ABILIFY ASIMTUFII® (aripiprazole) FOR THE MAINTENANCE TREATMENT OF BIPOLAR I DISORDER IN ADULTS

960MG
AbilifyAsimtufii®
(aripiprazole) extended release suspension for injection

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

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

INDICATIONS

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

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

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

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

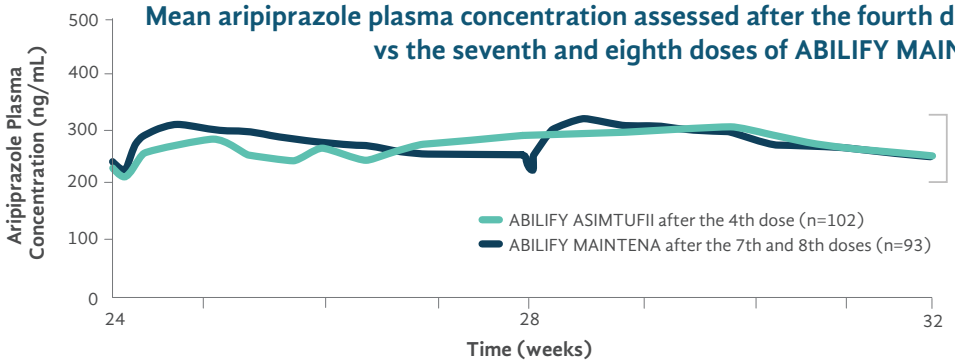
WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

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 ASIMTUFII and ABILIFY MAINTENA are not approved for the treatment of patients with dementia-related psychosis.

ABILIFY ASIMTUFII is the only FDA-approved long-acting injectable (LAI) that is administered once every 2 months for the maintenance monotherapy treatment of bipolar I disorder in adults. It uses the same active molecule as ABILIFY MAINTENA, but works over a longer time frame.[1]

In a 32-week open-label, pharmacokinetic bridging study, in adult patients living with schizophrenia or bipolar I disorder, ABILIFY ASIMTUFII 960 mg demonstrated comparable aripiprazole plasma concentrations, and thus comparable efficacy, to ABILIFY MAINTENA 400 mg throughout the 2-month dosing interval.[1]

Mean aripiprazole plasma concentration assessed after the fourth dose of ABILIFY ASIMTUFII vs the seventh and eighth doses of ABILIFY MAINTENA



Over this 2-month dosing interval, the mean aripiprazole plasma concentration of ABILIFY ASIMTUFII remained **between 200 ng/mL and 320 ng/mL[2]**

Contraindication

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

Please see **IMPORTANT SAFETY INFORMATION**, including **BOXED WARNING**, on pages 6 and 7.

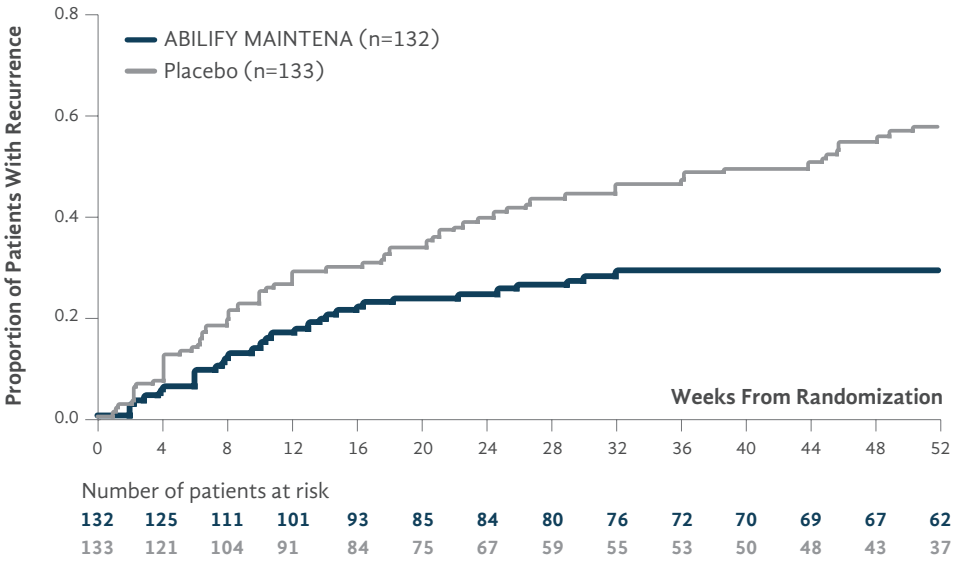
February 2025 23US25EXP0043

The efficacy of ABILIFY ASIMTUFII® (aripiprazole) is based on an adequate and well-controlled study of ABILIFY MAINTENA® (aripiprazole) for the treatment of bipolar I disorder in adults. In a 52-week multiphase maintenance study of ABILIFY MAINTENA, phases consisted of[3]

Phase 1 4-6 weeks	Phase 2 2-8 weeks	Phase 3 12-28 weeks	Phase 4 Up to 52 weeks
Conversion to oral aripiprazole (n=466)	**Stabilization** on oral aripiprazole (n=632)	**Conversion** to and **stabilization** on ABILIFY MAINTENA* (n=425)	**Randomization** to ABILIFY MAINTENA (n=133) or placebo (n=133)

Safety was assessed throughout the duration of the study.

Results from the 52-week pivotal study showed that ABILIFY MAINTENA significantly delayed the time to recurrence† of any mood episode compared to the placebo.[3]



PRIMARY ENDPOINT

Time from randomization to recurrence of any mood episode

55% reduced risk

of recurrence of any mood episode vs placebo

HR=0.45 (95% CI, 0.30-0.68), *P*<0.0001

*Patients continued on oral aripiprazole for the first 14 days following the initial ABILIFY MAINTENA dose.
†Recurrence was defined as one or more of the following: Clinical worsening, psychiatric hospitalization, or increase risk of suicide.

Important Warning and Precaution for 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.

CI=confidence interval. HR=hazard ratio.

Please see **IMPORTANT SAFETY INFORMATION**, including the **BOXED WARNING**, on pages 6 and 7.

Exploratory endpoint: Recurrence of manic, mixed, or depressive episodes in the ABILIFY MAINTENA® (aripiprazole) bipolar I disorder maintenance monotherapy study[4]

75% reduced risk
of recurrence of mixed/manic mood episodes vs placebo
HR=0.249 (95% CI, 0.137-0.451)

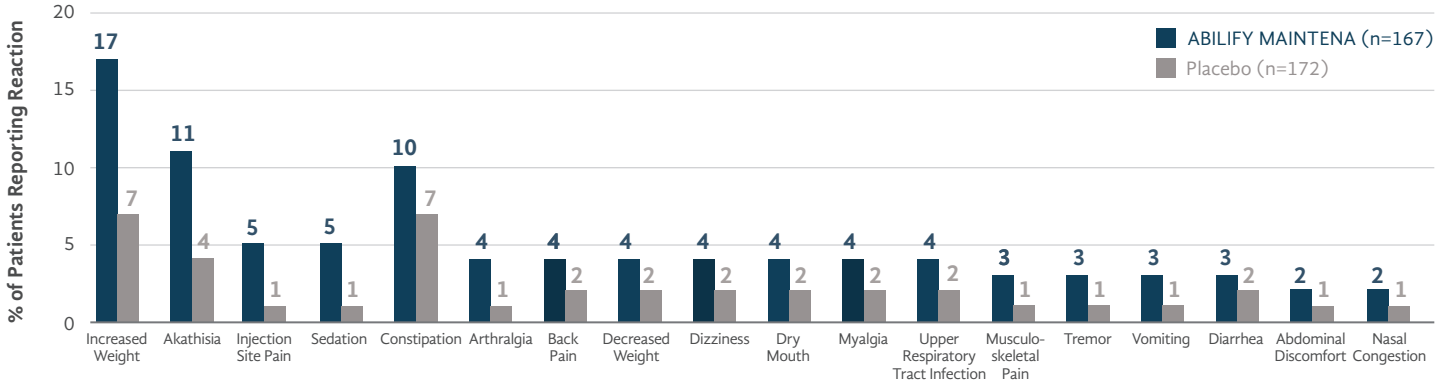
Delayed time to recurrence
for a manic episode
HR=0.259 (95% CI, 0.136-0.495)
or mixed episode
HR=0.202 (95% CI, 0.044-0.939)

No substantial difference
in the time to depressive episode
HR=0.932 (95% CI, 0.407-1.747)

Data limitation: The pivotal maintenance trial was not designed to assess, nor statistically powered to examine, the combined risk of mixed/manic episodes, excluding depressive episodes. These results require cautious interpretation and may represent chance findings.

Clinical safety profile: ABILIFY MAINTENA 12-week schizophrenia study[5]

Adverse Reactions in ≥2% of Patients Treated With ABILIFY MAINTENA*



In a 12-week study, 4.2% of patients on ABILIFY MAINTENA discontinued due to all adverse reactions vs 7.6% with placebo.

The safety profile of ABILIFY ASIMTUFII was comparable to that seen with ABILIFY MAINTENA.[1]

*Excludes adverse reactions that had an incidence equal to or less than placebo.

The percentage of patients in an open-label study reporting any injection site-related adverse reactions (all reported as injection site pain) was 19% for patients treated with ABILIFY ASIMTUFII 960 mg and 9% for patients treated with ABILIFY MAINTENA 400 mg.[1]

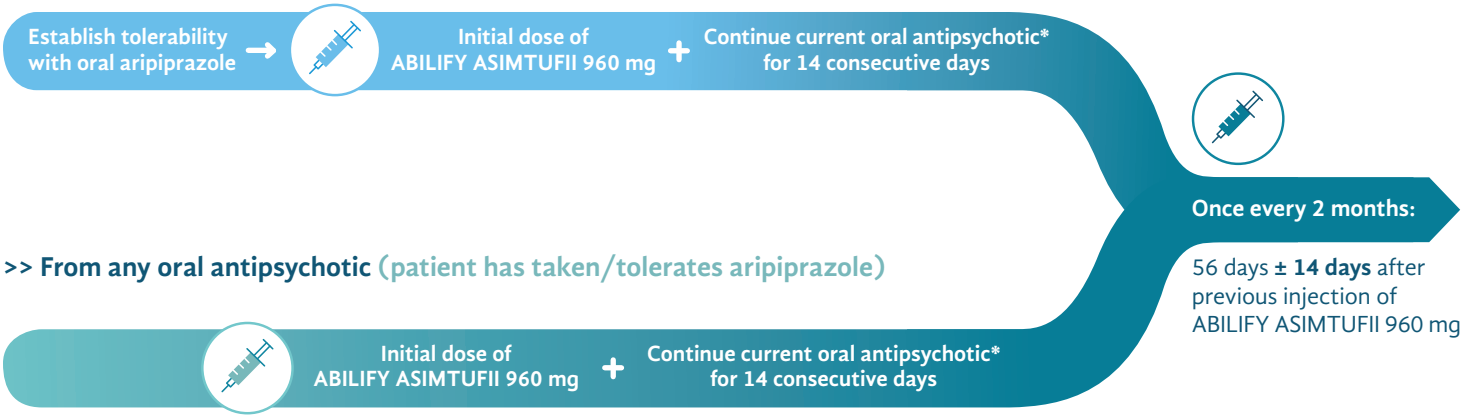
Important Warning and Precaution for Neuroleptic Malignant Syndrome (NMS)
NMS is a potentially fatal symptom complex reported in association with administration of antipsychotic drugs including aripiprazole. Clinical signs of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of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

Please see **IMPORTANT SAFETY INFORMATION**, including the **BOXED WARNING**, on pages 6 and 7.

The recommended dosage of ABILIFY ASIMTUFII® (aripiprazole) is 960 mg, administered once every 2 months (56 days after previous injection). If a patient is new to aripiprazole, tolerability must be established before initiating treatment with ABILIFY ASIMTUFII. Due to the half-life of oral aripiprazole, this may take up to 2 weeks.

Initiating ABILIFY ASIMTUFII

>> From any oral antipsychotic (patient is naïve to aripiprazole)



Administer ABILIFY ASIMTUFII by intramuscular injection in the gluteal muscle by a healthcare professional. **Do not administer by any other route**. If there are adverse reactions with the ABILIFY ASIMTUFII 960 mg dosage, the dosage may be reduced to 720 mg once every 2 months.
*Oral aripiprazole (10 mg to 20 mg) or current oral antipsychotic.

The dosing window for ABILIFY ASIMTUFII is flexible. Patients may be given the ABILIFY ASIMTUFII injection up to 2 weeks before or 2 weeks after the 2-month scheduled timepoint.

Recommendations for missed doses

Important Warning and Precaution for Tardive Dyskinesia
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.

Please see **IMPORTANT SAFETY INFORMATION**, including the **BOXED WARNING**, on pages 6 and 7.

Dosage adjustments can be made for patients who are CYP2D6 poor metabolizers and/or in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors for more than 14 days.

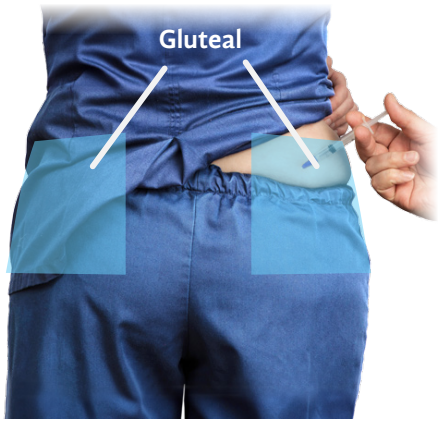
Adjustments based on CYP2D6 metabolism or concomitant medications

○ 720 mg once every 2 months ⊖ Avoid use

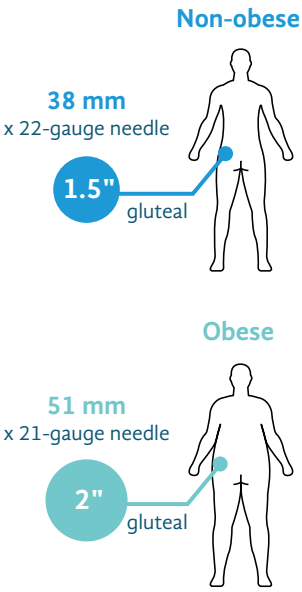
Factors		ABILIFY ASIMTUFII® (aripiprazole) adjusted dose
CYP2D6 poor metabolizers	Known CYP2D6 poor metabolizers	○
	Known CYP2D6 poor metabolizers taking concomitant CYP3A4 inhibitors	⊖
Patients taking ABILIFY ASIMTUFII	Concomitant use of strong CYP2D6 inhibitors	○
	Concomitant use of strong CYP3A4 inhibitors	○
	Concomitant use of strong CYP2D6 **and** CYP3A4 inhibitors	⊖
	Concomitant use of CYP3A4 inducers	⊖

ABILIFY ASIMTUFII administration

Ease of injection
just below the waistline



- Intramuscular **gluteal injection**
- Do not administer **by any other route**
- **Prefilled syringe** (no reconstitution required)



Important Warning and Precaution for 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 antidiabetic treatment despite discontinuation of the suspect drug.

Please see **IMPORTANT SAFETY INFORMATION**, including the **BOXED WARNING**, on pages 6 and 7.

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

INDICATIONS

ABILIFY ASIMTUFII® (aripiprazole) is an atypical antipsychotic indicated for:
- Treatment of schizophrenia in adults
- Maintenance monotherapy treatment of bipolar I disorder in adults

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 ASIMTUFII and ABILIFY MAINTENA are 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 ASIMTUFII. 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 ASIMTUFII, intensive symptomatic treatment, and monitoring.

Tardive Dyskinesia (TD): Risk of TD, and the potential to become irreversible, is 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 antidiabetic 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 or Syncope: ABILIFY ASIMTUFII and 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. Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension.

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.

(Continued on next page)

Please See **FULL PRESCRIBING INFORMATION**, including **BOXED WARNING**, for ABILIFY ASIMTUFII and ABILIFY MAINTENA.

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

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 ASIMTUFII or ABILIFY MAINTENA at the first sign of a clinically significant decline in WBC and in severely neutropenic patients.

Seizures: ABILIFY ASIMTUFII and 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 ASIMTUFII and ABILIFY MAINTENA may impair judgment, thinking, or motor skills. Patients should be cautioned about performing activities that require mental alertness such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that therapy with ABILIFY ASIMTUFII or ABILIFY MAINTENA does not affect them adversely.

Body Temperature Regulation: Use ABILIFY ASIMTUFII or 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 aripiprazole. Use caution in patients at risk for aspiration.

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

Concomitant Medications: Dosage reductions are recommended in patients who are CYP2D6 poor metabolizers and/or in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors for greater than 14 days. Avoid concomitant use of CYP3A4 inducers with ABILIFY ASIMTUFII and 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 of ≥5% and at least twice that for placebo) were increased weight, akathisia, injection site pain, and sedation.

Injection Site Reactions:

- **ABILIFY MAINTENA:** In a short-term, clinical trial with ABILIFY MAINTENA in patients with schizophrenia treated with gluteally 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.
- **ABILIFY ASIMTUFII:** In an open-label study in patients with schizophrenia or bipolar I disorder, the percent of patients reporting any injection site-related adverse reactions was 19% for ABILIFY ASIMTUFII and 9.0% for ABILIFY MAINTENA. In both treatment groups, the majority of the injection site pain events coincided with the first injection and were reported with decreasing frequency upon subsequent injections. Patient-reported rating of pain was similar in both treatment groups at the last injection.

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 aripiprazole, during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms. There are risks to the mother associated with untreated schizophrenia or bipolar I disorder and with exposure to antipsychotics, including ABILIFY ASIMTUFII and ABILIFY MAINTENA, during pregnancy.

Lactation: Aripiprazole is present in human breast milk. Monitor the breastfed infant for dehydration and lack of appropriate weight gain. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ABILIFY ASIMTUFII or ABILIFY MAINTENA and any potential adverse effects on the breastfed infant from ABILIFY ASIMTUFII or ABILIFY MAINTENA or from the underlying maternal condition.

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 accompanying FULL PRESCRIBING INFORMATION, including **BOXED WARNING**, for ABILIFY ASIMTUFII and ABILIFY MAINTENA.

1. Harlin M, Yildirim M, Such P, Madera-McDonough J, Jan M, Jin N, et al. A randomized, open-label, multiple-dose, parallel-arm, pivotal study to evaluate the safety, tolerability, and pharmacokinetics of aripiprazole 2-month long-acting injectable in adults with schizophrenia or bipolar I disorder. *CNS Drugs*. 2023;37:337-350. **2.** Data on file. ABIASI-023. **3.** 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. **4.** Data on file. ABIMAI-178. **5.** Kane JM, Peters-Strickland T, Baker RA, et al. Aripiprazole once-monthly in the acute treatment of schizophrenia: findings from a 12-week, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*. 2014;75(11):1254-1260.

February 2025 23US25EXP0043