ABILIFY MAINTENA® (aripiprazole) may be an appropriate choice for your adult patients living with bipolar I disorder

Bipolar I disorder patient profile

Current presentation

- Currently prescribed an oral antipsychotic
- Patient presents as stable

Patient history

- Unclear if patient consistently refills prescriptions
- Family has reported verbal aggression or arguing in the past
- 2 psychiatric hospitalizations in the past year due to manic episodes
- Diagnosed with bipolar I disorder after history of manic, mixed, and depressive episodes*

*ABILIFY MAINTENA demonstrated no substantial difference in the time to a depressive episode vs placebo.

BP-I=bipolar I disorder.

INDICATIONS

ABILIFY MAINTENA® (aripiprazole) is an atypical antipsychotic indicated for:

- Treatment of schizophrenia in adults
- Maintenance monotherapy treatment of bipolar I disorder in adults

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

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at increased risk of death (1.6 to 1.7 times) compared to placebo-treated patients. ABILIFY MAINTENA is not approved for the treatment of patients with dementia-related psychosis.

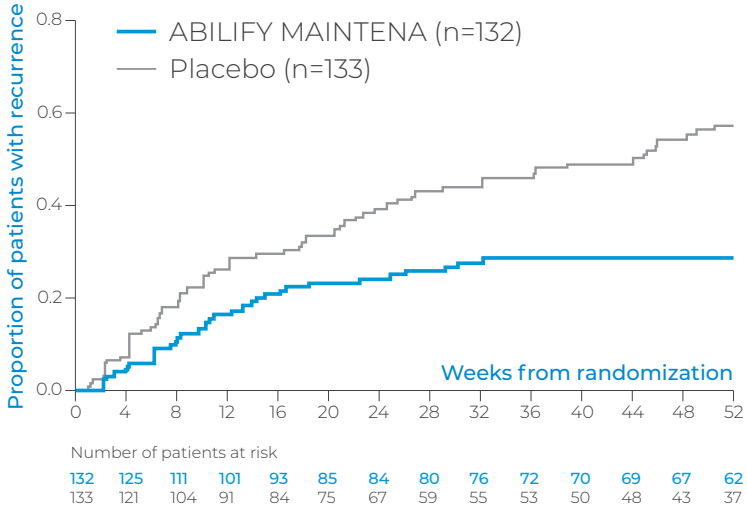
Please see IMPORTANT SAFETY INFORMATION on pages 5 and 6.

400MG
Abilify Maintena
(aripiprazole) for extended release injectable suspension

PIVOTAL 52-WEEK MAINTENANCE STUDY OF ADULT PATIENTS WITH BIPOLAR I DISORDER

ABILIFY MAINTENA® (aripiprazole) significantly delayed time to recurrence* of any mood episode vs placebo (*P*<0.0001)[1†]

Primary endpoint: **Time from randomization to recurrence* of any mood episode**[1]



- Significantly delayed time to recurrence for a manic episode and mixed episode. No substantial difference in the time to a depressive episode[1]
- Significantly reduced the risk of recurrence of any mood episode by 55% vs placebo (HR=0.45 [95% CI, 0.30-0.68], *P*<0.0001)[1†]
- The hazard ratio was used to calculate the reduction in risk of recurrence for patients on ABILIFY MAINTENA vs placebo[1]

*Recurrence was defined as clinical worsening, psychiatric hospitalization, or increased risk of suicide.[1]
†This figure is based on a total of 103 recurrences.
CI=confidence interval; HR=hazard ratio; IM=intramuscular; YMRS=Young Mania Rating Scale.

Study design

52-week multiphase maintenance study of patients with bipolar I disorder with a history of ≥1 manic or mixed episode that required hospitalization or treatment with either a mood stabilizer or antipsychotic. Baseline patient characteristics included patients currently experiencing a manic episode and ≥20 YMRS total score; patients were excluded if they experienced ≥9 episodes (rapid cycling) in the past year.[1]

Phases consisted of an open-label Phase 1 (conversion to oral aripiprazole), an open-label Phase 2 (stabilization on oral aripiprazole 15 mg to 30 mg once daily), a single-blind Phase 3 (conversion and stabilization on ABILIFY MAINTENA 400 mg; patients continued on oral aripiprazole 10 mg to 20 mg for the first 14 days following the initial ABILIFY MAINTENA dose), and a double-blind, placebo-controlled, randomized Phase 4 in which patients received either ABILIFY MAINTENA (n=133) or placebo IM depot (n=133).[1]

Contraindication

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

Important Warning and Precaution Regarding 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.

Please see IMPORTANT SAFETY INFORMATION on pages 5 and 6.

PIVOTAL 52-WEEK MAINTENANCE STUDY OF ADULT PATIENTS WITH BIPOLAR I DISORDER

ABILIFY MAINTENA® (aripiprazole) significantly reduced the risk of recurrence of manic or mixed mood episodes over 1 year vs placebo[2]*

Secondary endpoint: **Recurrence of manic or mixed episodes**

75%

REDUCED RISK OF RECURRENCE OF **MANIC** OR **MIXED MOOD EPISODES** vs PLACEBO
(HR=0.249 [95% CI, 0.137-0.451], *P*<0.0001)[2]

- Significantly delayed time to recurrence for a manic episode (HR=0.259 [95% CI, 0.136-0.495], *P*<0.0001) or mixed episode (HR=0.202 [95% CI, 0.044-0.939], *P*=0.0237)[2]
- No substantial difference in the time to a depressive episode (HR=0.932 [95% CI, 0.497-1.747], *P*=0.8247)[2]
- The hazard ratio was used to calculate the reduction in risk of recurrence for patients on ABILIFY MAINTENA vs placebo

*Recurrence was defined as clinical worsening, psychiatric hospitalization, or increased risk of suicide.[1]
CI=confidence interval; HR=hazard ratio.

Important Warning and Precaution Regarding Neuroleptic Malignant Syndrome (NMS)

NMS is a potentially fatal symptom complex reported in association with administration of antipsychotic drugs including ABILIFY MAINTENA. Clinical signs of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability. Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. Manage NMS with immediate discontinuation of ABILIFY MAINTENA, intensive symptomatic treatment, and monitoring.

Please see IMPORTANT SAFETY INFORMATION on pages 5 and 6.

References: 1. Calabrese JR, Sanchez R, Jin N, et al. Efficacy and safety of aripiprazole once-monthly in the maintenance treatment of bipolar I disorder: a double-blind, placebo-controlled, 52-week randomized withdrawal study. *J Clin Psychiatry*. 2017;78(3):324-331.
2. Data on file. ABIMAI-178.

PLACEBO-CONTROLLED, 12-WEEK STUDY OF ADULT PATIENTS WITH SCHIZOPHRENIA

ABILIFY MAINTENA® (aripiprazole) clinical safety profile

Adverse reactions in ≥2% of patients

		PERCENTAGE OF PATIENTS REPORTING REACTION*	
SYSTEM ORGAN CLASS	PREFERRED TERM	ABILIFY MAINTENA (n=167)	PLACEBO (n=172)
GASTROINTESTINAL DISORDERS	Constipation	10	7
	Dry mouth	4	2
	Diarrhea	3	2
	Vomiting	3	1
	Abdominal discomfort	2	1
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Injection site pain	5	1
INFECTIONS AND INFESTATIONS	Upper respiratory tract infection	4	2
INVESTIGATIONS	Increased weight	17	7
	Decreased weight	4	2
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Arthralgia	4	1
	Back pain	4	2
	Myalgia	4	2
	Musculoskeletal pain	3	1
NERVOUS SYSTEM DISORDERS	Akathisia	11	4
	Sedation	5	1
	Dizziness	4	2
	Tremor	3	1
RESPIRATORY, THORACIC, AND MEDIASTINAL	Nasal congestion	2	1

*Table excludes adverse reactions that had an incidence ≤ placebo.

ADVERSE EVENTS (≥5% and at least twice that for placebo)

Based on a 12-week, placebo-controlled pivotal trial of ABILIFY MAINTENA in adults with schizophrenia, the most commonly observed adverse reactions associated with the use of ABILIFY MAINTENA were:

	ABILIFY MAINTENA % (n=167)	PLACEBO % (n=172)
Increased weight	16.8	7.0
Akathisia	11.4	3.5
Injection site pain	5.4	0.6
Sedation	5.4	1.2

Please see IMPORTANT SAFETY INFORMATION on pages 5 and 6.

INDICATIONS and IMPORTANT SAFETY INFORMATION for ABILIFY MAINTENA® (aripiprazole)

INDICATIONS

ABILIFY MAINTENA is an atypical antipsychotic indicated for:

- Treatment of schizophrenia in adults
- Maintenance monotherapy treatment of bipolar I disorder in adults

IMPORTANT SAFETY INFORMATION

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

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at increased risk of death (1.6 to 1.7 times) compared to placebo-treated patients. 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): NMS is a potentially fatal symptom complex reported in association with administration of antipsychotic drugs including ABILIFY MAINTENA. Clinical signs of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability. Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. Manage NMS with immediate discontinuation of ABILIFY MAINTENA, intensive symptomatic treatment, and monitoring.

Tardive Dyskinesia (TD): Risk of TD, and the potential to become irreversible, are believed to increase with duration of treatment and total cumulative dose of antipsychotic drugs. TD can develop after a relatively brief treatment period, even at low doses, or after discontinuation of treatment. Prescribing should be consistent with the need to minimize TD. If antipsychotic treatment is withdrawn, TD may remit, partially or completely.

Metabolic Changes: Atypical antipsychotic drugs have caused metabolic changes including:

- **Hyperglycemia/Diabetes Mellitus:** Hyperglycemia, in some cases extreme and associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients treated with atypical antipsychotics including aripiprazole. Patients with diabetes mellitus should be regularly monitored for worsening of glucose control; those with risk factors for diabetes (e.g., obesity, family history of 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.
- **Weight Gain:** Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Pathological Gambling and Other Compulsive Behaviors: Intense urges, particularly for gambling, and the inability to control these urges have been reported while taking aripiprazole. Other compulsive urges have been reported less frequently. Prescribers should ask patients or their caregivers about the development of new or intense compulsive urges. Consider dose reduction or stopping aripiprazole if such urges develop.

Orthostatic Hypotension: ABILIFY MAINTENA may cause orthostatic hypotension and should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or conditions which would predispose them to hypotension.

(Continued on following page)

IMPORTANT SAFETY INFORMATION for ABILIFY MAINTENA® (aripiprazole) *(cont'd)*

Falls: Antipsychotics may cause somnolence, postural hypotension, motor and sensory instability, which may lead to falls causing fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating treatment and recurrently during therapy.

Leukopenia, Neutropenia, and Agranulocytosis: Leukopenia, neutropenia and agranulocytosis have been reported with antipsychotics. Monitor complete blood count in patients with pre-existing low white blood cell count (WBC)/absolute neutrophil count or history of drug-induced leukopenia/neutropenia. Discontinue ABILIFY MAINTENA at the first sign of a clinically significant decline in WBC and in severely neutropenic patients.

Seizures: 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: Use ABILIFY MAINTENA with caution in patients who may experience conditions that increase body temperature (e.g., strenuous exercise, extreme heat, dehydration, or concomitant use with anticholinergics).

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. Avoid concomitant use of CYP3A4 inducers with ABILIFY MAINTENA for greater than 14 days. 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 Reactions: The most commonly observed adverse reactions with ABILIFY MAINTENA in patients with schizophrenia (incidence ≥5% and at least twice that for placebo) were increased weight, akathisia, injection site pain, and sedation.

Injection Site Reactions: In a short-term, clinical trial with ABILIFY MAINTENA in patients with schizophrenia treated with gluteal administered ABILIFY MAINTENA, the percent of patients reporting any injection site-related adverse reaction was 5.4%, and 0.6% for placebo. In an open label study of ABILIFY MAINTENA administered in the deltoid or gluteal muscle, injection site pain was observed at approximately equal rates.

Dystonia: Symptoms of dystonia may occur in susceptible individuals during the first days of treatment and at low doses.

Pregnancy: Neonates exposed to antipsychotic drugs, including ABILIFY MAINTENA, during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms. 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.

Lactation: Aripiprazole is present 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 and any potential risks to the infant.

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

Please see FULL PRESCRIBING INFORMATION, including BOXED WARNING.