Bi-Monthly Aripiprazole Monohydrate
(Abilify Asimtufii®)
FDA approved April 2023
Manufacturer: Otsuka and Lundbeck

Abilify Asimtufii is indicated for

- Treating schizophrenia in adults
- Maintenance monotherapy for adults with bipolar I disorder

Dosage and Administration

- Assess tolerability with oral aripiprazole for up to 2 weeks before starting Abilify Asimtufii
- Recommended dosage: 960 mg every 8 weeks
  - in case of adverse reactions, dosage may be reduced to 720 mg every 2 months
- Patients receiving oral antipsychotics
  - administer the first Abilify Asimtufii LAI along with oral aripiprazole (10 mg to 20 mg) for 14 days
  - patients stable on another oral antipsychotic & known to tolerate aripiprazole
    - administer the first Abilify Asimtufii LAI along with the oral antipsychotic for 14 days
- Conversion from monthly Abilify Maintena to Bi-monthly Abilify Asimtufii
  - Administer aripiprazole monohydrate 960 mg when the next Abilify Maintena LAI dose is scheduled
  - The first Abilify Asimtufii injection can replace the second or subsequent Abilify Maintena injections
  - Abilify Asimtufii can be given up to 2 weeks before or 2 weeks after the 2-month scheduled time

Administration

- Tap the syringe at least 10 times then shake vigorously for at least 10 seconds, until medication is uniform. Select needle size. Attach the needle, expel air and slowly inject the dose into gluteal muscle.


Dosage form & strengths
960 mg/3.2 mL and 720 mg/2.4 mL pre-filled ER injectable suspension syringes

Pharmacokinetics

Half-life elimination	2.9 to 6 days (IM?)
Metabolism	3 primary pathways: dehydrogenation, hydroxylation, & N-dealkylation. CYP3A4 & CYP2D6 facilitate dehydrogenation and hydroxylation respectively. CYP3A4 also catalyzes N-dealkylation
T_{max}	1 to 49 days (multiple administrations of 960 mg)
Steady state	Attained by the 4th dose
Excretion	urine 25%; feces 55% (~18% unchanged)

Drug Interactions

Adjust dosage for patients on CYP2D6, CYP3A4 inhibitors, or CYP3A4 inducers for over 14 days.

Factors	Dosage Recommendation
CYP2D6 Poor Metabolizers taking concomitant CYP3A4 inhibitors	Avoid use
Patients taking strong CYP2D6 **or** CYP3A4 inhibitors	720 mg
Patients taking CYP2D6 **and** CYP3A4 inhibitors	Avoid use
Patients taking CYP3A4 inducers	Avoid use

Adverse Reactions

The most common (≥5% and at least twice the placebo rate) adverse reactions were

- increased weight
- akathisia
- injection site pain, and
- sedation

Warnings and Precautions

- Cerebrovascular adverse reactions in elderly patients with Dementia-Related Psychosis: Increased risk of cerebrovascular AEs (stroke, TIA)

- Neuroleptic malignant syndrome, tardive dyskinesia, metabolic changes, pathological gambling & compulsive behaviors, orthostatic hypotension & syncope; leukopenia, neutropenia, & agranulocytosis; seizures, potential for cognitive & motor impairment

Missed dose

More than 8 weeks and less than 14 weeks: administer the next dose as soon as possible & resume the 2-month schedule
More than 14 weeks: restart concomitant oral aripiprazole for 14 days with the next Abilify Asimtufii injection

Figure 1

Dose of Patient's Last ARISTADA Injection	**Length of Time Since Last Injection**		
441 mg	≤ 6 weeks	> 6 and ≤ 7 weeks	> 7 weeks
662 mg	≤ 8 weeks	> 8 and ≤ 12 weeks	> 12 weeks
882 mg	≤ 8 weeks	> 8 and ≤ 12 weeks	> 12 weeks
1064 mg	≤ 10 weeks	> 10 and ≤ 12 weeks	> 12 weeks
Dosage and Administration for Re-initiation of ARISTADA	No Supplementation Required	Supplement with a Single Dose of ARISTADA INITIO **OR** 7 Days of Oral Aripiprazole[a]	Re-initiate with a Single Dose of ARISTADA INITIO and a Single Dose of Oral Aripiprazole 30 mg **OR** supplement with 21 Days of Oral Aripiprazole[a]

[a] The patient should supplement with the same dose of oral aripiprazole as when the patient began ARISTADA (see

Role in Therapy

- Abilify Asimtufii offers less frequent bimonthly dosing, potentially improving patient adherence and providing convenience for patients and providers
- It's the first 2-month LAI antipsychotic indicated for both schizophrenia and bipolar I disorder
    - efficacy based on studies originally conducted for Abilify Maintena's once-monthly dosing
    - same indications as Abilify Maintena with comparable safety and efficacy
    - approval based on a 32-week, open-label, randomized pharmacokinetic bridging study involving 266 patients with schizophrenia and bipolar I disorder
    - The bimonthly 960mg & 760 mg aripiprazole injections deliver sustained plasma concentrations similar to Abilify Maintena. Multiple 960mg bimonthly doses were shown to be safe and well-tolerated, matching the safety of 400mg monthly aripiprazole
    - Abilify Asimtufii does not require reconstitution and oral supplementation of aripiprazole or another antipsychotic is not needed, when switching from Abilify Maintena

- Less advantageous aspects include
    - gluteal administration only

    - fewer opportunities for dose adjustment
        - long dosing interval
        - available in 2 strengths only (720 mg & 960 mg)
- Selecting LAI involves various considerations, including injection site options, administration frequency, need for reconstitution, requirement for oral supplementation, storage, ease of administration, needle gauge, injection volume, as well as the permissible grace period for missed doses
- Currently there are 12 (including Aristada Initio) FDA-approved atypical long-acting injectables, including aripiprazole, risperidone, paliperidone, and olanzapine
    - All of them must be administered by a healthcare professional
    - None of them are FDA-approved for pediatric use
    - All have a black box warning due to the increased risk of mortality in elderly patients with dementia-related psychosis
    - Zyprexa Relprevv specifically, is subject to a REMS program due to risk of severe sedation /delirium
    - Please refer to the comparison table below for Abilify Maintena, Aristada, and Abilify Asimtufii
    - Uzedy and Abilify Asimtufii
        - both approved in April this year require bimonthly injections
        - both risperidone and aripiprazole have established safety with primary literature and post-marketing experience
        - Uzedy® the 2nd SQ risperidone-containing LAI and the first bi-monthly SQ LAI is approved for schizophrenia and is available in 7 strengths and does not require oral supplementation. On the other hand, Abilify Asimtufii is approved for schizophrenia and Bipolar I, is administered intramuscularly, is available in 2 strengths and requires two weeks of oral supplementation.
        - common adverse events of Abilify Asimtufii include weight gain, akathisia, pain at the injection site, and sedation
        - Uzedy's common adverse events include parkinsonism, akathisia, tremor, blurred vision, nausea/vomiting, stomach discomfort, constipation, increased appetite / weight, fatigue, rash, nasal congestion, and upper respiratory tract infections. The most common reactions at the injection site were itching and nodules
        - both have warnings for increased mortality in elderly patients with dementia-related psychosis, cerebrovascular adverse reactions, neuroleptic malignant syndrome, tardive dyskinesia, metabolic changes, orthostatic hypotension and syncope, falls, leukopenia, neutropenia, agranulocytosis, seizures, cognitive and motor impairment, body temperature regulation, and dysphagia
        - Abilify Asimtufii also has a warning for pathological gambling & other compulsive behaviors
        - Uzedy has extra warnings & precautions for hyperprolactinemia and priapism
        - Abilify Asimtufii is being marketed as a longer-lasting formulation of aripiprazole which offers a more convenient reliable treatment for schizophrenia and as a maintenance monotherapy for adults with bipolar I disorder, providing two months of sustained therapeutic concentrations per dose
        - Uzedy is being marketed as an important treatment option for patients with schizophrenia, aimed at addressing specific treatment challenges and potentially reducing the risk of relapse

- Like other LAI antipsychotics, its effects cannot be reversed if toxicity occur.

	Aripiprazole monohydrate Abilify Asimtufii®	**Aripiprazole Abilify Maintena®**	**Aripiprazole lauroxil Aristada®**
FDA approved	2023	2013	2015
Indication	▪Schizophrenia ▪ Bipolar I	▪Schizophrenia ▪ Bipolar I	Schizophrenia
Dosing	720 or 960 mg IM Q 8 weeks	300 or 400 mg IM once monthly	441, 662, 882 mg IM once monthly, or 882 mg Q6-weeks or 1064 mg Q2-months
Oral Supplementation	Yes 14 days	Yes 14 days	Yes 21 days
Injection interval	8 weeks	4 weeks	4 weeks (all doses) 6 weeks (882 mg) 8 weeks (1064 mg)
Missed Doses	> 8 weeks & <14 weeks: administer next dose asap & resume 2-month schedule > 14 weeks: restart concomitant oral aripiprazole for 14 days with the next Asimtufii dose	Missed 2nd or 3rd doses: if >4 & <5 weeks, give asap. If >5 weeks have passed, add PO aripiprazole for 14 days with the next injection Missed 4th or later doses: if >4 & <6 weeks, give asap. If >6 weeks, restart oral aripiprazole for 14 days with next injection	Please see figure 1 above
Dosage Form/Strength	Pre-filled single chamber injectable suspension syringe 720 mg or 960 mg	1) 300 mg & 400 mg vials 2) 300 mg & 400 mg pre-filled dual chamber syringe	Prefilled syringe 441 mg, 662 mg, 882 mg, 1064 mg
Tmax	1 to 49 days (repeated 960 mg dosing)	5 to 7 days (gluteal) 4 days (deltoid)	41 days (single dose) 24.4 to 35.2 days (repeated dosing)
$T_{1/2}$	?	29.9 days (300 mg) 46.5 days (400 mg)	53.9 to 57.2 days
Active Moiety	Aripiprazole, & dehydro-aripiprazole	Aripiprazole, & dehydro-aripiprazole	Aripiprazole, & dehydro-aripiprazole
Solubilization Vehicle	Low solubility particles in aqueous suspension	Low solubility particles in aqueous suspension	Low solubility particles in aqueous suspension
Requires Adding Diluent	No	Yes, dual-chamber syringe also available	No
Injection volume	3.2 mL (960 mg) 2.4 mL (720 mg)	0.8 mL (160 mg) 1 mL (200 mg) 1.5 mL (300 mg) 2 mL (400 mg)	3.9 mL (1064 mg) 3.2 mL (882 mg) 2.4 mL (662 mg) 1.6 mL (441 mg)

Injection Sites	Gluteal	Deltoid or gluteal	Deltoid (441 mg only) Gluteal (all doses)
Needle Gauge & Length	22G 1.5-inch or 21G 2-inch	21G 2-inch, 22G 1.5-inch, or 23G 1-inch	21G 1-inch, 20G 1.5-inch or 2-inch
Administration / Comments	▪ Tap 10 times, shake syringe vigorously for at least 10 seconds until the medication is uniform ▪ For non-obese patients, use 22-gauge, 1.5-inch needle. For obese patients, use 21-gauge, 2-inch needle	• Shake syringe vigorously for 20 seconds, shake vials for 30 sec. Inject *slowly* into deltoid or gluteal muscle	▪Tap 10 times, shake syringe vigorously for at least 30 seconds prior to use ▪ Inject over *≤10 seconds* into deltoid or gluteal muscle (441 mg), gluteal only (662 or 882 mg) ▪Use longer needles for larger amount of SQ tissue overlaying the muscle
Storage	Room temperature	Room temperature	Room temperature

Formulary Recommendation

Add to BHRS, CareAdvantage, and HealthWorx formulary with PA criteria:
Indication—FDA approved diagnoses
Age—Adults
Documentation—
Patient has tried and failed oral antipsychotic therapy Or
Transferred from hospital/facility/another provider stabilized on this medication
Quantity Limit --
#1/60DS for 760mg and 960mg

References upon request