FACTS ABOUT ABILIFY MAINTENA™ (aripiprazole) for extended-release injectable suspension in patients with schizophrenia

About ABILIFY MAINTENA™ (aripiprazole)

- ABILIFY MAINTENA (aripiprazole) for extended-release injectable suspension is an intramuscular (IM) depot formulation of oral aripiprazole. ABILIFY MAINTENA provides the efficacy and safety profile of oral aripiprazole in a once-monthly injection for the treatment of schizophrenia.1,2
  - The mechanism of action for aripiprazole in the treatment of schizophrenia is unknown. However, the efficacy of aripiprazole may be driven by a combination of partial agonist activity at D2 and 5-HT1A receptors and antagonist activity at 5-HT2A receptors.3
  - ABILIFY MAINTENA is available in 300mg and 400mg kits and is injected directly into the buttocks muscle.4
- Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk (1.6 to 1.7 times) of death compared to placebo (4.5% vs. 2.6%, respectively). Although the causes of death were varied, most of the deaths appeared to be cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. ABILIFY MAINTENA is not approved for the treatment of patients with dementia-related psychosis. (see Important Safety Information below).1

Product Characteristics

- ABILIFY MAINTENA is a sterile lyophilized powder that, when reconstituted with sterile water for injection, forms an injectable suspension that is administered monthly.1,2
- Tolerability with oral aripiprazole must be established prior to initiating treatment with ABILIFY MAINTENA.1
- After an initial injection of ABILIFY MAINTENA along with an overlapping 14-day dosing of oral antipsychotic treatment, subsequent injections of ABILIFY MAINTENA provide uninterrupted medication coverage for 30 days at a time.1,2
- The recommended starting and maintenance dose of ABILIFY MAINTENA is 400 mg monthly. Healthcare professionals may consider reducing the dosage to 300 mg monthly if a patient experiences adverse reactions.1

Addressing an Unmet Need

- Relapse prevention is an important consideration in the treatment of patients with schizophrenia. ABILIFY MAINTENA met the Phase 3 clinical trial primary endpoint of significantly delayed time to relapse.1
- Depot formulations of antipsychotic agents provide patients with blood concentrations of active drug that remain at a therapeutic range for an extended period of time.4
- Depot formulations also allow psychiatrists, nurses and caregivers to track when a patient does not return for a scheduled injection.5

Phase 3 Study Efficacy and Safety Data (See “Aripiprazole IM Depot Pivotal Phase 3 Study Backgrounder” for more information)

- The approval of ABILIFY MAINTENA is based on results from a 52-week, placebo-controlled, double-blind, randomized-withdrawal, Phase 3 maintenance trial of ABILIFY MAINTENA in patients with schizophrenia. Additional support for efficacy was derived from oral aripiprazole trials.1
  - The safety profile of ABILIFY MAINTENA is expected to be similar to that of oral aripiprazole.1
  - Serious AEs were reported by 4.1% for ABILIFY MAINTENA vs. 6.7% for placebo during the maintenance phase.2

Please see IMPORTANT SAFETY INFORMATION on following pages.

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INDICATION and IMPORTANT SAFETY INFORMATION for ABILIFY MAINTENA™ (aripiprazole) for extended-release injectable suspension

INDICATION

ABELIFY MAINTENA is an atypical antipsychotic 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.

IMPORTANT SAFETY INFORMATION

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk (1.6 to 1.7 times) of death compared to placebo (4.5% vs 2.6%, respectively). 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 cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. ABILIFY MAINTENA is not approved for the treatment of patients with dementia-related psychosis.

Contraindication: Known hypersensitivity reaction to aripiprazole. Reactions have ranged from pruritus/urticaria to anaphylaxis.

Cerebrovascular Adverse Events, Including Stroke: Increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, have been reported in clinical trials of elderly patients with dementia-related psychosis treated with oral aripiprazole.

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as NMS may occur with administration of antipsychotic drugs, including ABILIFY MAINTENA. Rare cases of NMS occurred during aripiprazole treatment. Signs and symptoms of NMS include hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (e.g., irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. 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.

Tardive Dyskinesia (TD): The risk of developing TD (a syndrome of abnormal, involuntary movements) and the potential for it to become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic increase. The syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. Prescribing should be consistent with the need to minimize TD. There is no known treatment for established TD, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.

Metabolic Changes: Atypical antipsychotic drugs have been associated with metabolic changes that include:

- **Hyperglycemia/Diabetes Mellitus:** Hyperglycemia, in some cases extreme and associated with ketoacidosis, coma, or death, has been reported in patients treated with atypical antipsychotics including aripiprazole. Patients with diabetes should be regularly monitored for worsening of glucose control; those with risk factors for diabetes should undergo baseline and periodic fasting blood glucose testing. 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 should also undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

- **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 low-density lipoproteins (LDLs), and fasting/nonfasting high-density lipoproteins (HDLs).

- **Weight Gain:** Weight gain has been observed. Clinical monitoring of weight is recommended.

(continued on next page)
Orthostatic Hypotension: Aripiprazole may cause orthostatic hypotension. ABILIFY MAINTENA should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or conditions which would predispose them to hypotension.

Leukopenia, Neutropenia, and Agranulocytosis: Leukopenia, neutropenia, and agranulocytosis have been reported. Patients with a history of clinically significant low white blood cell (WBC) count or drug-induced leukopenia/neutropenia should have their complete blood count monitored frequently during the first few months of therapy while receiving ABILIFY MAINTENA. In such patients, consider discontinuation of ABILIFY MAINTENA at the first sign of a clinically significant decline in WBC count in the absence of other causative factors.

Seizures/Convulsions: ABILIFY MAINTENA should be used with caution in patients with a history of seizures or with conditions that lower the seizure threshold.

Potential for Cognitive and Motor Impairment: ABILIFY MAINTENA may impair judgment, thinking, or motor skills. Instruct patients to avoid operating hazardous machinery including automobiles until they are certain ABILIFY MAINTENA does not affect them adversely.

Body Temperature Regulation: Disruption of the body’s ability to reduce core body temperature has been attributed to antipsychotic agents. Advise patients regarding appropriate care in avoiding overheating and dehydration. Appropriate care is advised for patients who may exercise strenuously, may be exposed to extreme heat, receive concomitant medication with anticholinergic activity, or are subject to dehydration.

Dysphagia: Esophageal dysmotility and aspiration have been associated with ABILIFY MAINTENA; use caution in patients at risk for aspiration pneumonia.

Alcohol: Advise patients to avoid alcohol while taking ABILIFY MAINTENA.

Concomitant Medication: 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. If the CYP3A4 inhibitor or CYP2D6 inhibitor is withdrawn, the ABILIFY MAINTENA dosage may need to be increased. 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.

Most commonly observed adverse reaction: The safety profile of ABILIFY MAINTENA is expected to be similar to that of oral aripiprazole. In patients who tolerated and responded to oral aripiprazole and single-blind ABILIFY MAINTENA and were then randomized to receive ABILIFY MAINTENA or placebo injections, the incidence of adverse reactions was similar between the two treatment groups. The adverse reaction ≥ 5% incidence and at least twice the rate of placebo for oral aripiprazole vs. placebo, respectively, was:

- Akathisia (8% vs 4%) in adult patients with schizophrenia.

Injection Site Reactions: 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.

Dystonia is a class effect of antipsychotic drugs. Symptoms of dystonia may occur in susceptible individuals during the first days of treatment and at low doses.

Pregnancy/Nursing: Based on animal data, may cause fetal harm. ABILIFY MAINTENA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. 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.

Please see accompanying FULL PRESCRIBING INFORMATION, including Boxed WARNING, for ABILIFY MAINTENA.
References

1. Prescribing Information. ABILIFY MAINTENATM (aripiprazole) for extended-release injectable suspension. August 2012.


