Aripiprazole Long-acting Injection (Abilify Maintena, ARISTADA)

National Drug Monograph

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

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary:

- Aripiprazole long-acting intramuscular injection (LAIM) is sixth antipsychotic and the fourth second generation antipsychotic to be marketed in a long-acting injection formulation.
- LAIM antipsychotics on the VA National Formulary: haloperidol and fluphenazine decanoate; risperidone; and paliperidone.
- Aripiprazole LAIM has FDA label indication for the treatment of schizophrenia.
- The initial and usual maintenance dose of aripiprazole is 400 mg once a month. The dose can be reduced to 300 mg or 200 mg monthly based on drug interactions or tolerability. Patients should have established tolerability to aripiprazole before receipt of the LAIM formulation. Oral aripiprazole, 10-30 mg/day, or another oral antipsychotic must be continued for 2-weeks after the initial dose, and then discontinued.
- Aripiprazole LAIM's efficacy and safety are based on experience with the oral formulation as well as pharmacokinetic trials and a 52-week randomized, double-blind, placebo-controlled trial. The randomized trial was terminated early because the difference in time to relapse met a predetermined statistically significant threshold (p=0.001) favoring aripiprazole LAIM [HR 5.03, 95% CI 3.15-8.02]. The rate of impending relapse was 10% with aripiprazole LAIM and nearly 40% in the placebo group in the final analysis.
- Insomnia, headache and tremor were the most common adverse events reported with aripiprazole LAIM relative to placebo. Extra pyramidal symptoms were more common in the aripiprazole LAIM group with the difference accounted for by Parkinson's symptoms.
- Aripiprazole shares the same contraindications, warnings and precautions as the oral form.
- Concurrent use of CYP 2D6 and 3A4 inhibitors requires a reduction in the monthly dose of aripiprazole. Aripiprazole LAIM should be avoided in patients taking aCYP3A4 inducer.
- Aripiprazole LAIM is an appropriate choice for patients who have responded to oral aripiprazole who require a LAIM antipsychotic for adherence.

Introduction

Long-acting intramuscular injection formulations (LAIM) of first and second generation antipsychotics are often used to treat patients who are none adherent to oral agents. Aripiprazole is the fourth atypical antipsychotic and sixth antipsychotic to be available as a LAIM.

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating aripiprazole LAIM for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics [1, 2]

Aripiprazole's mechanism of action is unknown. The proposed mechanism of action hypothesizes that aripiprazole is both a partial agonist of dopamine (D2) and serotonin (5HT1A) receptors and an antagonist of 5HT2A receptors. Aripiprazole may also affect other receptors resulting in other pharmacologic effects such as orthostatic hypotension due to inhibition of adrenergic alpha1 receptors.

Steady-state is reached after the fourth monthly injection of aripiprazole. The concentrations of the active metabolite, dehydro-aripiprazole, are approximately 30% of aripiprazole concentrations (Table 1). The steady-state pharmacokinetics of LAIM doses of aripiprazole 300 mg and 400 mg are comparable to oral doses of 15 mg and 20 mg, respectively.

Table 1 Pharmacokinetic Profile of Aripiprazole LAIM and active metabolite dehydro-aripiprazole

Parameter Mean (SD)	Aripip LAIM 300 mg	Aripip LAIM 400mg	Dehydro-aripip 300 mg	Dehdro-aripip 400 mg
$Cmax_{ss}$, ng/mL	269 (28.8)	316 (160)	74.7 (20.8)	89.4 (37.9)
$Cmin_{ss}$, ng/mL	156 (67.2)	212 (113)	54.1 (21.1)	64.1 (27.0)
$Cave_{ss}$, ng/mL	208 (87)	242 (132)	NA	NA
AUC_T, hr*ug/mL	140 (58.4)	163 (88.8)	38.8 (13.2)	47.8 (19.1)
Tmax, day	6.5 (0.5-21.2)	7.1 (3-11.2)	12.5 (0.5-22.2)	6.6 (3.0-14.0)
T1/2, day	29.9 (8.0)	46.5 (10.8)	30-47	30-47
Metabolism	CYP3A4 & 2D6 & glucuronidation			

NA = not available

FDA Approved Indication[1]

Aripiprazole LAIM is approved for the treatment of schizophrenia.

Potential Off-label Uses

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's Guidance on "Off-label" Prescribing (available on the VA PBM Intranet site only).

Potential off-label uses for the LAIM formulation would include the labeled uses for the oral formulation: bipolar disorder, major depressive disorder and treatment of irritability associated with autistic disorder; and other off-label uses for the class including PTSD, substance use

disorder, schizoaffective disorder, and dementia. Aripiprazole LAIM has not been studied for any of these potential off-label uses.

Current VA National Formulary Alternatives

Haloperidol decanoate LAIM
Fluphenazine decanoate LAIM
Risperidone LAIM – restricted to criteria for use
Paliperidone LAIM– restricted to criteria for use

Dosage and Administration[1]

Initiation of Aripiprazole LAIM

Patients who are naïve to aripiprazole should establish tolerability with oral aripiprazole prior to receipt of the LAIM formulation. The initial dose of aripiprazole LAIM is 400 mg IM unless factors are present that would require a lower dose (See Dosage Adjustment). In conjunction with the first dose of LAIM, patients must continue oral aripiprazole 10 mg to 20 mg daily or their existing oral antipsychotic for 14 days. The dosing frequency for aripiprazole LAIM is monthly. The dosing window for monthly doses is no sooner than 26 days and less than 5 weeks. The dose can be lowered to 300 mg monthly after the first dose as needed for tolerability.

Dosage Adjustment

Table 2 Dose Adjustment based on CYP Status and Drug Interactions

Cytochrome P450 Considerations	Dosage Adjustment
CYP2D6 Poor Metabolizer (PM)	300 mg
CYP2D6 PM taking CYP3A4 inhibitor	200 mg
Patients taking 400 mg	
Strong CYP2D6 or 3A4 inhibitor	300 mg
CPY2D6 and 3A4 inhibitor	200 mg
CYP3A4 inducer	Avoid use
Patients taking 300 mg	
Strong CYP 2D6 or 3A4 inhibitor	200 mg
CYP2D6 and 3A4 inhibitor	160 mg
CYP3A4 inducer	Avoid use

Missed Dose

If the second or third doses are missed:

- If more than 4 weeks and less than 5 weeks have elapsed since the last injection, administer the injection as soon as possible.
- If more than 5 weeks have elapsed since the last injection, restart concomitant oral aripiprazole for 14 days with the next administered injection.

If the fourth or subsequent doses are missed:

- If more than 4 weeks and less than 6 weeks have elapsed since the last injection, administer the injection as soon as possible.
- If more than 6 weeks have elapsed since the last injection, restart concomitant oral aripiprazole for 14 days with the next administered injection.

Administration

- Aripiprazole LAIM is provided as a lyophilized powder requiring reconstitution prior to administrations. See the product information for detailed instructions.

- Aripiprazole LAIM is only to be administered by intramuscular injection in the gluteal muscle by a healthcare professional.

Efficacy [2-5]

Efficacy Measures

Clinical Global Impression Severity Scale (CGI-S) and Suicidality (CGI-SS) are subscales of the CGI that measure the subject's current severity of illness and risk of suicide, relative to the clinician's past experience with patients who have the same diagnosis. The CGI is a validated clinician-rated scale that is rated on a 7-point spectrum (1 = normal, 7 = severely ill). The CGI-SS is composed of two parts: severity and change is suicidal thoughts.
Positive and Negative Syndrome Scale (PANSS) is a validated 30-item rating scale used to assess the effects of drug treatment in schizophrenia. It is a multi-item inventory of general psychopathology that evaluates items such as positive and negative symptoms of schizophrenia. PANSS is rated by physician observation and scored from 1 to 7 (1 = absent, 7 = extreme). PANSS total scores may range from 30 to 210.

Summary of efficacy findings

Citing aripiprazole's established efficacy, FDA required a single additional efficacy and safety trial for aripiprazole LAIM's approval. The study was 52-weeks in duration and used a multicenter, randomized, double-blind, placebo-controlled design. The study was conducted between July 2008 and February 2011 in 108 international centers including the United States. Patients were eligible if they were:

- 18 – 60 years of age
- Had a diagnosis of schizophrenia as defined by DSM-IV-TR for ≥3 years
- Required chronic antipsychotic treatment
- A history of symptom exacerbation or relapse when not receiving antipsychotic treatment
- Ability to comply with the study protocol

Key exclusion criteria included:

- A DSM-IV-TR diagnosis other than schizophrenia
- Any clinically significant medical or neurological disorder, abnormal medical test or ECG
- Refractory to antipsychotic treatment or responsive to clozapine
- Use of other antipsychotics, antidepressants or mood stabilizers during the study

The study design included five phases.
Phase 0 Screening (2 – 42 days) – eligibility determined
Phase 1 (4-6 weeks) – cross titration from other antipsychotics to oral aripiprazole monotherapy
Phase 2 (4-12 weeks) – subjects stabilized on oral aripiprazole 10 mg – 30 mg/day. Stability was defined as meeting all of the following for 4 consecutive weeks:

- Outpatient status
- Total PANSS score ≤80
- Lack of specific psychotic symptoms on PANSS subscales (≤4 on each) conceptual disorganization, suspiciousness, hallucinatory behavior, unusual thought content
- CGI-S score ≤4 (moderately ill)
- CGI-SS scores: Part 1 ≤2 (mildly suicidal) and Part 2 ≤5 (minimally worsened)

Phase 3 (12-36 weeks) – receipt of single-blind 400 mg dose of aripiprazole LAIM with continuation of oral aripiprazole for the first 2 weeks. The monthly LAIM dose could be decreased to 300 mg and increased back to 400 mg during this stabilization phase.
Subjects moved to **Phase 4** after meeting stability criteria (see Phase 2) for 12 weeks on aripiprazole LAIM monotherapy. Subjects were randomized to continue their same dose of

aripiprazole LAIM or placebo (2:1) every 4 weeks at the start of Phase 4 (up to 52 weeks). Benzodiazepines and benzotropine use were permitted during the study.

Time to exacerbation of psychotic symptoms/impending relapse during Phase 4 was the primary outcome variable. An exacerbation/relapse was defined as meeting any of the following:

- Clinical worsening – CGI-S score ≥5 and an increase in any PANSS subscale score to >4 with an absolute increase >2 on the specific subscale since randomization or an increase >4 on a subscale or an absolute increase of ≥4 on the combined subscale score since randomization.
- Hospitalization due to worsening of psychotic symptoms
- CGS-SS score – Part 1 = 4 (severely suicidal) or 5 (attempted suicide), Part 2 = 6 (much worse) or 7 (very much worse)
- Violent behavior resulting in clinically significant self-harm, injury to other, or property damage.

Two pre-specified interim analyses were planned at 50% and 75% of impending relapses for all randomized subjects. The study was discontinued prematurely at the first planned interim analysis (64 events) because of the significantly great efficacy (as time to impending relapse) of aripiprazole LAIM (p=0.001).
A total of 843 subjects enrolled in the study with 710 achieving stabilization on oral aripiprazole (mean daily dose 19.2 mg). Four hundred-three subjects were randomized to aripiprazole LAIM (n=269) or placebo (n=134). At the start of Phase 3 (LAIM stabilization) the mean CGI-S and PANSS (range) scores were 3.2 (1-4) and 59.4 (30-80), respectively. At the beginning of Phase 4 (randomization), these scores were 2.9 (1-4) and 54.5 (31-80), respectively. The two randomized groups did not differ in their demographics: mean age ~41 years, 61% male, 60.5% White, 20% Black/African American, and 14.45% Asian. Forty-five percent of subjects were in the United States.

The duration of exposure to aripiprazole LAIM was limited due to the study's premature termination. As seen in Table 3, less than 75 subjects were exposed to aripiprazole for 1 year. It is unclear how many of the subjects who had 13 or more injections in the Phase 3 arm completed the 52 week study.

Table 3 Treatment Exposure: Phase 3 and 4

Exposure	***Phase 3***	***Phase 4***	
	LAIM (n=576)	**LAIM (n=269)**	**Placebo (n=134)**
≥7 injections (6 mo)	194 (33.7%)		
≥13 injections (12 mo)	51 (8.9%)		
Completed 52 weeks		23 (8.6%)	3 (2.2%)

The randomized trial was terminated early because the difference in time to impending relapse met a predetermined statistically significant threshold favoring aripiprazole LAIM [HR 5.03, 95% CI 3.15-8.02]. The rates of impending relapse at the study's termination were 10% with aripiprazole LAIM and nearly 40% in the placebo group (Table 4). Worsening of the CGI-S or PANSS scores was the most common reason for relapse. Mean changes for aripiprazole and placebo in Phase 4 were 0.1 and 0.7 on the CGI-S, and 1.4 and 11.6 on the PANSS, respectively. The proportion of subjects with a relapse due to hospitalization was greater in the aripiprazole arm; no explanation was provided.

Table 4 Relapse Rate and Reasons for Relapse

Measure	***Aripiprazole***	***Placebo***
Relapse Rate (Final)	10% (27/269)	39.6% (53/134)
Reason for Relapse		
Worsening CGI-S/PANSS	74.1% (20/27)	86.8% (46/53)
Hospitalization	25.9% (7/27)	9.4% (5/53)
Suicide risk	3.7% (1/27)	1.9% (1/53)
Violent behavior	3.7% (1/27)	7.5% (4/53)

Preliminary results from a multi-center, open-label, retrospective-prospective mirror image study compared psychiatric hospitalizations rates in the 3-months prior to and 3- months following initiation of aripiprazole LAIM. During the retrospective phase, patients were treated with oral antipsychotics, while in the prospective phase the received 400 mg aripiprazole LAIM monthly. One hundred and eighty-three patients entered the prospective phase. Among the121 patients who received 3 months or more of aripiprazole LAIM, 4.1% were hospitalized in both 3-month periods, 2.5% were only hospitalized in the prospective period (while receiving aripiprazole LAIM), 24.0% were only hospitalized in retrospective period, and 69.4% were not hospitalize in either period ($p<0.0001$).

Adverse Events (Safety Data)[1, 3-5]

Deaths and Other Serious Adverse Events

Serious ADEs were reported with aripiprazole LAIM in 4.3% of patients during Phase 3 and 4.1% in Phase 4 (vs. 6.7% for placebo). Two deaths were reported in the trial: 1 due to coronary insufficiency during Phase 3 and the other was due to pancreatic carcinoma in a patient receiving aripiprazole LAIM during Phase 4. Neither death was considered attributable to the study treatments. Four suicide-related AEs were reported in Phase 4 (all in the aripiprazole LAIM group): 3 patients experienced suicidal ideation and 1 patient attempted suicide.

Common Adverse Events

Insomnia, headache and tremor were the most common adverse events reported with aripiprazole LAIM relative to placebo in Phase 4 (Table 5). Extra pyramidal symptoms (EPS) were more common in the aripiprazole LAIM group with the difference accounted for by Parkinson's symptoms. Mean changes in scores on Abnormal Involuntary Movement Scale, Barnes Akathisia Rating Scale and Simpson-Angus Scale did not differ significantly between treatments. Corresponding to the increased tremor and EPS, the use of anticholinergic agents was higher with aripiprazole. Prolactin concentrations exceeding the upper limit of normal were greater in the placebo arm, while changes in weight and injection site pain and site reactions did not differ between the treatments (Table 5).

Table 5 Adverse Events Reported by >5% of Subjects during Phase 3 and Phase 4

Adverse Event	Phase 3 Aripip. LAIM n=576	Phase 4	
		Aripip. LAIM n=269	Placebo n=134
Any ADE	59.9%	63.2%	61.9%
Insomnia	8.0%	10.0%	9.0%
Headache	5.9%	5.9%	5.2%
Anxiety	6.6%	5.9%	7.5%
Tremor	3.6%	5.9%	1.5%
Nasopharyngitis	1.9%	3.7%	5.2%
EPS		14.9%	9.7%
• Akathisia		5.6%	6.0%
• Dyskinetic		0.7%	1.5%
• Dystonic		1.9%	1.5%
• Parkinsonism		8.2%	3.0%
Tardive dyskinesia		None	1 case
Anticholinergic use		16.7%	10.4%
Prolactin [>ULN]		1.9%	7.1%
Weight gain, any	6.9%	9.7%	9.7%
>7% BBW	5.4%	6.4%	5.2%
Mean change, kg	-0.2	-0.2	-0.4
Injection site pain/rxn	5.9%	5.9%	5.2%
*Pain score 1st/Last injection	6.1/4.9	5.1/4.0	5.1/4.9
Induration		1.9%	None

EPS = Extra Pyramidal Symptoms; BBW = Baseline Body Weight
*Pain score on a 100 point visual analog scale (0 = no pain, 100 = unbearably painful)

Other Adverse Events

There were no clinically meaningful changes in metabolic parameters or in the incidence of new-onset metabolic abnormalities including glucose, cholesterol or triglycerides with either treatment. Changes in vital signs including QTc interval were similar between groups.

Tolerability

Study participation was discontinued secondary to treatment emergent events during Phase 4 in 7.1% (19/269) of subjects receiving aripiprazole LAIM compared to 13.4% (18/134) assigned to placebo.

Contraindications[1]

- Known hypersensitivity to aripiprazole

Warnings and Precautions[1]

- Boxed warning on the increased mortality in elderly patients with dementia-related psychosis
- Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis: Increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic Attack, including fatalities)
- Neuroleptic Malignant Syndrome: Manage with immediate discontinuation and close monitoring

- Tardive Dyskinesia: Discontinue if clinically appropriate
- Metabolic Changes: Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, diabetes mellitus, dyslipidemia, and weight gain
- Orthostatic Hypotension: Use with caution in patients with known 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 count (WBC). 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

Special Populations[1, 6]

Pregnancy Category C: Risk Summary

Pregnancy Category C: Risk Summary
Adequate and well controlled studies with aripiprazole have not been conducted in pregnant women. In animal studies, aripiprazole demonstrated developmental toxicity occurred at maternal doses 1 - 10 times the oral maximum recommended human dose [MRHD] of 30 mg/day based on body surface area. Adverse outcomes included possible teratogenic effects (increased rates of hepatodiaphragmatic nodules and diaphragmatic hernia and increased stillbirths), developmental delays (including reduced fetal and pup weights, undescended testes, and delayed skeletal ossification), and impaired reproductive performance in exposed offspring. Published data on the use of aripiprazole during human pregnancy are limited to only a small number of case reports, which did not show any birth defects or abnormal development to age 6 months.

Neonates exposed to antipsychotic drugs (including aripiprazole LAIM) during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery.

Aripiprazole LAIM should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. See the product information for more detailed information and discussion. The National Pregnancy Registry for Atypical Antipsychotics enrolls pregnant women using newer antipsychotic agents (including aripiprazole). The registry is run by the Massachusetts General Hospital Center for Women's Mental Health. Contact the registry at 1-866-961-2388.

Nursing Mothers

Based on only a few patients, aripiprazole is excreted in human breast milk at low levels. Aripiprazole levels are below detectable limits in some women sampled. No adverse effects in exposed infants have been reported but data are very limited. Based on one patient, infant exposure for a fully breastfed infant was calculated to be less than 1% of the weight-adjusted maternal dose. Aripiprazole's label states that a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. In isolated cases, it may be acceptable to evaluate milk and infant serum drug levels and observe for infant adverse effects.

Geriatric Use

Safety and effectiveness of aripiprazole LAIM in patients >60 years of age have not been evaluated.

CYP2D6 Poor Metabolizers

Approximately 8% of Caucasians and 3–8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers (PM). Dosage adjustment is recommended in CYP2D6 poor metabolizers due to high aripiprazole concentrations.

Sentinel Events

No data

Look-alike / Sound-alike (LA / SA) Error Risk Potential

As part of a Joint Commission standard, LASA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LASA information from three ~~four~~ data sources (Lexi-Comp, ~~USP Online LASA Finder,~~ First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:
LA/SA for generic name aripiprazole: rabeprazole, aripiprazole oral or IM
LA/SA for trade name Abilify: Abelcet, Abilify oral or IM

Drug Interactions[1]

Drug-Drug Interactions

- Carbamazepine or Other CYP3A4 Inducers - Concomitant use of aripiprazole LAIM with carbamazepine or other CYP3A4 inducers decreases the concentrations of aripiprazole. avoid use of aripiprazole LAIM in combination with carbamazepine and other inducers of CYP3A4 for greater than 14 days.
- Ketoconazole or Other Strong CYP3A4 Inhibitors - Concomitant use of aripiprazole LAIM with ketoconazole or other CYP3A4 inhibitors for more than 14 days increases the concentrations of aripiprazole and reduction of the aripiprazole LAIM dose is recommended. Due to prolonged-release characteristics of aripiprazole LAIM, short-term co-administration of ketoconazole or other inhibitors of CYP3A4 with aripiprazole LAIM does not require a dose adjustment.
- Quinidine or Other Strong CYP2D6 Inhibitors - Concomitant use of aripiprazole LAIM with quinidine or other CYP2D6 inhibitors increases the concentrations of aripiprazole after longer-term use (i.e., over 14 days) and a reduction in the dose of the aripiprazole LAIM is recommended. Due to prolonged-release characteristics of aripiprazole LAIM, short-term co-administration of quinidine or other CYP2D6 inhibitors with aripiprazole LAIM does not require a dose adjustment.
- CNS Depressants - Given the CNS depressant effects of aripiprazole, use caution when aripiprazole LAIM is taken in combination with other centrally-acting drugs or alcohol.
- Anti-Hypertensive Agents - Due to its alpha adrenergic antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.

Conclusions

Aripiprazole LAIM offers another long-acting injectable option for the treatment of schizophrenia. These formulations are typically reserved for patients who are nonadherent with oral medications. Aripiprazole's chief advantage over the long-acting IM formulations appears to be a lower risk for metabolic effects such as weight gain.

Possible disadvantages include the requirement that patient the patient continue oral aripiprazole for the 2 weeks following their first LAIM dose as this could mistakenly lead to continuation of oral antipsychotics. Unlike risperidone long-acting injection, aripiprazole LAIM does not have a label indication for bipolar I disorder and no trials have been published to support such off-label use. Nor does aripiprazole LAIM share other label indications with its oral form such as major depressive disorder. The cost of aripiprazole LAIM is markedly greater than haloperidol or fluphenazine decanoate and at a 400 mg dose is greater than risperidone or paliperidone LAIM.

Aripiprazole LAIM's efficacy and safety are based on a pivotal 52-week placebo controlled trial that was terminated early because the difference in time to impending relapse met a predetermined threshold and the established efficacy and safety profile of it oral form. Aripiprazole LAIM is an appropriate choice for patients who have responded to oral aripiprazole who require a LAIM antipsychotic for adherence.

References

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Addendum: Aripiprazole lauroxil (ARISTADA)

Aripiprazole lauroxil is an intramuscular depot formulation (LAIM) designed to provide slow dissolution of aripiprazole lauroxil particles which undergo hydrolysis resulting in extended systemic availability of aripiprazole.

Dosing

As with all LAIM antipsychotics, patients' naïve to aripiprazole should not receive aripiprazole LAIM until they have established tolerability with oral aripiprazole. In the event of early dosing, an aripiprazole lauroxil injection should not be given earlier than 14 days after the previous injection.

Refer to the following table to convert patients stable on oral aripiprazole to lauroxil:

Oral Aripiprazole Dose	Lauroxil (ARISTADA) Dose	Frequency	Injection site	Volume
10 mg/day	441 mg	Monthly	Deltoid or Gluteal	1.6 mL
15 mg/day	662 mg	Monthly	Gluteal	2.4 mL
≥ 20 mg/day	882 mg	Monthly	Gluteal	3.2mL

Oral aripiprazole should be continued for 21 days after the first aripiprazole lauroxil injection.

Refer to the following table to convert patients stable on Abilify Maintena to lauroxil (ARISTADA):

Abilify Maintena Dose/month	Aripiprzaole lauroxil (ARISTADA) Dose (mg aripiprazole)	Aripiprzaole lauroxil (ARISTADA) Frequency	Aripiprzaole lauroxil (ARISTADA) Injection site
300 mg	441 mg (300 mg)	Monthly	Deltoid or Gluteal
400 mg	662 mg (450 mg)	Monthly	Gluteal
600 mg	882 mg (600 mg)	Monthly or every 6 weeks	Gluteal

Administration of 882 mg every 6 weeks results in plasma aripiprazole concentrations that are within the established therapeutic range for 441 to 882 mg monthly.

Refer to the following table regarding missed doses:

Last dose of aripiprazole lauroxil	Length of time since last injection of aripiprazole		
	No oral supplement required	Supplement with 7 days of oral aripiprazole*	Supplement with 21 days of 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

*Supplemental dose should be the same dose of oral aripiprazole as when the patient began aripiprazole lauroxil.

Refer to the following table for dose adjustments based on concurrent medications and an individual's cytochrome 2D6 status:

Concomitant Medicine	Dose Change for Aripiprazole lauroxil*
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 Inducers	No dose adjustment for 662 mg and 882 mg dose, increase the 441 mg dose to 662 mg.

*For the 882 mg dose administered every 6 weeks, the next lower strength should be 441 mg administered every 4 weeks.

Bioavailability

Aripiprazole lauroxil's bioavailability was studied in an open-label, single dose, multicenter trial. Forty-six subjects with chronic stable schizophrenia or schizoaffective disorder received a 441 mg dose after being randomized (1:1) to deltoid or gluteal injection site. Subjects had not received aripiprazole for at least 60 days. Two subjects (4%) were CYP2D6 poor metabolizers; the remainder was extensive or intermediate metabolizers. Following injection aripiprazole concentrations rose steadily with median T_{max} of 44 and 50 days for deltoid and gluteal injections, respectively. Aripiprazole plasma concentrations then declined through Day 89. The Cmax and AUC following deltoid injection was 23% to 34% greater than gluteal injection; however, the values are considered comparable due to overlapping ranges.

Efficacy

Aripiprazole lauroxil's efficacy was established based on the existing evidence from oral aripiprazole and a 12-week, randomized, double-blind, placebo-controlled, fixed-dose study in adults with schizophrenia. To be eligible adults age 18-70 years of age had to have a total PANSS score of 70 – 120 with a score of ≥4 in at least 2 selected PANSS items, and a CGI-S score ≥4. Following 3-weeks of oral aripiprazole or placebo, subjects were randomized to aripiprazole lauroxil 441 mg (n=207), 882 mg (n=208), or placebo (n=207). Doses were administered on Days 1, 29 and 57. Change from baseline to Day 85 in the total PANSS score was the primary outcome measure. Both doses of aripiprazole resulted in a statistically significant improvement in total PANSS score from baseline compared to placebo. Significant differences in CGI-S scores were found for both doses of aripiprazole lauroxil. PANNS score results are shown in the table below.

Treatment Group	**Primary Efficacy Measure: PANSS Total Score**		
	Mean Baseline Score (SD)	**LS Mean Change from Baseline (SE)**	**Placebo-subtracted Difference[a] (95% CI)**
Aripip. lauroxil 441 mg[b]	92.6 (10.2)	-20.9 (1.4)	-10.9 (-14.5, -7.3)
Aripip. lauroxil 882 mg[b]	92.0 (10.8)	-21.8 (1.4)	-11.9 (-15.4, -8.3)
Placebo	93.9 (11.3)	-9.8 (1.4)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval, not adjusted for
multiple comparisons. [a] Difference (drug minus placebo) in least-squares mean change from baseline. [b] Doses that are demonstrated to be effective.

Safety

Single injections of aripiprazole lauroxil 441 mg resulted adverse events deemed to be mild or moderate. Subjects who received a deltoid injection had a greater proportion of adverse events (90.9%) compared to gluteal (77.3%). This difference carried over to injection site pain (63.6% vs. 27.3%). Headache, abdominal pain, constipation, diarrhea, dyskinesia and dystonia were more common with deltoid injections, however, the number of cases were 5 or fewer per group.

How Supplied

Aripiprazole lauroxil LAIM suspension is available in strengths of 441 mg in

1.6 mL, 662 mg in 2.4 mL, and 882 mg in 3.2 mL. The kit contains a 5-mL pre-filled syringe containing aripiprazole lauroxil sterile aqueous suspension and safety needles.

- The 441 mg strength kit (NDC 65757-401-03*; light blue label*) contains three safety needles; a 1-inch (25 mm) 21 gauge, a 1½-inch (38 mm) 20 gauge, and a 2-inch (50 mm) 20 gauge needle.
- The 662 mg strength kit (NDC 65757-402-03*; green label*) contains two safety needles; a 1½-inch (38 mm) 20 gauge and a 2-inch (50 mm) 20 gauge needle.
- The 882 mg strength kit (NDC 65757-403-03*; burgundy label*) contains two safety needles; a 1½-inch (38 mm) 20 gauge and a 2-inch (50 mm) 20 gauge needle.

Conclusion

Aripiprazole lauroxil (ARISTADA) is an alternative LAIM form to aripiprazole (MAINTENA). The two products have not been compared. When given as an 882 mg dose, aripiprazole lauroxil's dosing frequency can be extended to every 6 weeks as opposed to monthly.

References:

1. ARISTADA (aripiprazole lauroxil) [prescribing information] Alkermes, Inc., Waltham, MA. October 2015.
2. Turncliff R, Hard M, Du Y, et al. Relative bioavailability and safety of aripiprazole lauroxil, a novel once-monthly, long-acting injectable atypical antipsychotic, following deltoid and gluteal administration in adult subjects with schizophrenia. Schizophrenia Res 2014;159:404-410.

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