodermic safety needle with needle protection device for gluteal administration in obese patients

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

The 300 mg kit includes (NDC 59148-017-17):
- 300 mg single-use vial of ABILIFY MAINTENA (aripiprazole) extended-release injectable suspension lyophilized powder
- 5 mL single-use vial of Sterile Water for Injection, USP
- One 3 mL luer lock syringe with pre-attached 21 gauge, 1.5 inch hypodermic safety needle with needle protection device
- One 3 mL luer lock disposable syringe with luer lock tip
- One vial adapter
- One 23 gauge, 1 inch (25 mm) hypodermic safety needle with needle protection device for deltoid administration in non-obese patients
- One 22 gauge, 1.5 inch (38 mm) hypodermic safety needle with needle protection device for deltoid administration in non-obese patients or deltoid administration in obese patients
- One 21 gauge, 2 inch (50 mm) hypodermic safety needle with needle protection device for gluteal administration in obese patients

The 400 mg kit includes (NDC 59148-019-71):
- 400 mg single-use vial of ABILIFY MAINTENA (aripiprazole) extended-release injectable suspension lyophilized powder
- 5 mL single-use vial of Sterile Water for Injection, USP
- One 3 mL luer lock syringe with pre-attached 21 gauge, 1.5 inch hypodermic safety needle with needle protection device
- One 3 mL luer lock disposable syringe with luer lock tip
- One vial adapter
- One 23 gauge, 1 inch (25 mm) hypodermic safety needle with needle protection device for deltoid administration in non-obese patients
- One 22 gauge, 1.5 inch (38 mm) hypodermic safety needle with needle protection device for deltoid administration in non-obese patients or deltoid administration in obese patients
- One 21 gauge, 2 inch (50 mm) hypodermic safety needle with needle protection device for gluteal administration in obese patients

15.2 Storage
Pre-filled dual chamber syringes:
Store below 30°C (86°F). Do not freeze. Protect the syringes from light by storing in the original package until time of use.

Vials:
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

Advises the patient to read the FDA-approved patient labeling (MEDICATION GUIDE)

Pathological Gambling and Other Compulsive Behaviors

Inform patients and their caregivers of the possibility that they may experience compulsive urges to shop, increased urges to gamble, compulsive sexual urges, binge eating and/or other compulsive urges and the inability to control these urges unless taking ABILIFY MAINTENA. In some cases, but not all, the urges were reported to have stopped when the dose was reduced or stopped [see WARNINGS AND PRECAUTIONS (5.5)].

Neuroleptic Malignant Syndrome

Inform patients about a potentially fatal adverse reaction referred to as NMS that has been reported in association with the administration of antipsychotic drugs. Advise patients to notify their health care provider if they notice any movements which they cannot control in their face, tongue, or other body part [see WARNINGS AND PRECAUTIONS (5.3)].

Tardive Dyskinesia

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

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

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

Orthostatic Hypotension

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

Lactic Acidosis

Advise patients that they should have their BOC monitored while receiving ABILIFY MAINTENA [see WARNINGS AND PRECAUTIONS (5.8)].

Interference with Cognitive and Motor Performance

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

Heat Exposure and Dehydration

Inform patients regarding appropriate care in avoiding over-heating and dehydration [see WARNINGS AND PRECAUTIONS (5.11)].

Concurrent Medication

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

Pregnancy

Inform patients that ABILIFY MAINTENA may cause extrapyramidal and/or withdrawal symptoms in a neonate and to notify their healthcare provider with a known or suspected pregnancy. Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ABILIFY MAINTENA during pregnancy [see USE IN SPECIFIC POPULATIONS (8.1)].

Distributed and marketed by

Otsuka America Pharmaceutical, Inc., Rockville, MD 20850 USA
Marketed by Lundbeck, Deerfield, IL 60015 USA

Otsuka MAINTENA is a trademark of Otsuka Pharmaceutical Company, Inc., Japan

09US161BR004 08/2016
© 2016, Otsuka Pharmaceutical Co., Ltd., Tokyo, 101-8355 Japan
**MEDICATION GUIDE**

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

(aripiprazole)

for extended-release injectable suspension, for intramuscular use

---

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

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

ABILIFY MAINTENA may cause serious side effects, including:

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

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

---

**What is ABILIFY MAINTENA?**

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

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

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

---

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

- have never taken ABILIFY (aripiprazole) before
- have diabetes or high blood sugar or a family history of diabetes or high blood sugar. Your healthcare provider should check your blood sugar before you start receiving ABILIFY MAINTENA and during your treatment.
- have or had seizures (convulsions)
- have or had low or high blood pressure
- have or had heart problems or a stroke
- have or had a low white blood cell count
- have any other medical problems including problems that may affect you receiving an injection in your arm or buttocks
- are pregnant or plan to become pregnant. It is not known if ABILIFY MAINTENA will harm your unborn baby.
- If you become pregnant while taking ABILIFY MAINTENA, talk to your healthcare provider about registering with the National Pregnancy Registry for Atypical Antipsychotics. You can register by calling 1-866-961-2388 or visit [http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/](http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/)
- are breastfeeding or plan to breastfeed. ABILIFY MAINTENA can pass into your milk and may harm your baby. Talk to your healthcare provider about the best way to feed your baby if you receive ABILIFY MAINTENA.

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

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

Your healthcare provider can tell you if it is safe to take ABILIFY MAINTENA with your other medicines. Do not start or stop any medicines while taking ABILIFY MAINTENA without talking to your healthcare provider first. Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

---

**How should I receive ABILIFY MAINTENA?**

- Follow your ABILIFY MAINTENA treatment schedule exactly as your healthcare provider tells you to.
- ABILIFY MAINTENA is an injection given in your arm or buttock by your healthcare provider 1 time every month. You may feel a little pain in your arm or buttock during your injection.
- After your first injection of ABILIFY MAINTENA you should continue your current antipsychotic medicine for 2 weeks.
- You should not miss a dose of ABILIFY MAINTENA. If you miss a dose for some reason, call your healthcare provider right away to discuss what you should do next.
What should I avoid while taking ABILIFY MAINTENA?
- Do not drive, operate machinery, or do other dangerous activities until you know how ABILIFY MAINTENA affects you. ABILIFY MAINTENA may make you feel drowsy.
- Do not drink alcohol while you receive ABILIFY MAINTENA.
- Do not become too hot or dehydrated while you receive ABILIFY MAINTENA.
  - Do not exercise too much.
  - In hot weather, stay inside in a cool place if possible.
  - Stay out of the sun.
  - Do not wear too much clothing or heavy clothing.
  - Drink plenty of water.

What are the possible side effects of ABILIFY MAINTENA?
- Uncontrolled body movements (tardive dyskinesia). ABILIFY MAINTENA may cause movements that you cannot control in your face, tongue, or other body parts. Tardive dyskinesia may not go away, even if you stop receiving ABILIFY MAINTENA. Tardive dyskinesia may also start after you stop receiving ABILIFY MAINTENA.
- Problems with your metabolism such as:
  - High blood sugar (hyperglycemia): Increases in blood sugar can happen in some people who take ABILIFY MAINTENA. Extremely high blood sugar can lead to coma or death. If you have diabetes or risk factors for diabetes (such as being overweight or a family history of diabetes), your healthcare provider should check your blood sugar before you start receiving ABILIFY MAINTENA and during your treatment.
  
Call your healthcare provider if you have any of these symptoms of high blood sugar while receiving ABILIFY MAINTENA:
  > feel very thirsty
  > need to urinate more than usual
  > feel very hungry
  > feel weak or tired
  > feel sick to your stomach
  > feel confused, or your breath smells fruity
  > Increased fat levels (cholesterol and triglycerides) in your blood.
  > Weight gain. You and your healthcare provider should check your weight regularly.
- Unusual urges. Some people taking ABILIFY MAINTENA have had unusual urges such as gambling, binge eating or eating that you cannot control (compulsive), compulsive shopping and sexual urges.
  
If you or your family members notice that you are having unusual urges or behaviors, talk to your healthcare provider.
- Decreased blood pressure (orthostatic hypotension). You may feel lightheaded or faint when you rise too quickly from a sitting or lying position.
  
- Low white blood cell count
- Seizures (convulsions)
- Problems controlling your body temperature so that you feel too warm. See “What should I avoid while receiving ABILIFY MAINTENA?”
- Difficulty swallowing

The most common side effect of ABILIFY MAINTENA includes feeling like you need to move to stop unpleasant feelings in your legs (restless leg syndrome or akathisia), injection site pain, or sleepiness (sedation).

Tell your healthcare provider if you have any side effect that bothers you or does not go away.

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

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

General information about the safe and effective use of ABILIFY MAINTENA

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

What are the ingredients in ABILIFY MAINTENA?
- **Active Ingredient:** aripiprazole monohydrate
- **Inactive ingredients:** carboxymethyl cellulose sodium, mannitol, sodium phosphate monobasic monohydrate and sodium hydroxide

ABILIFY MAINTENA is a trademark of Otsuka Pharmaceutical Company.
© 2016, Otsuka Pharmaceutical Co., Ltd., Tokyo, 101-8535 Japan

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