Aripiprazole lauroxil nanocrystal suspension

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New long-acting injectable formulation simplifies the initiation regimen

Long-acting injectable (LAI) antipsychotics were developed due to the pervasive problem of oral medication nonadherence among patients with severe mental illnesses. While use of LAI antipsychotics reduces hospitalization rates, one issue in transitioning patients to certain LAI preparations is the need for prolonged oral coverage when beginning treatment with agents that cannot be loaded.[1,2] Nonadherence with this bridging oral therapy places the patient at risk for symptom exacerbation until effective antipsychotic plasma levels are achieved from the LAI.[1] To obviate the need for 3 weeks of oral medication coverage when commencing treatment with aripiprazole lauroxil (AL; Aristada), a new LAI form of AL was developed utilizing smaller nanomolecular-sized particles. The nanocrystal suspension has a shorter T_{max} and much shorter half-life than AL, provides effective plasma levels within 1 week of the injection when combined with a single 30 mg oral dose, and is administered at the same time the maintenance AL injection is given. Aristada lauroxil nanocrystal suspension (Aristada Initio) was approved on June 29, 2018 for the treatment of adults with schizophrenia (***Table 1***). The approval of this initiation regimen was based on pharmacokinetic studies demonstrating comparable plasma aripiprazole levels to that which would be achieved when using 21 days of oral aripiprazole coverage.[3,4]

Table 1

Fast facts about aripiprazole lauroxil nanocrystal suspension

Brand name: Aristada Initio
Class: Long-acting injectable atypical antipsychotic (aripiprazole)
Indication: Adults with schizophrenia
Approval date: June 29, 2018
Availability date: August 1, 2018
Manufacturer: Alkermes, Inc., Waltham, MA
Dosing forms: 675 mg IM injection
Recommended dosage for schizophrenia: After establishing oral aripiprazole tolerability, administer 675 mg IM along with a single 30 mg oral aripiprazole dose at the time of initiating aripiprazole lauroxil maintenance treatment. The maintenance dose of aripiprazole lauroxil should be given at the same time as aripiprazole lauroxil nanocrystal, but can be given up to 10 days thereafter. Aripiprazole lauroxil nanocrystal also can be administered with the maintenance aripiprazole lauroxil injection when resuming treatment in patients who meet the missed dose guidelines for supplemental medication coverage

Clinical implications

Nonadherence with oral antipsychotics is a common problem for patients with schizophrenia, one that is often underappreciated by clinicians.[5] Whether one uses 70% or 80% as the measure of oral medication adherence, at least 50% of schizophrenia patients are nonadherent, with resultant increased risks for symptom exacerbation

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Disclosure

Dr. Meyer is a consultant to Acadia Pharmaceuticals, Alkermes, Allergan, Neurocrine, and Teva Pharmaceutical Industries, and a speaker for Acadia Pharmaceuticals, Alkermes, Allergan, Merck, Neurocrine, Otsuka America, Inc., Sunovion Pharmaceuticals, and Teva Pharmaceutical Industries.

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Table 2

Aripiprazole lauroxil nanocrystal suspension: Basic kinetic information

Factor	Description
Bioavailability	100%
Half-life	15 to 18 days
Administration	Once
Dosage adjustments	None. As only one dosage form is available, the package insert contains cautionary language regarding situations with less-than-expected drug exposure (use of CYP3A4 inducers), more-than-expected drug exposure (strong CYP3A4 or 2D6 inhibitors or known 2D6 poor metabolizers), or increased pharmacodynamic effects (concurrent use of antihypertensives or benzodiazepines)

Source: References 7,8

and hospitalization.[5,6] Although 2 LAI forms of aripiprazole have been introduced over the past few years, neither was designed to be loaded, resulting in the need for 2 or 3 weeks of oral antipsychotic coverage following the first injectable dose.[1] The primary reason for LAI antipsychotic therapy is oral medication nonadherence, and thus the need for 14 to 21 days of oral coverage at the outset of treatment creates a risk for symptom exacerbation if the patient is nonadherent with this oral bridging therapy which is needed to achieve the necessary serum concentrations until the long-acting formulation takes over.

One approach was to create a new form of AL using smaller nanomolecular particles rather than the micron-sized particles used for maintenance AL injections.[3,4] This nanocrystal suspension is called Aristada Initio (ALNCD) and has a median T_{max} that ranges from 16 to 35 days, compared with 41 days for single-dose injections of AL. ALNCD also has a much shorter median half-life of 15 to 18 days, compared with 53.9 to 57.2 days for AL (***Table 2***[7,8]). Utilizing these kinetic differences, a 1-day initiation regimen was developed to dispense with the need for 3 weeks of oral medication coverage when commencing AL treatment.[3,4] In lieu of 3 weeks of oral coverage starting at the time of the first AL injection, patients instead will receive an injection of ALNCD 675 mg, and a single oral 30 mg aripiprazole dose. The combination of ALNCD and the single 30 mg oral dose when added to the initial AL injection provides aripiprazole levels in the first weeks of therapy that are comparable to those seen in the previous paradigm, when patients took 21 days of oral aripiprazole after the first AL injection.[3]

Use in adults with schizophrenia. After establishing tolerability with oral aripiprazole, ALNCD 675 mg is administered as an IM injection by a health care professional, and the patient is concomitantly given a single 30 mg oral dose of aripiprazole. Only one dosage form of ALNCD is available: 675 mg. The maintenance AL dose chosen by the clinician (441, 662, 882, or 1,064 mg) is also administered at the same time, but must be injected in the other deltoid or gluteal muscle. The injection volume for ALNCD is 2.4 mL and can be administered in the deltoid or gluteus muscle.[9] If the patient prefers not to have 2 injections on the same day, the AL dose can be administered up to 10 days thereafter.[9] This 10-day window for administering AL relates to the long time to maximum plasma levels from single AL injections. The relevant drug levels during the first weeks are provided predominantly from

Clinical Point

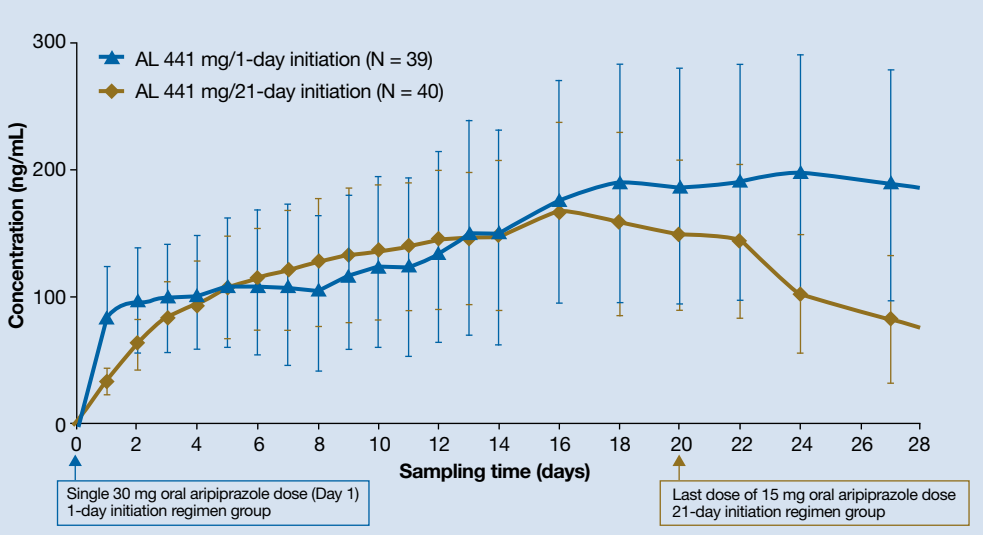
This 1-day initiation regimen dispenses with the need for 3 weeks of oral coverage when starting aripiprazole lauroxil

Clinical Point

The maintenance AL dose is given at the same time as the new nanocrystal suspension formulation, plus a 30 mg oral dose

Figure 1

Comparison of mean plasma aripiprazole levels when 441 mg IM aripiprazole lauroxil is initiated with 21 days of oral aripiprazole coverage (15 mg/d) or 675 mg IM aripiprazole lauroxil nanocrystal suspension plus a single 30 mg oral aripiprazole dose



Source: Adapted from reference 4

the initiation regimen of ALNCD injection plus the single 30 mg oral dose.[3] In instances when a patient agrees to receive both ALNCD and AL injections but refuses the 30 mg oral dose, effective plasma levels will be seen in the middle of the second week of therapy.

Pharmacologic profile, adverse reactions

Aripiprazole is a dopamine partial agonist atypical antipsychotic that has been commercially available in the United States since November 15, 2002, and its adverse effect profile is well characterized. The LAI formulation AL was approved on October 5, 2015. In the pivotal, 12-week, fixed-dose, placebo-controlled clinical trial of AL 441 mg or 882 mg monthly for adults with an acute exacerbation of schizophrenia, the only adverse effect that occurred in ≥5% of AL-treated patients and a rate at least twice that of placebo was akathisia (441 mg: 11%; 882 mg: 11%; placebo: 4%).[10] Only 2 of 415 AL-treated patients discontinued the study due to akathisia. Injection-site reactions were reported by 4%, 5%, and 2% of patients treated with AL 441 mg, AL 882 mg, and placebo, respectively. Most of these were injection-site pain associated with the first injection, and decreased with each subsequent injection. Other injection-site reactions (induration, swelling, and redness) occurred at rates <1%.[11]

Having established that the range of plasma aripiprazole levels consistent with effective treatment is bounded by levels seen with AL 441 mg or 882 mg monthly, the FDA did not require additional efficacy studies for new AL doses provided that pharmacokinetic (PK) studies could demonstrate levels within the effective range. This is consistent with how new doses of other LAI antipsychotic preparations have been addressed in the past. For example, the 37.5 mg dose of

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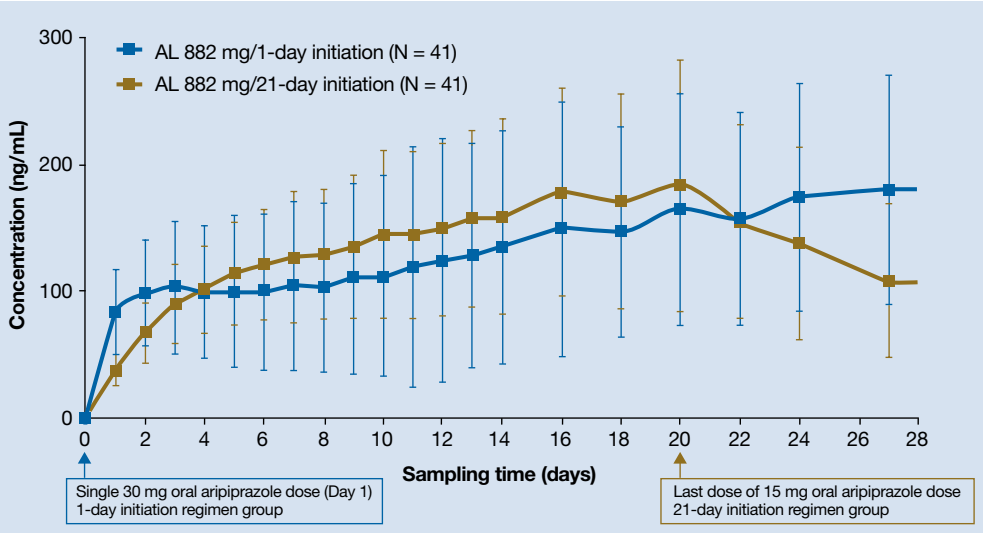
Figure 2

Comparison of mean plasma aripiprazole levels when 882 mg IM aripiprazole lauroxil is initiated with 21 days of oral aripiprazole coverage (15 mg/d) or 675 mg IM aripiprazole lauroxil nanocrystal suspension plus a single 30 mg oral aripiprazole dose



Source: Adapted from reference 4

Clinical Point

The safety profile of aripiprazole lauroxil nanocrystal suspension is consistent with that of aripiprazole lauroxil

risperidone microspheres was approved based on PK data, although the pivotal efficacy trials included doses of 25 mg, 50 mg, and 75 mg.[12] Based on PK studies, AL doses of 662 mg monthly, 882 mg every 6 weeks, and 1,064 mg every 8 weeks were previously approved.[13] The approval process for ALNCD followed a similar pathway, and is based on PK results combined with tolerability data amassed during the PK studies. The package insert thus notes that in PK studies the safety profile of ALNCD was generally consistent with that observed for AL (see Tolerability).

Pharmacokinetic outcomes. A comparative phase 1 PK study was performed to evaluate initiation regimens: either 21 days of oral aripiprazole (15 mg/d) and one AL dose (n = 81) or one injection of ALNCD plus a single dose of 30 mg oral aripiprazole and one AL dose (n = 80). Patients were randomized 1:1:1:1 to receive an AL dose of either 441 mg or 882 mg combined with the oral or the new ALNCD initiation regimen. As shown in ***Figure 1*** (***page 36***) and ***Figure 2***, the mean plasma levels seen with 675 mg IM ALNCD plus a single dose of 30 mg oral aripiprazole were comparable with levels achieved using 21 days of oral aripiprazole coverage, regardless of whether the regimen was paired with a maintenance AL dose of 441 mg or 882 mg.[4]

Tolerability. In PK studies, the safety profile and incidences of injection site reactions of ALNCD were generally consistent with those observed for aripiprazole lauroxil.[9] In the phase I PK study comparing oral initiation with ALNCD plus a single 30 mg oral aripiprazole dose, there were 2 mild cases of akathisia in the 21-day oral aripiprazole groups (n = 81) and 4 cases in the ALNCD groups (n = 80) (3 mild cases, 1 moderate

Table 3

Missed dose guidelines for aripiprazole lauroxil

Dose of last aripiprazole lauroxil maintenance injection	Length of time since last injection[a]	
441 mg	>6 and ≤7 weeks	>7 weeks
662 mg or 882 mg	>8 and ≤12 weeks	>12 weeks
1,064 mg	>10 and ≤12 weeks	>12 weeks
Dosage and administration for reinitiation of aripiprazole lauroxil	Supplement with a single dose of aripiprazole lauroxil nanocrystal[b]	Supplement with a single dose of aripiprazole lauroxil nanocrystal and a single dose of oral aripiprazole 30 mg[c]

[a]Patients should receive their maintenance injection of aripiprazole lauroxil in addition to any supplementation with aripiprazole lauroxil nanocrystal suspension
[b]If the patient refuses the injection of aripiprazole lauroxil nanocrystal suspension, supplement with 7 days of oral aripiprazole
[c]If the patient refuses the injection of aripiprazole lauroxil nanocrystal suspension plus 30 mg oral dose, supplement with 21 days of oral aripiprazole

Source: Reference 9

case). None of the adverse events related to akathisia were deemed serious, and no patients discontinued participation in the trial due to akathisia.[9]

Clinical considerations

ALNCD is not a substitute for AL due to the very different kinetic properties of the 2 preparations. ALNCD is approved only to be used for initiating treatment with AL, or in those instances where the revised missed dose guidelines for AL permit use of ALNCD to obviate the need for oral coverage.[9] ***Table 3***[9] presents these revised AL missed dose guidelines focusing on those time periods when some form of supplementation is required in addition to the established maintenance AL dose. Clinicians should be reminded that ALNCD must be paired with a dose of AL, although the latter can be given up to 10 days later when commencing therapy.

Unique properties. When combined with a single 30 mg oral dose, ALNCD was engineered to mimic the kinetic profile seen when patients were adherent with 21 days of oral aripiprazole needed when starting AL treatment.

Why Rx? The reasons to prescribe ALNCD for adult patients with schizophrenia include:

- it obviates the need for 21 days of oral coverage previously required at the initiation of AL treatment
- clinically relevant plasma levels are seen within the first week when ALNCD is combined with a single 30 mg oral aripiprazole dose
- per the revised missed dose guidelines for AL, it can be used in those situations that previously demanded 7 days of oral coverage, and, when combined with a single 30 mg oral dose, can be used for resumption of therapy after prolonged absences that required 21 days of oral coverage. In all instances, the patient will also receive their usual maintenance dose of AL.

Dosing. There is only one dose available for ALNCD, 675 mg IM. As the dose cannot be modified, the package insert contains cautionary language regarding situations with less-than-expected drug exposure (use of cytochrome P450 [CYP] 3A4 inducers), greater-than-expected drug exposure (strong CYP3A4 or 2D6 inhibitors or known 2D6 poor metabolizers),

Clinical Point

Aripiprazole lauroxil nanocrystal suspension is used only to initiate AL treatment, or as specified by missed dose guidelines

Related Resource

- Khan AY, Ovais DM. Long-acting injectable aripiprazole lauroxil for schizophrenia. Current Psychiatry. 2016;15(7): 50-52,58.

Drug Brand Names

Aripiprazole lauroxil • Aristada
Aripiprazole lauroxil nanocrystal • Aristada Initio
Risperidone microspheres • Risperdal Consta

Clinical Point

A known hypersensitivity to aripiprazole is the only contraindication to the use of ALNCD

or increased pharmacodynamic effects (concurrent use of antihypertensives or benzodiazepines).

Contraindications. The only contraindication is a known hypersensitivity to aripiprazole.

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Bottom Line

Aripiprazole lauroxil nanocrystal suspension (Aristada Initio) was specifically developed to obviate the need for 21 days of oral aripiprazole coverage when commencing treatment with aripiprazole lauroxil (Aristada). The plasma levels achieved when an injection of aripiprazole lauroxil nanocrystal suspension is combined with a single 30 mg oral dose are comparable to those achieved with 21 days of oral coverage. This initiation regimen, including a aripiprazole lauroxil nanocrystal injection and a 30 mg oral dose, should be administered on the same day as the maintenance aripiprazole lauroxil injection, although the latter can be administered on any of the next 10 days.