



Aripiprazole Lauroxil (Aristada)

An Extended-Release, Long-Acting Injection For the Treatment of Schizophrenia

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INTRODUCTION

Schizophrenia, a chronic brain disorder that affects about 1% of the adult population in the United States and approximately 26 million people worldwide, is considered among the most disabling and economically catastrophic medical disorders as ranked by the World Health Organization.^{1,2} In 2013, the economic burden of schizophrenia in the U.S. was estimated at \$155.7 billion, including excess direct health care costs of \$37.7 billion, direct non-health care costs of \$9.3 billion, and indirect costs of \$117.3 billion (compared to individuals without schizophrenia).³ Only about 10% to 15% of people who suffer from schizophrenia maintain full-time employment of any type.³

Characteristics of the illness involve positive symptoms, including delusions, hallucinations, trouble with thinking and concentration, and lack of motivation, as well as negative symptoms, such as having a flat affect or poverty of speech, and impairments in cognition and executive functions.⁴ When their symptoms are treated, most people with schizophrenia, which affects more men than women, will greatly improve over a period of time. However, the mortality rate among patients with the disease is approximately 50% higher than that of the general popu-

lation, which results from high incidence of suicides and violent deaths, and a wide range of health problems.⁵

There is no cure for schizophrenia, and researchers are working to unravel its genetics, conduct behavioral studies, and analyze advanced imaging of the brain, all in anticipation of novel approaches and more effective treatments. One recent therapy to have reached the market is aripiprazole lauroxil (Aristada, Alkermes, Inc.), an extended-release, long-acting intramuscular (IM) injection indicated for the treatment of adults 18 to 65 years of age with schizophrenia.

CHEMISTRY AND PHARMACOLOGY

Aripiprazole lauroxil is an atypical antipsychotic available as a white to off-white sterile aqueous extended-release suspension for IM injection with the chemical name 7-[4-[4-(2,3-dichlorophenyl)-piperazin-1-yl]butoxy]-2-oxo-3,4-dihydro-2H-quinolin-1-yl methyl dodecanoate, empirical formula of C₃₆H₅₁C₁₂N₃O₄, and molecular weight of 660.7 g/mol (Figure 1).⁶

Aripiprazole lauroxil is available in the following strengths and deliverable volumes from single-use, prefilled syringes: 441 mg (1.6 mL), 662 mg (2.4 mL), and 882 mg (3.2 mL). Sorbitan monolaurate, polysorbate 20, sodium chloride, sodium phosphate dibasic anhydrous, sodium phosphate monobasic, and water for injection are the inactive ingredients.⁶

Aripiprazole lauroxil, a prodrug of aripiprazole, acts as a partial agonist at the D₂ and 5-HT_{1A} receptors, and as an antagonist at the 5-HT_{2A} receptors. Enzyme-mediated hydrolysis likely converts the injected aripiprazole lauroxil to N-hydroxymethyl aripiprazole, which is then hydrolyzed to aripiprazole. Adverse reactions reported during clinical studies may have been due to the actions

of the drug at other receptors, such as antagonist activity at the alpha₁ receptors resulting in orthostatic hypotension.⁶

PHARMACOKINETICS AND PHARMACODYNAMICS

Aripiprazole lauroxil works primarily as a result of the activity and affinities for the D₂ receptors of the parent drug, aripiprazole, and to a lesser extent, its major metabolite, dehydroaripiprazole, which also represents 30% to 40% of the aripiprazole exposure in plasma. Systemic absorption of aripiprazole following single IM administration occurs within five to six days and continues to be released for an additional 36 days. Concentrations of the drug continue to build and reach steady state following the fourth monthly administration. A therapeutic concentration of aripiprazole is achieved in four days with oral aripiprazole coadministration for 21 days at the start of therapy. Aripiprazole exhibits extensive extravascular distribution following absorption with an apparent volume of distribution of 268 L.⁶

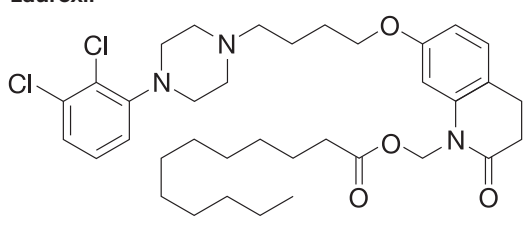
Aripiprazole lauroxil 441 mg yields similar concentrations when administered in either the deltoid or gluteal muscles. Administration of 882 mg every six weeks results in plasma aripiprazole concentrations that are within the established therapeutic range of 441–882 mg monthly.⁶

Aripiprazole lauroxil is metabolized extensively in the liver via cytochrome P450 (CYP) isoenzymes 3A4 and 2D6. It undergoes an enzyme-mediated

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Figure 1 Chemical Structure of Aripiprazole Lauroxil⁶



hydrolysis to form N-hydroxymethyl-aripiprazole, which is then converted by water-mediated hydrolysis to aripiprazole.⁶

The mean elimination half-life of aripiprazole lauroxil after administration of 441 mg, 662 mg, or 882 mg ranges from 29.2 to 34.9 days.⁶

Aripiprazole exhibits high affinity for dopamine D₂ and D₃, and serotonin 5-HT_{1A} and 5-HT_{2A} receptors (K_i values, 0.34 nM, 0.8 nM, 1.7 nM, and 3.4 nM, respectively); moderate affinity for dopamine D₄, serotonin 5-HT_{2C} and 5-HT₇, alpha₁-adrenergic, and histamine H₁ receptors (K_i values, 44 nM, 15 nM, 39 nM, 57 nM, and 61 nM, respectively); and moderate affinity for the serotonin reuptake site (K_i value, 98 nM). Aripiprazole has no appreciable affinity for cholinergic muscarinic receptors. Aripiprazole functions as a partial agonist at the dopamine D₂ and the serotonin 5-HT_{1A} receptors, and as an antagonist at the serotonin 5-HT_{2A} receptor.⁶

CLINICAL TRIALS

A 12-week, randomized, double-blind, placebo-controlled, fixed-dose study that enrolled 622 adult patients 18–70 years of age demonstrated the efficacy of aripiprazole lauroxil. Eligible patients met the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (text revision), criteria for schizophrenia. Patients also had to have a score of 70 to 120 on the Positive and Negative Syndrome Scale (PANSS), including a score of 4 or more for at least two positive scale items, and a score of 4 or more on the Clinical Global Impression Improvement Scale (CGI-I).⁶

Once tolerance was shown for oral aripiprazole, study participants received

either oral aripiprazole or placebo once daily for the first three weeks of treatment. The IM injections were administered on days 1, 29, and 57. Two hundred and seven patients received aripiprazole lauroxil 441 mg, 208 patients received aripiprazole lauroxil 882 mg, and 207 patients received placebo.⁶

The primary outcome variable was the change from baseline to day 85 in PANSS total score. Statistically significant separation from placebo on PANSS total score change was observed in each aripiprazole lauroxil dose group (Table 1, Figure 2). No statistical difference in treatment outcome was observed with regard to age, gender, race, or weight.⁶

The secondary outcome variable was CGI-I score at day 85, with the drug treatment groups showing statistically significant superior CGI-I scores when compared with the placebo group.⁶

In addition to this clinical study, the efficacy of aripiprazole lauroxil was established, in part, on the efficacy data from trials of the oral formulation of aripiprazole.⁶

SAFETY PROFILE

Warnings and Precautions

A boxed warning is included in the prescribing information to reflect an increased mortality rate in elderly patients with dementia-related psychosis treated with antipsychotic drugs, such as aripiprazole lauroxil.⁶

As with other atypical antipsychotics, serious adverse effects may occur. Antipsychotic drugs have been associated with cerebrovascular adverse reactions, including stroke, in elderly patients with dementia-related psychosis; neuroleptic malignant syndrome; tardive dyskinesia;

metabolic abnormalities, such as hyperglycemia/diabetes mellitus, dyslipidemia, and weight gain; orthostatic hypotension; leukopenia, neutropenia, and agranulocytosis; seizures; potential for cognitive and motor impairment; disruption of body temperature regulation; and dysphagia. In addition, post-marketing case reports suggest that some patients can develop pathological gambling and impulse-control problems while taking aripiprazole.⁶

Adverse Reactions

During clinical trials, the most commonly observed adverse reaction with aripiprazole lauroxil (incidence of 5% or greater and at least twice the rate of placebo) was akathisia. The most common injection site reaction was pain (4% and 5% in the 441-mg and 882-mg treatment groups, respectively; and 2% in the placebo group), which occurred mostly during the first injection and decreased with subsequent administration. Induration, swelling, and redness at the injection site were reported in less than 1% of patients receiving aripiprazole lauroxil. Adverse reactions occurring in 2% or more of aripiprazole lauroxil-treated patients (and that occurred at greater incidence than in the placebo-treated patients) are listed in Table 2.⁶

Reactions observed during the post-marketing period of oral aripiprazole include allergic reaction (anaphylactic reaction, angioedema, laryngospasm, pruritus/urticaria, or oropharyngeal spasm), pathological gambling, hiccups, and blood glucose fluctuation.⁶

Contraindications

Aripiprazole lauroxil is contraindicated in patients with a known hypersensitivity to aripiprazole. Hypersensitivity reactions have ranged from pruritus/urticaria to anaphylaxis.⁶

Monitoring Requirements

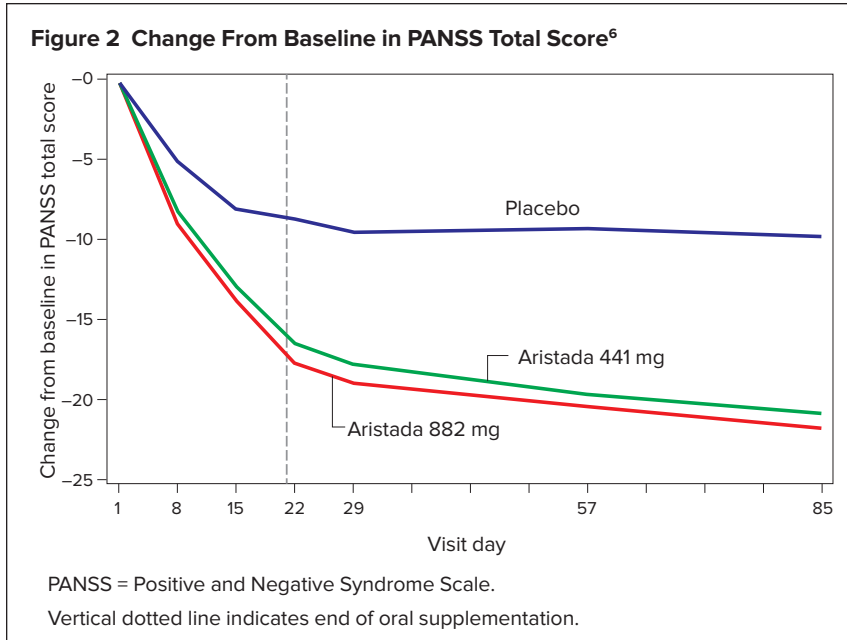
Patients on aripiprazole lauroxil should be monitored for any symptoms of metabolic change and should be educated about the risks associated with the drug's use. Routine blood glucose, lipids, and weight assessments should be conducted frequently. Patients with a pre-existing low white blood cell count or a history of drug-induced leukopenia/neutropenia should have their complete blood count monitored while undergoing treatment.⁶

Study Number	Treatment Group	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-Subtracted Difference ^a (95% CI)
Study 1	Aripiprazole lauroxil 441 mg ^b	92.6 (10.2)	-20.9 (1.4)	-10.9 (-14.5 to -7.3)
	Aripiprazole lauroxil 882 mg ^b	92.0 (10.8)	-21.8 (1.4)	-11.9 (-15.4 to -8.3)
	Placebo	93.9 (11.3)	-9.8 (1.4)	-

CI = confidence interval, not adjusted for multiple comparisons; LS Mean = least-squares mean; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation; SE = standard error.

^a Difference (drug minus placebo) in least-squares mean change from baseline

^b Doses that are demonstrated to be effective



effects on milk production are unknown. The manufacturer recommends evaluation of the need for the drug versus any potential adverse effects of the drug on the infant and the mother.⁶

Drug Interactions

When given in combination with strong CYP3A4 or CYP2D6 inhibitors for more than two weeks, aripiprazole lauroxil dosage must be reduced due to the increased exposure of aripiprazole. In contrast, dosage must be increased when the drug is given in combination with strong CYP3A4 inducers for more than two weeks due to decreased aripiprazole concentration (Table 3).⁶

Because aripiprazole lauroxil may potentially enhance the effects of some antihypertensive drugs through alpha-adrenergic antagonism, monitor patient blood pressure when the medications are coadministered.⁶

Monitor patients for sedation and orthostatic hypotension when aripiprazole lauroxil and lorazepam are given concomitantly.⁶

DOSAGE AND ADMINISTRATION

Aripiprazole-naïve patients should be assessed for tolerability by establishing them on the oral formulation for up to 14 days before initiating the IM aripiprazole lauroxil injections. Depending on condition and response, some patients may require treatment with aripiprazole lauroxil 441 mg (deltoid or gluteal), 662 mg (gluteal only), or 882 mg (gluteal only) every month, which corresponds to 300 mg, 450 mg, and 600 mg of aripiprazole, respectively, while others may require a starting dose of 882 mg every six weeks. Oral aripiprazole should be taken daily for 21 days in addition to the first IM injections.⁶

Adjustments may be necessary for doses that are missed, but administer the missed injection as soon as possible, and give oral aripiprazole supplementation with the next scheduled injection (Table 4). Dosage adjustments are also required when aripiprazole lauroxil is administered to CYP2D6 poor metabolizers, or to patients taking CYP3A4 inhibitors, CYP2D6 inhibitors, or CYP3A4 inducers for more than two weeks (Table 3).

Patients with mild-to-severe hepatic impairment (Child–Pugh score, 5–15)

Table 2 Adverse Reactions That Occurred in 2% or More of Aripiprazole Lauroxil-Treated Patients and at Greater Incidence Than in Placebo-Treated Patients⁶

Adverse Reaction System Organ Class Preferred Term	Placebo n = 207 (%)	Aripiprazole Lauroxil	
		441 mg n = 207 (%)	882 mg n = 208 (%)
General disorders and administration site conditions			
Injection site pain	2	3	4
Investigations			
Increased weight	1	2	2
Increased blood creatine phosphokinase	0	2	1
Nervous system disorders			
Akathisia	4	11	11
Headache	3	3	5
Psychiatric disorders			
Insomnia	2	3	4
Restlessness	1	3	1

Use in Specific Populations

Pediatric and Geriatric Use

The safety and effectiveness of aripiprazole lauroxil in patients younger than 18 years or older than 65 years of age have not been evaluated.⁶

Pregnancy and Lactation

Women exposed to aripiprazole lauroxil should register during pregnancy with the National Pregnancy Registry for Atypical Antipsychotics at (866) 961-2388, or visit <http://tinyurl.com/pregnancy-registry> for more information.⁶

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms after delivery. The limited published data on aripiprazole use in pregnant women are not sufficient to inform any drug-associated risks for birth defects or miscarriage. Advise pregnant women of the potential risk to a fetus.⁶

Aripiprazole is present in human breast milk. Because there are insufficient data at this time, the amount in human milk, the effects on the breastfed infant, or the

Table 3 Dose Adjustments for CYP450 Considerations⁶

Concomitant Drug	Dose Change for Aripiprazole Lauroxil ^a
Strong CYP3A4 inhibitor	Reduce the dose of aripiprazole lauroxil to the next lower strength. No dosage adjustment is necessary in patients taking 441 mg aripiprazole lauroxil, if tolerated. For patients known to be poor metabolizers of CYP2D6: Reduce dose to 441 mg from 662 mg or 882 mg. No dosage adjustment is necessary in patients taking 441 mg aripiprazole lauroxil, if tolerated.
Strong CYP2D6 inhibitor	Reduce the dose of aripiprazole lauroxil to the next lower strength. No dosage adjustment is necessary in patients taking 441 mg aripiprazole lauroxil, if tolerated. For patients known to be poor metabolizers of CYP2D6: No dose adjustment required.
Both strong CYP3A4 inhibitor and strong CYP2D6 inhibitor	Avoid use for patients at 662-mg or 882-mg dose. No dosage adjustment is necessary in patients taking 441 mg aripiprazole lauroxil, if tolerated.
CYP3A4 inducer	No dose adjustment for 662-mg and 882-mg dose, but increase the 441-mg dose to 662 mg.

^a For the 882-mg dose administered every six weeks, the next lower strength should be 441 mg administered every four weeks.

Table 4 Recommended Concomitant Oral Aripiprazole Supplementation Following Missed Injections^{a,6}

Dose of Patient's Last Aripiprazole Injection	Length of Time Since Last Injection		
	No Oral Supplementation Required	Supplement with 7 Days Oral Aripiprazole	Supplement with 21 Days Oral Aripiprazole
441 mg monthly	≤ 6 weeks	> 6 and ≤ 7 weeks	> 7 weeks
662 mg monthly	≤ 8 weeks	> 8 and ≤ 12 weeks	> 12 weeks
882 mg monthly	≤ 8 weeks	> 8 and ≤ 12 weeks	> 12 weeks
882 mg every 6 weeks	≤ 8 weeks	> 8 and ≤ 12 weeks	> 12 weeks

^a The patient should supplement with the same dose of oral aripiprazole as when the patient began aripiprazole injection.

or mild-to-severe renal impairment (glomerular filtration rate, 15–90 mL/min) do not require dosage adjustment for aripiprazole lauroxil injection.⁶

COST

Aripiprazole lauroxil is supplied as an extended-release injectable suspension in prefilled, single-use syringes. The cost of the drug is dose-dependent. The average wholesale prices for the 441-mg, 662-mg, and 882-mg injections are \$1,304, \$1,956, and \$2,606, respectively.⁷

P&T COMMITTEE CONSIDERATIONS

Schizophrenia is a lifelong mental disorder that is a major public health issue and a burden on families and the community. Current therapies for the illness focus on eliminating symptoms with antipsychotic medications and psychosocial treatment.

Aripiprazole lauroxil is a novel long-acting atypical IM agent approved in October 2015 by the Food and Drug Administration for the treatment of schizophrenia. The efficacy data have been evaluated for doses of 441 mg and 882 mg and have shown statistically significant separation

of the treatment groups from the placebo group using PANSS and CGI-I criteria.

Patients with no prior use of aripiprazole should be established on the oral formulation to determine tolerability before starting on the long-acting injection. Based on the patient's current condition, the starting dose can be 441 mg, 662 mg, or 882 mg every month, or 882 mg every six weeks. Oral aripiprazole supplementation should be provided in conjunction with the first injection and continue for 21 days. Because the injection is administered only every four to six weeks, patient adherence to therapy may be improved.

Akathisia stands out as the most common adverse effect reported in clinical trials. As with other atypical antipsychotics, adverse effects such as movement disorders, metabolic abnormalities, and cardiac problems may occur; however, the drug poses a minimal potential risk for nausea, vomiting, sedation, and dizziness.

In comparison to other long-acting injectable atypical antipsychotics, aripiprazole lauroxil's favorable metabolic profile, low incidence of extrapyramidal symptoms, low risk of QTc prolongation, and longer half-life make it a valuable agent to be considered when making a formulary decision.

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