



Aripiprazole lauroxil
(Aristada Initio™)

Classification: Atypical Antipsychotic

Pharmacology:¹

Aristada Initio (aripiprazole lauroxil) is a prodrug of aripiprazole. Following intramuscular injection, aripiprazole lauroxil is likely converted by enzyme-mediated hydrolysis to N-hydroxymethyl aripiprazole, which is then hydrolyzed to aripiprazole. The mechanism of action of aripiprazole in schizophrenia is unclear. However, efficacy could be mediated through a combination of partial agonist activity at dopamine D₂ and serotonin 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors. ¹

Pharmacokinetics:¹

Absorption	Following a single intramuscular injection of Aristada Initio, the appearance of aripiprazole in systemic circulation occurs on the day of injection; the median time to reach peak plasma exposure is approximately 27 days (range: 16-35 days). With the addition of a single intramuscular injection of Aristada Initio and 30mg oral aripiprazole at the time of the first Aristada dose, aripiprazole concentrations reach relevant levels within 4 days. Aripiprazole exposure was similar for deltoid and gluteal intramuscular injections of Aristada Initio.
Distribution	Based on population pharmacokinetic analysis, the apparent volume of distribution of aripiprazole following intramuscular injection of ARISTADA was 268L, indicating extensive extravascular distribution following absorption. Aripiprazole and its major metabolite are greater than 99% bound to serum proteins, primarily to albumin. In healthy human volunteers administered 0.5mg/day to 30 mg/day oral aripiprazole for 14 days, there was dose-dependent D ₂ receptor occupancy indicating brain penetration of aripiprazole in humans.
Elimination	The biotransformation of Aristada Initio likely involves enzyme-mediated hydrolysis to form N-hydroxymethyl-aripiprazole, which subsequently undergoes hydrolysis to aripiprazole. Elimination of aripiprazole is mainly through hepatic metabolism involving CYP3A4 and CYP2D6.

For Aristada Initio, the mean aripiprazole terminal elimination half-life was 15-18 days after injection. The significantly longer aripiprazole apparent half-life compared to oral aripiprazole (mean 75 hours) is attributed to the dissolution and formation rate-limited elimination of aripiprazole following Aristada Initio administration.
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Indications and Usage:¹

- Aristada Initio, in combination with oral aripiprazole, is indicated for the initiation of Aristada when used for the treatment of schizophrenia in adults.¹

Dosage and Administration:^{1,2}

- Aristada Initio is only to be used as a single dose to initiate Aristada treatment or as a single dose to re-initiate Aristada treatment following a missed dose of Aristada. Aristada Initio is not for repeated dosing.
- After establishing tolerability with oral aripiprazole, administer the first Aristada intramuscular injection (441 mg, 662 mg, 882 mg, or 1064 mg) in conjunction with both:
 - One 675 mg injection of Aristada Initio in the deltoid or gluteal muscle (which corresponds to 459 mg of aripiprazole); **and**
 - One 30 mg dose of oral aripiprazole.
- Aristada Initio is not interchangeable with Aristada due to differing pharmacokinetic profiles.
- Aristada Initio is to be administered as an intramuscular injection by a healthcare professional.
- The first Aristada injection may be administered on the same day as Aristada Initio or up to 10 days thereafter.
- Avoid injecting both Aristada Initio and Aristada concomitantly into the same deltoid or gluteal muscle.
- For patients who have never taken aripiprazole, establish tolerability with oral aripiprazole prior to initiating treatment with Aristada Initio. Due to the half-life of oral aripiprazole, it may take up to 2 weeks to fully assess tolerability. Refer to the prescribing information of oral aripiprazole for the recommended dosage and administration of the oral formulation.

Dosing for Missed Doses of Aristada:

Recommendation for Concomitant Supplementation Following Missed Doses of Aristada			
Dose of Patient's Last Aristada Injection	Length of Time Since Last Injection		
441 mg	≤6 weeks	>6 and ≤7 weeks	>7weeks
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 <u>single dose of Aristada Initio</u> OR 7 days of Oral Aripiprazole	<u>Re-initiate with a single dose of Aristada Initio and a single dose of oral aripiprazole 30 mg</u> OR supplement with 21 days of oral aripiprazole

Storage:¹

Store at room temperature 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C and 30°C (between 59°F and 86°F). Do not freeze.

Contraindications:¹

Aristada Initio is contraindicated in patients with known hypersensitivity reaction to aripiprazole.

Precautions:¹

- *Increased Mortality in Elderly Patients with Dementia-related Psychosis:* Aristada Initio is not approved for the treatment of patients with dementia-related psychosis.
- *Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia:* Aristada Initio is not approved for the treatment of patients with dementia-related psychosis.
- *Potential for Dosing and Medication Errors:* Substitution and dispensing errors between Aristada Initio and Aristada could occur. Do not substitute Aristada Initio for Aristada.
- *Neuroleptic Malignant Syndrome:* Manage with immediate discontinuation of antipsychotic drugs, symptomatic treatment, and close monitoring.
- *Tardive Dyskinesia:* Discontinue if clinically appropriate.
- *Metabolic Changes:* Monitor for hyperglycemia, dyslipidemia, and weight gain.
- *Pathological Gambling and Other Compulsive Behaviors:* Consider discontinuation of antipsychotic.
- *Orthostatic Hypotension:* Monitor heart rate and blood pressure and educate patients at increased risk of these adverse reactions or at an increased risk of developing complications from hypotension, including patients with dehydration, hypovolemia, treatment with antihypertensive medication, and history of cardiovascular or cerebrovascular disease.
- *Leukopenia, Neutropenia, and Agranulocytosis:* Perform complete blood counts in patients with a history of a clinically significant low white blood cell (WBC) count. Consider discontinuation if clinically significant decline in WBC in the absence of other causative factors.
- *Seizures:* Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold.

- *Potential for Cognitive and Motor Impairment:* Use caution when operating machinery.
- *Body Temperature Regulation:* Antipsychotics may disrupt the body's ability to reduce core body temperature.
- *Dysphagia:* Antipsychotic drug use has been associated with esophageal dysmotility and aspiration. Use caution in patients at risk for aspiration pneumonia.

Interactions:¹

Drug Interaction	Example Medications	Clinical Impact	Management
Strong CYP3A4 Inhibitors and Strong CYP2D6 Inhibitors	Fluoxetine Paroxetine Itraconazole Clarithromycin Quinidine	Increased the exposure of aripiprazole	Avoid use of Aristada Initio
Strong CYP3A4 Inducers	Carbamazepine Rifampin	Decreased the exposure of aripiprazole	Avoid use of Aristada Initio
Antihypertensive Drugs	Carvedilol Lisinopril Prazosin	Enhanced effect of certain antihypertensive agents	Avoid use of Aristada Initio
Benzodiazepines	Lorazepam	Greater intensity of sedation when lorazepam and oral aripiprazole were combined. The orthostatic hypotension observed was greater with the combination compared to lorazepam alone.	Avoid use of Aristada Initio

Adverse Reactions:¹

In pharmacokinetic studies, the safety profile of Aristada Initio was generally consistent with that observed for Aristada. Commonly observed adverse reactions with Aristada (aripiprazole lauroxil) occurring in $\geq 5\%$ of the population and at least twice the rate of placebo in patients treated with aripiprazole lauroxil was akathisia. Reactions occurring at an incidence of 2% or more in aripiprazole lauroxil were: injection site pain, increased weight, increased blood creatinine phosphokinase, akathisia, headache, insomnia and restlessness.

In pharmacokinetic studies, the incidences of injection site reactions with Aristada Initio were similar to the incidence observed with Aristada (aripiprazole lauroxil). In Aristada trials, injection site reactions were reported by 4% of patients treated with 441 mg aripiprazole lauroxil and 5% of patients treated with 882 mg aripiprazole lauroxil compared to 2% of patients treated with placebo.

Use in special populations:¹

Pregnancy: Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There is limited published data on aripiprazole use in pregnant women. No teratogenicity was observed in animal reproductive studies with intramuscular administration of aripiprazole lauroxil to rats and rabbits during organogenesis at equivalent maximum recommended human dose. However, oral aripiprazole caused developmental toxicity and possible teratogenic effects in rats and rabbits. Pregnant women should be advised of the potential risk. A pregnancy exposure registry is available.

Lactation: 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. Risks and benefits should be weighed in women who breastfeed.

Pediatric use: Safety and effectiveness of Aristada Initio has not been established in pediatric patients.

Geriatric use: Safety and effectiveness of Aristada Initio has not been established in patients > 65 years of age.

CYP2D6 Poor Metabolizers: Avoid use of Aristada Initio in patients who are CYP2D6 poor metabolizers because dosage adjustments are not possible.

Hepatic Impairment: No dosage adjustment for mild to severe hepatic impairment (Child-Pugh score between 5 and 15).

Renal Impairment: No dosage adjustment for mild to severe renal function (glomerular filtration rate between 15 and 90 mL/minute).

Cost Comparison:

Dosage Form and Dose	Treatment Duration (days)	Unit Cost	Total Cost
Aristada Initio 675mg	1	\$1,665.31	\$1666.99
Aripiprazole 30 mg orally	1	\$1.68	
Aripiprazole 20mg orally	21	\$1.72	\$36.12

Monitoring:³

- Improvement in signs and symptoms of schizophrenia indicates efficacy
- Need for continued treatment: evaluate periodically
- Fasting glucose: baseline and periodically in patients with risk factors for diabetes mellitus and in any patient who develops symptoms of hyperglycemia during treatment
- Worsened glucose control: regularly in patients with diabetes mellitus

- CBC: frequently during the first few months in patients with a history of low WBC or absolute neutrophil count, and in those with a history of drug-induced leukopenia or neutropenia
- Dyslipidemia and/or weight gain
- Orthostatic vital signs, including heart rate and blood pressure: in patients who are antipsychotic-naïve, or at risk of complications from hypotension (e.g., dehydration, hypovolemia, concomitant use of antihypertensives, those with a history of cardiovascular or cerebrovascular disease)
- Fall risk assessment: high risk patients, especially the elderly when initiating treatment and recurrently in patients on long term therapy

Efficacy:^{4,5}

One pharmacokinetic bridging study was performed to determine if aripiprazole concentrations with Aristada Initio, one aripiprazole 30 mg oral tablet, and the Aristada injection would be comparable to Aristada treatment initiated with 21 days of oral aripiprazole overlap. This 1-day regimen was designed to achieve plasma aripiprazole concentrations in the therapeutic range within 4 days, which is consistent with the 21 day oral initiation regimen indicated in the Aristada prescribing information. This was a 6-month, double-blind, placebo-controlled, phase 1 study in patients with schizophrenia. Patients were randomized to receive one of the following four treatments:

1. 441 mg Aristada + 662 mg aripiprazole lauroxil nanocrystalline dispersion + 30 mg oral aripiprazole once
2. 441 mg Aristada + 15 mg oral aripiprazole x 21 days
3. 882 mg Aristada + 662 mg aripiprazole lauroxil nanocrystalline dispersion + 30 mg oral aripiprazole once
4. 882 mg Aristada + 15 mg oral aripiprazole x 21 days

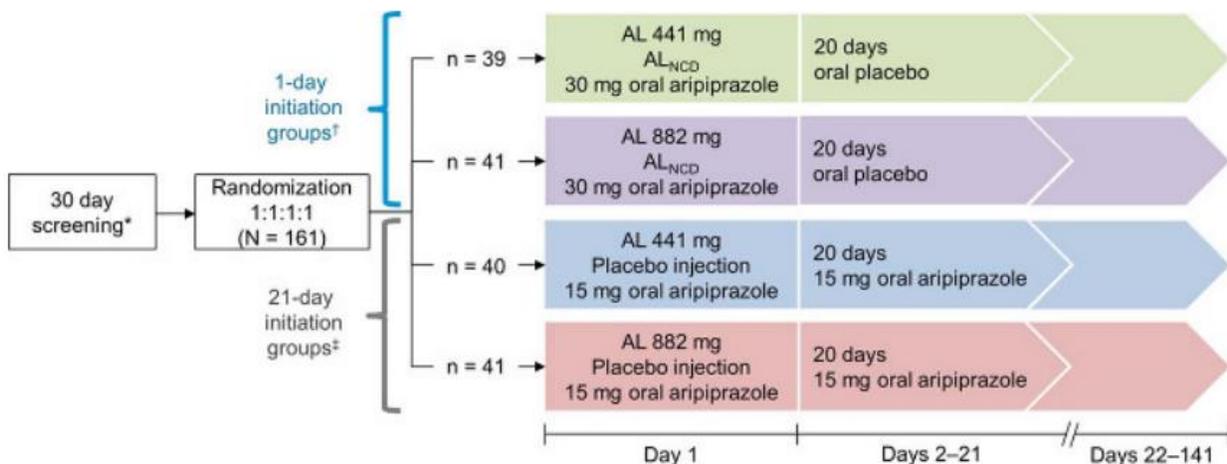


Figure 1. Hard ML et al. J Clin Psychopharmacol 2018;38:435-441.

Blood samples for liquid chromatography-tandem mass spectrometry were collected for analysis within 1 hour predose and 1, 2, 3, 4, 5, and 8 hours (+/- 15 minutes) postdose on day 1. On postinitiation days 2 to 21, a single sample was collected before oral aripiprazole (or oral placebo) administration. On day 21, samples were collected at the same time frames as on day 1. Further samples were collected up to day 141.

133 patients completed the study. Results from the 1-day initiation regimen groups showed mean plasma aripiprazole concentrations and exposures within the first month that were comparable to those of the 21-day initiation regimen groups (Figure 2). This study shows that the 1-day initiation regimen is a suitable alternative option to the current 21 days of oral aripiprazole overlap for starting Aristada.

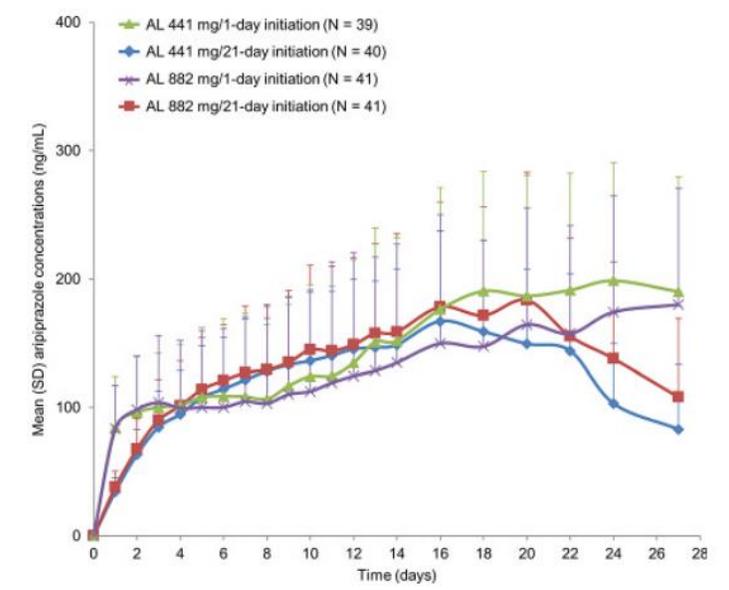


Figure 2. Hard ML et al. J Clin Psychopharmacol 2018;38:435-441.

Another study developed a population pharmacokinetic model to describe aripiprazole pharmacokinetics following administration of aripiprazole lauroxil nanocrystalline dispersion, aripiprazole lauroxil, and oral aripiprazole. In this study, researchers used 12,768 plasma aripiprazole concentrations from 343 patients (from 4 previous clinical studies) for the analysis and to construct the model. Based on these models, the authors concluded that the 1-day initiation regimen (Aripiprazole Initio + 30 mg oral aripiprazole) with all approved Aristada dosing regimens is predicted to achieve aripiprazole concentrations associated with therapeutic doses of Aristada using the 21-day initiation regimen within 4 days. This model was also used to determine that the first Aristada injection can be given up to 10 days after the 1-day initiation regimen, and that Aristada Initio can be used to re-establish concentrations associated with missed doses of Aristada.

Conclusions:

Aristada Initio 675 mg, in combination with one dose of 30 mg oral aripiprazole and the first dose of Aristada, offers the advantage of achieving therapeutic levels rapidly and eliminates the need for oral aripiprazole supplementation for 21 days when starting Aristada. This 1-day initiation regimen of aripiprazole lauroxil will be particularly beneficial for patients with schizophrenia with medication adherence issues, although the significant cost of Aristada Initio should be considered. The adverse effects with Aristada Initio are consistent with those seen with Aristada.

Recommendation:

Consider the addition of Aristada Initio to the formulary as it may be a beneficial initiation option for patients starting Aristada. If added, recommend adding it in "Reserve Drug" status due to cost with the condition that it be used only for patients whose anticipated length of inpatient stay is less than 3 weeks from the first dose of Aristada.

References:

1. Product Information: ARISTADA INITIO™ extended release injectable suspension for intramuscular use. Alkermes Inc., Waltham, MA, 2018.
2. Product Information: ARISTADA® extended release injectable suspension for intramuscular use. Alkermes Inc., Waltham, MA, 2018.
3. In Depth Answers; www.Micromedex.com. Greenwood Village (CO): Truven Health Analytics; 2017; March 11, 2019
4. Hard ML, Wehr AY, Du Y, Weiden PJ, Walling D, von Moltke L. Pharmacokinetic evaluation of a 1-day treatment initiation option for starting long-acting aripiprazole lauroxil for schizophrenia. J Clin Psychopharmacol. 2018;38: 435-441.
5. Hard ML, Wehr AY, Sadler BM, Mills RJ, von Moltke L. Population pharmacokinetic analysis and model-based simulations of aripiprazole for a 1-day initiation regimen for the long-acting antipsychotic aripiprazole lauroxil. Eur J Drug Metab Pharmacokinet. 2018;43: 461-469.

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