Aripiprazole Monohydrate 2-month (Abilify Asimtufii) National Drug Monograph November 2023

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action

- Aripiprazole is an atypical antipsychotic which is present in aripiprazole monohydrate 1-month (Abilify Maintena) and aripiprazole monohydrate 2-month (Abilify Asimtufii) as its monohydrate polymorphic form.
- The mechanism of action of aripiprazole in the treatment of schizophrenia and bipolar I disorder is unknown. The efficacy of aripiprazole could be mediated through a combination of partial agonist activity at dopamine D_2 and serotonin 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors.

Indication(s) Under Review in This Document

- Aripiprazole monohydrate 2-month is indicated for the treatment of schizophrenia in adults and for maintenance monotherapy treatment of bipolar I disorder in adults.

Dosage Form(s) Under Review

- Injection: 720 mg/2.4 ml to be given as an intramuscular (IM) gluteal injection every 2 months.
- Injection: 960 mg/3.2 ml to be given as an intramuscular (IM) gluteal injection every 2 months.

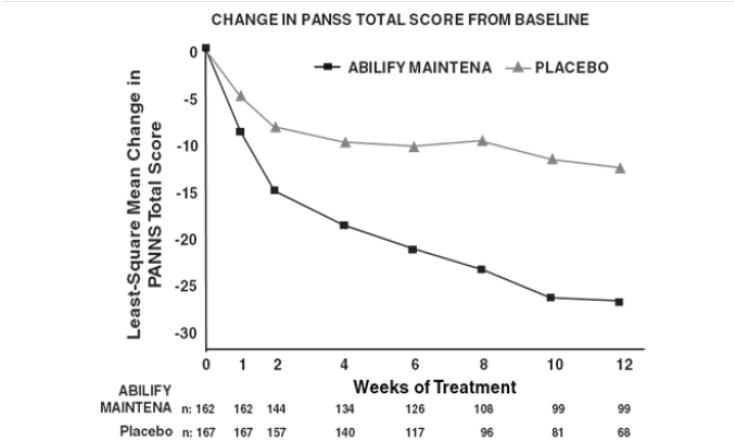
Clinical Evidence Summary

Efficacy Considerations

Schizophrenia

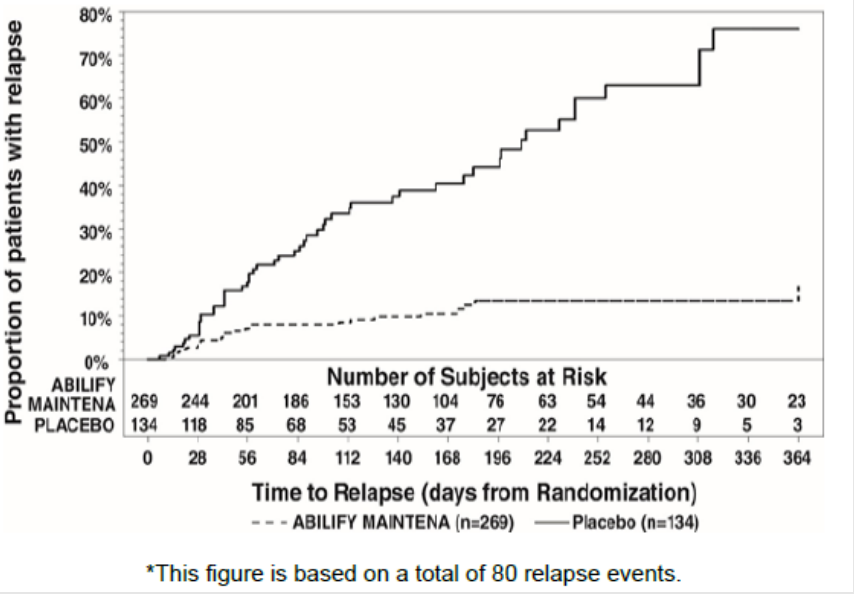
- The efficacy of aripiprazole monohydrate 2-month for the treatment of schizophrenia in adults is based on adequate and well-controlled studies of aripiprazole monohydrate 1-month The results of these adequate and well-controlled studies are presented below.
- The efficacy of aripiprazole monohydrate 1-month for treatment of schizophrenia was established in:
    - One short-term (12-week), randomized, double-blind, placebo-controlled trial in acutely relapsed adults (Study 1).[13]

- In this 12-week study (n=339) comparing aripiprazole monohydrate 1-month (n=167) to placebo (n=172), patients were administered 400 mg aripiprazole monohydrate 1-month or placebo on days 0, 28, and 56. The dose could be adjusted down and up within the range of 400 to 300 mg on a one-time basis. Aripiprazole monohydrate 1-month was superior to placebo in improving the Positive and Negative Syndrome Scale (PANSS) total score at the end of week 10 (primary outcome).[13]



n = the number of patients remaining in the respective study arm at each time point

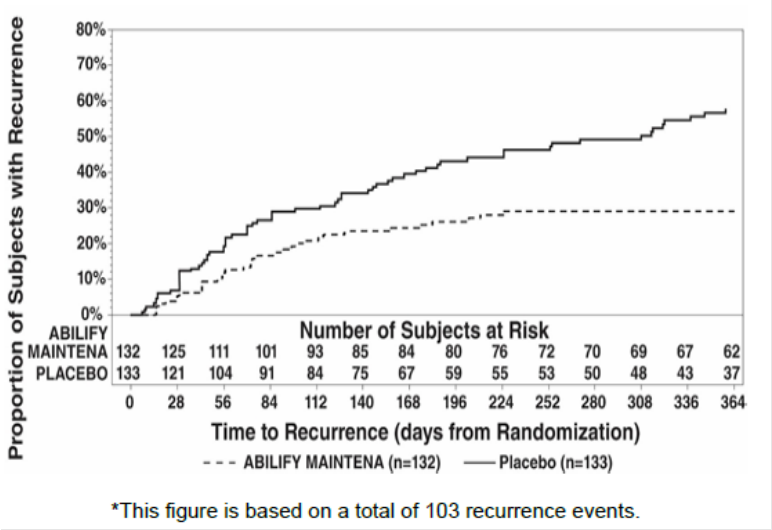
- One longer-term, double-blind, placebo-controlled, randomized-withdrawal (maintenance) trial in adults (Study 2).[12]
  - The primary efficacy endpoint was time from randomization to relapse. A pre-planned interim analysis demonstrated a statistically significantly longer time to relapse in patients randomized to the aripiprazole monohydrate 1-month 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 aripiprazole monohydrate 1-month group than compared to placebo-treated patients.[12]



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

Bipolar 1 Disorder

- The efficacy of aripiprazole monohydrate 2-month for the treatment of maintenance monotherapy treatment of bipolar I disorder in adults is based on an adequate and well-controlled study of aripiprazole monohydrate 1-month. The results of the adequate and well-controlled study are presented below.
- The efficacy of aripiprazole monohydrate 1-month for the maintenance treatment of bipolar I disorder was established in a 52-week, double-blind, placebo-controlled, randomized withdrawal trial in adult patients who were experiencing a manic episode at trial entry, met DSM-IV-TR criteria for bipolar I disorder, and had a history of at least one previous manic or mixed episode with manic symptoms of sufficient severity to require one of the following interventions: hospitalization and/or treatment with a mood stabilizer, and/or treatment with an antipsychotic agent.[10]
    - The primary efficacy endpoint was time from randomization to recurrence of any mood episode. Analysis demonstrated a statistically significantly longer time to recurrence of any mood episode in subjects randomized to the aripiprazole monohydrate 1-month group than compared to placebo-treated subjects.[10]



*This figure is based on a total of 103 recurrence events.

- Analysis by type of mood recurrence demonstrated a statistically significantly longer time to recurrence for both manic and mixed mood episodes in subjects treated with aripiprazole monohydrate 1-month compared to those treated with placebo. There was no substantial difference between treatment groups in delaying time to recurrence of depressive mood episodes.[10]

Safety Considerations

- The safety of aripiprazole monohydrate 2-month for the treatment of schizophrenia in adults and maintenance monotherapy treatment of bipolar I disorder in adults is based on adequate and well-controlled studies of aripiprazole monohydrate 1-month.[1] The safety data from the 12-Week Double-Blind, Placebo-Controlled Study is presented in the table below.[13]

Adverse Reactions in ≥2% of Adult Patients with Schizophrenia Treated with aripiprazole monohydrate 1-month (Abilify Maintena) in a 12-Week Double-Blind, Placebo-Controlled Study*[13]

Preferred Term	Aripiprazole monohydrate 1- month (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
* This table does not include adverse reactions which had an incidence equal to or less than placebo.		

Other warnings / precautions

- Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.
- Aripiprazole monohydrate 2-month is not approved for the treatment of patients with dementia-related psychosis.
- Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis
- Neuroleptic Malignant Syndrome
- Tardive Dyskinesia
- Metabolic Changes
- Pathological Gambling and Other Compulsive Behaviors
- Orthostatic Hypotension and Syncope
- Leukopenia, Neutropenia, and Agranulocytosis
- Seizures
- Potential for Cognitive and Motor Impairment

Use In Specific Populations

Pregnancy[1]

- There is insufficient data with aripiprazole monohydrate 2-month use in pregnant women to inform a drug-associated risk.
- Neonates exposed to antipsychotic drugs, including aripiprazole monohydrate 2-month, during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms.
    - Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder have been reported in neonates who were exposed to antipsychotic drugs, including oral aripiprazole, during the third trimester of pregnancy. These symptoms have varied in severity. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization. Monitor neonates exhibiting extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately.
- Animal Data:
    - No developmental toxicity studies were conducted with intramuscular aripiprazole suspension.
    - In animal oral or intravenous studies, aripiprazole demonstrated developmental toxicity, including possible teratogenic effects in rats and rabbits.
- Consider the benefits and risks of aripiprazole monohydrate 2-month and possible risks to the fetus when prescribing aripiprazole monohydrate 2-month to a pregnant woman.

Lactation[1]

- Aripiprazole is present in human breast milk; however, there are insufficient data to assess the amount in human milk, the effects on the breastfed infant, or the effects on milk production.
- The development and health benefits of breastfeeding should be considered along with the mother's clinical need for aripiprazole monohydrate 2-month and any potential adverse effects on the breastfed infant from aripiprazole monohydrate 2-month or from the underlying maternal condition.

Other Therapeutic Options[1-8]

Drug	Aripiprazole IM	Aripiprazole IM	Aripiprazole lauroxil IM	Risperidone SC	Risperidone SC	Paliperidone IM	Paliperidone IM
Brand name	**Asimtufii**	**Maintena**	**Aristada**	**Uzedy**	**Perseris**	**Sustenna**	**Trinza**
Formulary Status	**NF**	**PA-F**	**PA-F**	**NF**	**NF**	**PA-F**	**PA-F**
Approved indications	Schizophrenia: monotherapy for the maintenance of bipolar I disorder	Schizophrenia: monotherapy for the maintenance of bipolar I disorder	Schizophrenia	Schizophrenia	Schizophrenia	Schizophrenia; schizoaffective disorder as monotherapy and as an adjunct to mood stabilizers or antidepressants	Schizophrenia
Requires reconstitution	No	Yes	No	No	Yes	No	No
Injection type	IM	IM	IM	SubQ	SubQ	IM	IM
Approved injection sites	Gluteal muscle	Deltoid or gluteal muscle	Deltoid (441 mg dose only) or gluteal muscle (441 mg, 662 mg, 882 mg or 1064 mg)	Abdomen or back of upper arm	Abdomen or back of upper arm	Deltoid or gluteal muscle	Deltoid or gluteal muscle
Needle gauge	21/22	21/22/23	20/21	21	18	22/23	22
Injection interval (weeks)	8	4	4,6,8	4 or 8	4	4	12
Oral supplementation required	Yes; 14 days after initial injection	Yes; 14 days after initial injection	Regimen dependent: 1. No, if initiating with Aristada Initio plus one oral 30 mg dose in conjunction with the first dose of Aristada or 2. Yes, may continue oral therapy for 21 days	No	No	No	No
Early maintenance dose allowed	Yes, 2 weeks before next dose due	No data	Yes, 2 weeks before next dose due	No data	No data	Yes, one week before next dose due	Yes; 2 weeks before next dose due
Refrigeration required	No	No	No	Yes	Yes	No	No

Projected Place in Therapy

- Aripiprazole monohydrate 2-month offers another long-acting injectable option for the treatment of schizophrenia and maintenance therapy for bipolar 1 disorder. These formulations are typically reserved for patients who are nonadherent with or do not prefer oral medications. Aripiprazole's chief advantage over other atypical antipsychotics formulations appears to be a lower risk for metabolic effects such as weight gain. Aripiprazole monohydrate 2-month offers the additional advantage of only requiring administration every 2 months, which may present a convenient option for patients who have difficulty making/scheduling appointments due to conflicts/poor adherence.
- A disadvantage of aripiprazole monohydrate 2-month is that it may present a barrier for patients who are unable/unwilling to receive a gluteal injection, unlike some risperidone long-acting injections that have a subcutaneous injection formulation. The requirement for overlap of oral aripiprazole for a period of 2 weeks following their first injection may also represent a barrier to use. The oral overlap could result in patients mistakenly continuing their oral antipsychotic past the 2-week period causing an increased risk of side effects, or non-adherence resulting in the risk of decreased treatment efficacy and risk of relapse. Further, there are no manufacturer-recommended conversions when switching from oral to aripiprazole monohydrate 2-month.
- Aripiprazole monohydrate 2-month may be an appropriate choice for patients who have responded to oral aripiprazole who require a LAI antipsychotic for adherence.

References

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