

# Aripiprazole Lauroxil NanoCrystal<sup>®</sup> Dispersion Technology (Aristada Initio<sup>®</sup>)

Megan J. Ehret<sup>1</sup>, Erica Davis<sup>1</sup>, Sarah E. Luttrell<sup>2</sup>, Caroline Clark<sup>3</sup>

## Abstract

Nonadherence to antipsychotic medications for the treatment of schizophrenia is a widely recognized concern, leading to poorer clinical outcomes and higher treatment costs. Long-acting injectable (LAI) antipsychotics offer an extended dosing interval option for patients, although the current options may require an oral overlap at initiation. Aripiprazole lauroxil is an LAI that offers multiple dosing options but requires oral treatment overlap during initiation for the first 21 consecutive days. As an alternative to oral overlap, a novel nano-crystalline milled dispersion delivery system of aripiprazole lauroxil was recently approved as a one-day regimen to be added to aripiprazole lauroxil treatment.

**Key Words:** Schizophrenia, Antipsychotic, Aripiprazole

## Introduction

Antipsychotic medications are currently the gold standard treatment for schizophrenia, a persistent illness which requires long-term pharmacotherapy in order to manage symptoms and prevent relapses (1-3). While these medications are generally effective, nonadherence is widely recognized as a significant problem, leading to poor clinical outcomes and high-treatment costs (4, 5). Long-acting injectable (LAI) antipsychotics have extended dosing intervals for patients who are either nonadherent to oral antipsychotics, or who prefer non-orally administered medications (1, 6, 7). Current U.S. treatment guidelines recommend LAI antipsychotics for patients with recurrent relapses related to nonadherence to oral preparations and for those who prefer that mode of administration (2, 8).

Aripiprazole is an established second-generation antipsychotic available in both oral and LAI formulations. Aripiprazole monohydrate (Abilify Maintena<sup>®</sup>) is available as a once monthly injection and requires oral overlap for 14 consecutive days following the first injection. However, there is limited flexibility, as almost all patients are maintained on one dosing regimen (400 mg administered monthly). Aripiprazole lauroxil (Aristada<sup>®</sup>) is an extended-release aripiprazole prodrug and offers more than one dosing regimen (441, 662, and 882 mg administered monthly, 882 mg every 6 weeks, or 1,064 mg every 8 weeks), but requires oral overlap for 21 consecutive days when initiating the medication (9, 10).

Aripiprazole lauroxil is a prodrug of N-hydroxymethyl aripiprazole, which is, in turn, a prodrug of aripiprazole. It uses a proprietary technology (LinkeRx<sup>®</sup>; Alkermes, Inc., Waltham, MA) resulting in extended systemic release after administration. The LinkeRx<sup>®</sup> system is used to attach the aripiprazole molecule to a lauroyloxymethyl chain via a carbon-nitrogen (C-N) bond (11, 12). This approach lowers the solubility of aripiprazole, and allows for controlled release after each injection and extended exposure of the active molecule (13). Once the aqueous suspension is injected into the gluteal or deltoid muscle, the conversion of aripiprazole lauroxil to aripiprazole is governed by slow dissolution

<sup>1</sup>University of Maryland School of Pharmacy, Baltimore, MD

<sup>2</sup>University of Maryland Eastern Shores, School of Pharmacy, Princess Anne, MD

<sup>3</sup>U.S. Army Field Artillery Center, Fort Sill, OK

Address for correspondence: Megan J. Ehret, PharmD, MS, BCPP, University of Maryland, School of Pharmacy, 20 North Pine Drive, Baltimore, MD 21201

Phone: 410-706-6006; E-mail: mehret@rx.umaryland.edu

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of aripiprazole lauroxil and subsequent enzyme-mediated cleavage by esterases, generating N-hydroxymethyl aripiprazole and lauric acid. Lauric acid, also called dodecanoic acid, is a fatty acid found in coconut oil, human breast milk, and cow's milk (14). Subsequent rapid, nonenzymatic spontaneous cleavage (water-mediated hydrolysis) of N-hydroxymethyl aripiprazole yields aripiprazole and formaldehyde. Formaldehyde creation is approximately 1 mg/d for 882 mg monthly and is well below the amount generated by basic metabolism and diet (15). Once aripiprazole is formed, elimination of plasma aripiprazole is primarily by cytochrome P450 (CYP) 3A4 and 2D6 enzymes into the active metabolite dehydro-aripiprazole (16). After the injection of aripiprazole lauroxil, aripiprazole becomes detectable in systemic circulation by day five or six and continues to be released for an additional 36 days (10).

The aripiprazole lauroxil formulation consists of micron-sized particles specifically designed for slow dissolution, which supports the long dosing intervals (up to 2 months with the 1,064 mg dose). The current dosing regimen requires three weeks of oral aripiprazole supplementation to achieve and maintain therapeutic aripiprazole concentrations (10).

In order to reduce the time needed for oral supplementation, a one-day initiation regimen—a nano-crystalline milled dispersion of aripiprazole lauroxil, Aristada Initio<sup>®</sup>—was recently approved. Nanocrystal medications are formulated as nanometer-sized medication crystals ranging between 10 to 1,000 nm. When compared to the microcrystals, the smaller medication particle size of nanocrystals increases the rate of dissolution, thereby enhancing bioavailability (17). The nanometer-sized drug crystals in the aripiprazole lauroxil nanocrystal<sup>®</sup> dispersion (AL<sub>NCD</sub>) technology formulation have been designed to accelerate the dissolution of aripiprazole lauroxil to provide a faster time to therapeutic concentration (18). The therapeutic intent of this dosage form is to minimize the need for oral aripiprazole treatment overlap that follows the first injection of aripiprazole lauroxil.

## Current Studies with Aripiprazole Lauroxil NanoCrystal<sup>®</sup> Dispersion Technology

Currently, three tolerability and pharmacokinetic studies of AL<sub>NCD</sub> have been completed. Study ALK9072-B101 enrolled 41 patients with schizophrenia to study a single dose of AL<sub>NCD</sub> technology formulation intramuscular gluteal injection. The mean age of the participants in the study was 44.2 (SD: 11.5) and 32 (78%) were male. This study was an ascending dose study to evaluate the safety, tolerability and

pharmacokinetics of AL<sub>NCD</sub> technology. The study included an 84-day pharmacokinetic profile. At time of publication, the results have not been released for this study (19).

Study ALK9072-B103 enrolled 47 patients with schizophrenia to examine a single-dose study comparing a deltoid intramuscular injection of AL<sub>NCD</sub> technology to a gluteal intramuscular injection of AL<sub>NCD</sub> technology. The mean age of the participants in the study was 48.6 (SD: 9.9) and 34 (72%) were male. It planned for an 84-day pharmacokinetic profile. Results have not been released for this study (19).

Study ALK9072-B102A was a blinded, randomized, Phase 1, pharmacokinetic, safety and tolerability study of the one-day initiation regimen of AL<sub>NCD</sub> technology formulation versus the standard twenty-one day oral overlap regimen. All three studies enrolled patients who met the following criteria: 18–65 years of age with demonstrated tolerability to aripiprazole, on a stable oral antipsychotic medication (excluding aripiprazole or clozapine) without regimen changes for ≥2 months prior to screening, and a *Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5)* diagnosis of schizophrenia (20, 21). Patients were excluded from the study if they had recent aripiprazole exposure (depot aripiprazole ≤6 months prior to inpatient admission or oral aripiprazole ≤28 days prior to randomization) or another LAI antipsychotic ≤3 months prior to admission, were a CYP2D6 poor metabolizer, or were taking a potent CYP3A4 inducer or inhibitor or a CYP2D6 inhibitor (including prescription medications, over-the-counter medications, or dietary supplements) within 30 days prior to admission.

In study ALK9072-B102A, clinical assessments and statistical analysis included the pharmacokinetics of all patients who received any study drug and had ≥1 measurable concentration of plasma aripiprazole. The outcomes included the area under the concentration-time curve from Day 0 to Day 28 post-dose (AUC<sub>0–28</sub>), which was computed using the linear trapezoidal rule and included only oral pre-dose concentrations. Actual elapsed time from dosing was used to estimate parameters. The safety analyses were carried out with the same population and included a collection of adverse effects, movement disorder measures, and injection-site evaluation.

One hundred and sixty-one adult patients with schizophrenia were enrolled, and 133 patients completed the study. The mean age of the participants was 44 (SD: 10.6) and 118 (73%) were male. Patients randomized to the one-day initiation regimen were given an AL<sub>NCD</sub> gluteal intramuscular injection, a one-time 30 mg oral aripiprazole tablet, and then either a contralateral gluteal aripiprazole lauroxil injection of 882 mg (n=41) or a deltoid injection of 441 mg (n=39) on Day 1. During the next 20 days, patients received oral

**Table 1** Area Under the Concentration-Time Curve Outcomes for AL<sub>NCD</sub> Technology (21)

Treatment Group	AL 441 mg/1-day	AL 441 mg/21-day	AL 882 mg/1-day	AL 882 mg/21-day
<b>AUC<sub>0-28</sub> (dayXng/mL)</b>				
Mean (SD)	4,256.4 (1,703.6)	3,371.6 (1,110.5)	3,570.7 (1,935.3)	3,911.9 (1,661.6)
Range	1,854.8–7,930.1	836.2–5,320.3	1,314.7–9,179.2	978.8–8,409.3

AL=Aripiprazole Lauroxil; AUC<sub>0-28</sub>=Area under the Concentration-Time Curve calculated from Day 0–28; SD=standard deviation

placebo. Subjects randomized to the 21-day oral overlap regimen received a gluteal placebo injection, 15 mg of oral aripiprazole, and a deltoid intramuscular injection of aripiprazole lauroxil 441 mg (n=40) or contralateral gluteal intramuscular injection of aripiprazole lauroxil 882 mg (n=41) on Day 1 followed by 20 days of 15 mg of oral aripiprazole. Both groups (882 and 441 mg) had comparable aripiprazole exposure to the standard 21-day aripiprazole lauroxil 441 mg or 882 mg initiation regimens. See Table 1 for AUC<sub>0-28</sub> outcomes (21).

Adverse effects experienced by five percent or more of the study participants included injection site pain, headache, increased weight, insomnia, dyspepsia, and anxiety. Nine akathisia events occurred during the study, including four events in four patients in the 1-day regimen group and five events in two patients in the 21-day oral overlap regimen group. Eight of these events were mild and none led to discontinuation from the study (21).

Although the study demonstrated a similar pharmacokinetic profile of the 1-day initiation regimen to the 21-day oral overlap regimen, the study was small in size, and only two of the four available doses of aripiprazole lauroxil were evaluated in conjunction with the AL<sub>NCD</sub> technology formulation. The 441 mg/1-day regimen had the highest AUC<sub>0-28</sub> possibly due to the deltoid administration of the 441 mg aripiprazole lauroxil dose given. Previous pharmacokinetic modeling and serum concentrations from other AL studies have demonstrated that, for the first 28 days, the deltoid injection of 441 mg can result in higher AUCs, although higher doses eventually result in a higher AUC past 28 days (11). The results demonstrate that the 1-day regimen may offer an alternative to the current 21-day regimen for patients starting aripiprazole lauroxil therapy.

### Pharmacokinetic Model Study

A population pharmacokinetic model (PopPK) has been developed to describe the one-day initiation regimen of AL<sub>NCD</sub> technology. It was designed to perform model-based simulation of relevant treatment scenarios regard-

ing AL<sub>NCD</sub> technology use. The PopPK model study used the three above studies and a fourth study of aripiprazole lauroxil (ALK9072-A105) (22). The study included 2,536 dosing records (1,742 oral aripiprazole, 626 aripiprazole lauroxil, and 168 AL<sub>NCD</sub> technology). The model used non-linear mixed-effects modeling with NONMEM version 7.3.0 (ICON, Gaithersburg, MD, USA). The model evaluated the one-day initiation regimen and impact of the co-administration of aripiprazole lauroxil on the same day, or administration on a separate day (1, 3, 7, or 10 days after AL<sub>NCD</sub>) (19, 22).

The PopPK simulation predicted that concomitant administration of the one-day regimen with any approved dosage regimen of aripiprazole lauroxil (441, 662, or 882 mg every four weeks, 882 mg every six weeks, or 1,064 mg every 8 weeks) would achieve therapeutic aripiprazole concentrations within four days of initiation and maintain therapeutic concentrations until the next dose of aripiprazole lauroxil. Further, when there was administration of aripiprazole lauroxil ten days after the one-day initiation regimen, the predicted median aripiprazole concentrations immediately before the second dose of aripiprazole lauroxil were ≥77% of that attained with same-day administration.

Additionally, a simulation was completed to determine the utility of missing an aripiprazole lauroxil dose and the use of AL<sub>NCD</sub> versus oral aripiprazole to reinitiate the patient. A dose of aripiprazole lauroxil was administered 1, 2, 3, 4, or 6 weeks late (depending on the dosing regimen) alone, with 7 days of oral aripiprazole supplementation, or a single dose of AL<sub>NCD</sub> without the single oral aripiprazole dose. The simulations demonstrated that when an aripiprazole lauroxil dose is missed, co-administration with either seven days of oral aripiprazole supplementation or a single dose of AL<sub>NCD</sub> is effective in returning aripiprazole concentrations within the range associated with therapeutic doses of aripiprazole lauroxil. Further simulations indicated that longer delays (requiring 21 days of oral aripiprazole supplementation according to the package insert) would require resumption of aripiprazole lauroxil treatment with the 1-day initiation regimen (22, 23).

Overall, the model-based simulations indicated that the proposed 1-day initiation regimen is suitable for initiating treatment with all aripiprazole lauroxil doses. Additionally, the model-based simulations also demonstrated that aripiprazole lauroxil could be initiated on the same day or up to ten days after administration of the one-day regimen (19, 22).

## Pharmacokinetics, Recommended Dosage and Administration

AL<sub>NCD</sub> and aripiprazole lauroxil are not interchangeable due to differing pharmacokinetic profiles (23). A single dose of AL<sub>NCD</sub> is adequate for all dose levels of oral aripiprazole and aripiprazole lauroxil. After a single intramuscular injection of AL<sub>NCD</sub>, the appearance of aripiprazole in the systematic circulation occurs on the day of injection. The median time to reach peak plasma exposures is approximately 27 days (range: 16 to 35 days). With the addition of the single intramuscular injection of AL<sub>NCD</sub> and a 30-mg oral aripiprazole at the time of the first aripiprazole lauroxil dose, aripiprazole concentrations reach relevant levels within 4 days. Aripiprazole exposure was similar for deltoid and gluteal intramuscular injections of AL<sub>NCD</sub> (23). For AL<sub>NCD</sub>, the mean aripiprazole terminal elimination half-life was 15–18 days after injection (23).

According to the FDA-approved package insert, after establishing tolerability with oral aripiprazole, the first dose of aripiprazole lauroxil intramuscular injection (441 mg, 662 mg, 882 mg, or 1,064 mg) can be given in conjunction with both one 675 mg injection (2.4 mL) of AL<sub>NCD</sub> in the deltoid or gluteal muscle (this corresponds to 459 mg of aripiprazole) and one 30-mg dose of oral aripiprazole (23). The first aripiprazole lauroxil injection may also be administered on the same day as the AL<sub>NCD</sub> or up to 10 days thereafter. The injection of both the aripiprazole lauroxil and AL<sub>NCD</sub> concomitantly into the same deltoid or gluteal muscle should be avoided. AL<sub>NCD</sub> is only available as a single strength pre-filled syringe, so dosage adjustments are not possible. The medication should be avoided in those who are known CYP2D6 poor metabolizers or those taking strong CYP3A4 inhibitors, strong CYP2D6 inhibitors, or strong CYP3A4 inducers.

## Conclusions

The FDA approval of AL<sub>NCD</sub> provides a new effective initiation strategy for a long-acting treatment option for patients with schizophrenia. Compared to other LAIs, the ability to initiate AL<sub>NCD</sub> expeditiously and without oral overlap provides a quicker time to therapeutic concentration. The new nanocrystal dispersion technology will place aripiprazole lauroxil in a similar category as paliperidone pal-

mitate in being able to avoid oral overlap when initiating the medication. The availability of only one dose will need to be further evaluated to determine its utility in those who may be taking interacting medications or require a decreased dose of aripiprazole. Clinicians will also need to consider the patient's acceptability of receiving two injections on day one, although the dosing recommendations do allow for ten days between the AL<sub>NCD</sub> and the first aripiprazole lauroxil injection. This novel dispersion technology also allows for reinitiation of aripiprazole lauroxil without oral overlap in given situations. Compared to other LAIs, the nanocrystal technology offers a novel delivery system while avoiding oral overlap, providing another treatment option in our armamentarium available for the treatment of schizophrenia.

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