CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209830Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	{See Appended Electronic Signature Page}
From	CDR Javier A. Muniz
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	NDA 209830 000
Applicant	Alkermes, Inc.
Date of Submission	August 31, 2017
PDUFA Goal Date	June 30, 2018
Proprietary Name / **Established (USAN) names**	Aristada Initio Aripiprazole lauroxil
Dosage forms / Strength	675mg single intramuscular injection
Proposed Indication(s)	Initiation of treatment of schizophrenia with Aristada
Recommended:	Approval

1. Introduction and Background

Aripiprazole lauroxil, proprietary name "Aristada," is an atypical antipsychotic developed by Alkermes, Inc. It has a combination of receptor activities, including partial agonist activity at D_2 and $5HT_{1A}$ receptors and antagonist activity at $5HT_{2A}$ receptors. The molecule is a covalent modification of aripiprazole (Abilify; NDA 021436) to form *N*-lauroyloxymethyl aripiprazole, which acts as a prodrug of aripiprazole. Aripiprazole lauroxil (AL) is an extended-release injectable suspension that received approval in the United States on October 5, 2015, for the treatment of schizophrenia (NDA 207533). It is intended to be administered by healthcare providers.

Aripiprazole lauroxil takes several weeks to reach steady-state plasma levels. Currently, initiation of treatment requires starting the patient on concurrent oral aripiprazole at the time of the first injection of AL. Daily oral aripiprazole must then be continued for three weeks, after which the oral aripiprazole is discontinued and treatment with AL continues with injections given every four, six, or eight weeks (depending on the dose). Because patients considered for intramuscular medication tend to be those who have had difficulty with oral medication compliance, an obvious limitation of this strategy is that it requires the patient's compliance with oral medication for the first 21 days of treatment.

With this submission, the Applicant (Alkermes) is seeking approval of a new formulation of aripiprazole lauroxil (the Applicant refers to it as aripiprazole lauroxil NanoCrystal Dispersion or AL-NCD) designed to simplify the treatment-initiation regimen. The new formulation (proprietary name "Aristada Initio") is also given by intramuscular injection, but it has a smaller particle size than the original formulation. The smaller particle size accelerates the rate of dissolution, resulting in earlier therapeutic blood levels of aripiprazole. As with the original Aristada formulation, AL-NCD also requires some time to reach a steady-state blood level. Therefore, the requirement for oral medication at the beginning of treatment is not eliminated,

but has been reduced to a single dose of oral aripiprazole at the beginning of treatment.

The Applicant is proposing three components for the aripiprazole lauroxil initial treatment regimen:

1. A single injection of AL-NCD (Aristada Initio) 675mg
2. A single tablet of aripiprazole 30 mg taken orally
3. AL (Aristada) first injection 441 mg, 662 mg, 882 mg, or 1064 mg, to be repeated every 4, 6, or 8 weeks.

The dose of AL-NCD and the dose of oral aripiprazole given on the first day of treatment will be the same regardless of the dose of AL that is planned for the patient's ongoing maintenance treatment.

To support the new treatment initiation strategy, the Applicant has submitted data from three pharmacokinetic (PK) studies. This application does not include additional efficacy studies. The application relies on the Agency's previous findings of safety and effectiveness for oral aripiprazole tablets and AL. Oral aripiprazole and AL serve as the Listed Drugs (LD) for this NDA.

2. CMC/Device

The Office of Pharmaceutical Quality (OPQ) team recommends approval.

The CMC information on the drug substance was previously reviewed for AL (NDA 207533) and found acceptable. All NDA 207533 supplements related to CMC changes made in the drug substance have also been reviewed and approved.

For this application, the drug substance (b) (4) Due to its smaller particle size, it may be that the risk of needle clogs is lower for this product compared to AL. On the other hand, the smaller particle size causes the suspension to irreversibly agglomerate on exposure to temperatures ≤ (b) (4)C. The OPQ team concluded that this is unlikely to present a direct risk to patients, as the agglomeration will render the product uninjectable. The OPQ team recommended labeling language to minimize the risk of needle clogging and agglomeration.

The drug product is supplied as a kit containing a 5 ml syringe prefilled with 2.4 ml of drug suspension and three safety needles. The drug product is similar to the 662 mg strength of the original AL in terms of composition and suspension volume. The main difference between these formulations is the greater amount of polysorbate-20 in AL-NCD, (b) (4)

Needle components are commercially available and are supported by 510(k)s (b) (4) The Center for Devices and Radiological Health (CDRH) Office of Device Evaluation found that the applicant provided adequate design control documentation in the

form of design inputs, outputs, verification testing, validation/risk analysis and design transfer for the device constituent parts of the combination product. There were no significant differences between the clinical and commercial product likely to impact the functional performance of the product. The Applicant provided a detailed traceability matrix including all requirements of the device constituent parts of the combination product. Appropriate verification testing (including stability and shipping conditions) was linked to each requirement and the results demonstrate that the Applicant has successfully verified the device constituent per its requirements.

The nominal strength of this product in the initial NDA submission was (b) (4) identified this as a problem (b) (4) and the same non-proprietary name as AL, potentially leading to medication errors. The OPQ team raised potential solutions to the Applicant, such as additions under the nonproprietary name of 'submicron' or 'nano-sized'. Ultimately, the Applicant revised the nominal dosage strength of this product (b) (4) to 675 mg to distinguish the products. Distinguishing the products is important to reduce the potential medication error of delivering the wrong formulation during maintenance treatment. Additional measures will be added to the labeling to distinguish these products (i.e., AL and AL-NCD), and having different strengths will continue to distinguish the formulations during the generic lifecycle of the drug.

Based on the stability data of the registration batches on 17 months long-term storage and six months at accelerated storage conditions, the OPQ review team found the proposed 24-months expiry period to be acceptable at USP room temperature storage conditions. However, a linear trend to increasing particle size distribution throughout the entire range was observed with time. These changes accelerated with increasing temperatures but were not found to significantly impact drug release through the expiry period; however, this should be considered if a postmarketing expiry period extension is proposed.

OPQ team members participated in a pre-approval inspection at the drug product manufacturing site (Alkermes, Ohio) on May 2018, finding the firm in compliance. CDRH OC also provided the consult memo on the device component of the product (i.e., Design Quality plan, management responsibility, design controls, design history, purchasing controls, etc.) and an acceptable recommendation was made.

Below are OPQ's labeling recommendations:

1. Unlike AL, AL-NCD did not have any instructions on the speed required to administer the injection. OPQ recommended removing (b) (4) and replacing it with the time specified on the AL label (i.e., less than 10 seconds).
2. Increased prominence of 'do not freeze' statements.
3. Suggested addition of other labeling language to distinguish this product from AL (e.g., use of 'submicron' or 'submicronized' after nonproprietary name). This was rejected by the Applicant.

3. Nonclinical Pharmacology/Toxicology

The nonclinical reviewer, Amy Avila, PhD, recommends approval of this application.

Nonclinical studies conducted with AL-NCD include a 4-week (once weekly injections) intramuscular PK study in rats, and 4-week repeat-dose (once weekly injections) intramuscular toxicity studies in rats and dogs with 4-week recovery periods. CNS, cardiovascular, and respiratory function assessments were incorporated into the dog repeat-dose toxicity study. Dr. Avila notes in her review that "a couple of the dogs administered AL-NCD had more severe local toxicity, however the design of the studies conducted with AL-NCD were different, once weekly injections for a month compared to monthly injections in studies conducted with AL." Dr. Avila states that a possible explanation for the increased severity of local injection site toxicity could be due to trauma associated with more frequent IM injections to the same muscle group. The clinically relevant finding of local toxicity at the injection site (injection site reactions) in rats and dogs will be detailed in the animal toxicology section of the label 13.2.

Hypersensitivity reactions (reddened skin, excessive scratching, facial swelling, and injected sclera) were observed in a few high dose AL-NCD treated dogs and in all control-treated dogs. Because these hypersensitivity reactions were observed at a higher frequency in control dogs, the reactions were attributed to excipients in the vehicle, most likely polysorbate-20, which is known in published literature to cause hypersensitivity reactions in dogs. The amount of polysorbate-20 in AL-NCD is higher than that of any FDA-approved drug product for intramuscular administration. However, Dr. Avila notes that the Applicant provided sufficient nonclinical data and information from published literature to adequately qualify the levels of polysorbate-20 in the proposed product.

4. Clinical Pharmacology/Biopharmaceutics

Praveen Balimane, PhD, was the clinical pharmacology reviewer for this supplement; he recommends approval of this supplement.

This submission is supported by three clinical pharmacology studies:

1. ALK9072-B101: Single ascending dose safety, tolerability, PK study with different formulations of AL-NCD in 114 subjects.
2. ALK9072-B102: PK bridging study to demonstrate the adequacy of AL-NCD in obviating the need for supplemental oral dosing for aripiprazole for 21 days in 161 subjects.
3. ALK9072-B103: Single-dose safety, tolerability, PK study of AL-NCD in gluteal vs. deltoid muscle in 47 subjects.

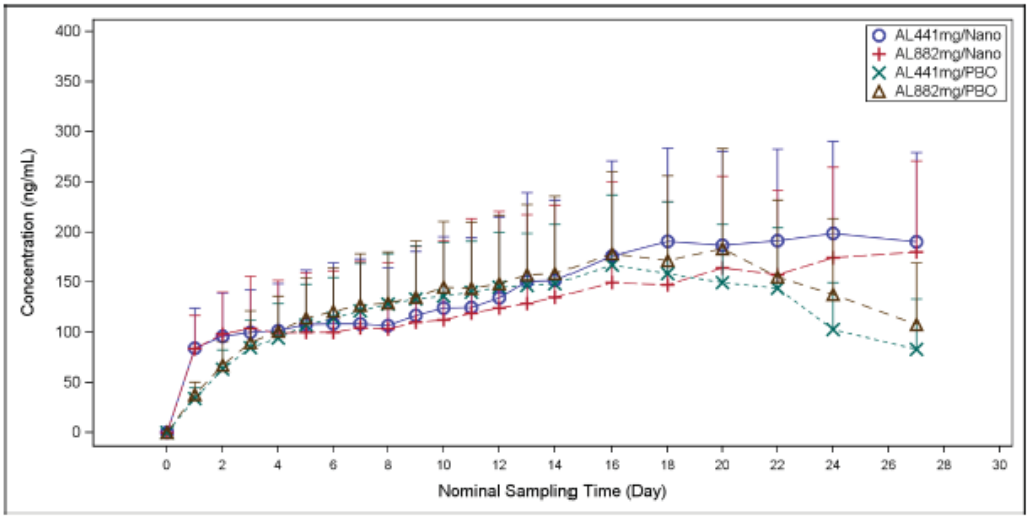
Study ALK9072-B102 (Study B102) provided the pivotal PK bridging data to demonstrate the adequacy of AL-NCD in replacing the need for supplemental oral dosing of aripiprazole for 21 days per the current approved dosing regimen with AL. Study B102 was a randomized, double-blind, , single-dose, PK study which compared the aripiprazole exposure when AL was

initiated with AL-NCD and a single 30 mg dose of oral aripiprazole (the proposed new regimen) vs. the currently approved regimen of AL with 21 days of oral aripiprazole. The following dosing regimens were used in Study B102:

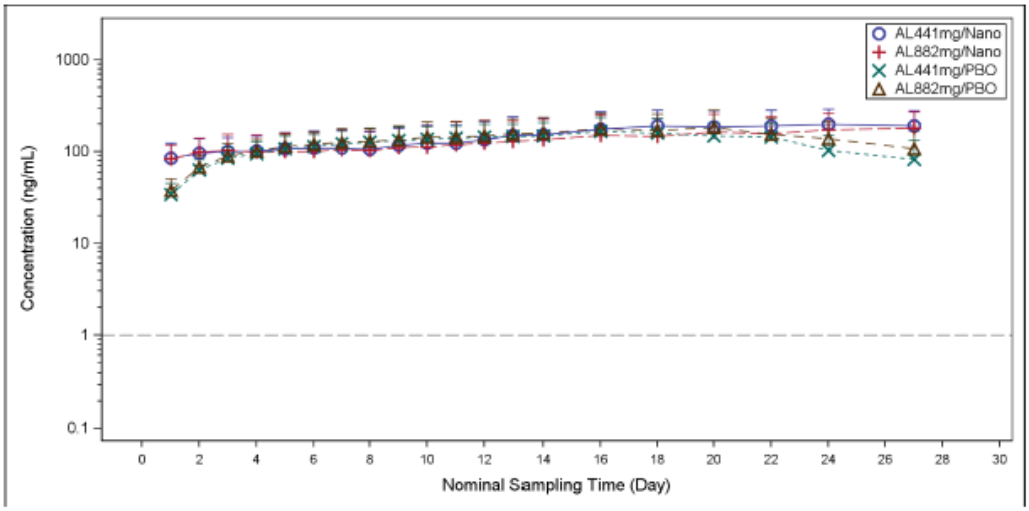
1. AL-NCD arms = AL INTIO at 675 mg, single oral aripiprazole dose of 30 mg and either 441 mg or 882 mg of AL.
2. Approved dosage arms = 21 days of oral aripiprazole at 15 mg/day and either 441 mg or 882 mg of AL.

Study B102 demonstrated that initiation regimen with AL-NCD resulted in achievement of aripiprazole concentrations that (a) were similar to the concentrations achieved with the approved regimen of AL plus 21 days of oral regimen and (b) were within the range of aripiprazole concentrations (102 – 435 ng/ml) that were considered tolerable and effective, obtained from the approved oral aripiprazole dose range of 10 mg/day up to 30 mg/day (OCP review/NDA 207533/October 1, 2015). The results are summarized in Figure 1.

Figure 1: Mean (Standard Deviation) Plot of Aripiprazole Concentrations Over Time for the different Treatment Groups (AL-NCD vs. approved AL regimen)



Semi-log Scale



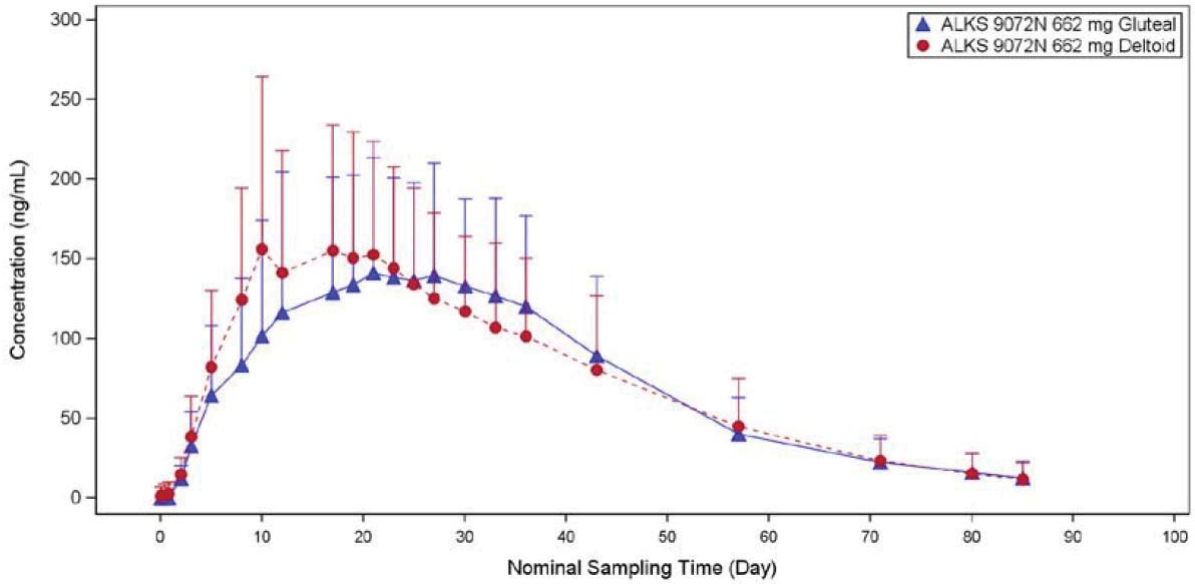
Legend: AL 441/Nano=30 mg oral aripiprazole on Day 1 followed by oral placebo for 20 days + AL-NCD 662 mg (gluteal) + 441 mg AL (deltoid) on Day 1.
AL 882/Nano=30 mg oral aripiprazole on Day 1 followed by oral placebo for 20 days + AL-NCD 662 mg (gluteal) + 882 mg AL (gluteal) on Day 1.
AL 441/PBO=15 mg oral aripiprazole for 21 days (Days 1-21) + placebo NCD IM injection (gluteal) + 441 mg AL (deltoid) on Day 1.
AL 882/PBO=15 mg oral aripiprazole for 21 days (Days 1-21) + placebo NCD IM injection (gluteal) + 882 mg AL (gluteal) on Day 1.
[Source: ALK9072-B102' CSR, Figure 3, Page 55]

The mean plasma aripiprazole concentrations over time overlapped across each of the initiation regimens through Day 21 (the last day of administration of oral aripiprazole in the oral initiation regimen). After Day 21, plasma aripiprazole concentrations persisted in each AL-NCD initiation regimen group, whereas plasma aripiprazole concentrations began to

decline in each oral initiation regimen group. Mean aripiprazole concentrations in the initiation regimen with AL-NCD began to decline after Day 30, at an apparently less rapid rate as compared to the decline following the end of the oral initiation regimen (Figure 1). The AL-NCD initiation regimen could achieve aripiprazole concentrations that were tolerable and effective (i.e., >102 ng/mL; the mean steady state Cmin of aripiprazole following administration with the lowest approved 10 mg ABILIFY once/daily tablets—based on OCP review/NDA 207533/10-1-2015) within four days after treatment initiation. Additionally, it was also noted that a larger proportion of subjects in each AL-NCD initiation regimen group had plasma concentrations >102 ng/mL as compared to each corresponding oral initiation regimen group by Day 4, as well as at the end on Day 28. This suggests that the initiation regimen with AL-NCD is similar to the intended exposure range of the approved initiation regimen with AL and 21 days of oral dosing.

Study ALK9072-B103 (Study B103) assessed the PK of AL-NCD after a single dose administration to deltoid or gluteal muscle in adults with schizophrenia or schizoaffective disorder. The mean PK profiles of aripiprazole following the single IM injection to the deltoid or gluteal muscle were comparable (see Figure 2). The overall safety profiles are also similar when AL-NCD was administered in the deltoid or gluteal muscle, thus supporting the recommendation that AL-NCD can be dosed at either of the two injection sites.

Figure 2: Mean (SD) Aripiprazole Concentrations Over Time Following Deltoid or Gluteal Administration of ALKS 9072N 675 mg



[Source: ALK9072-B103's CSR, Figure 2, Page 42]

In addition to the PK studies submitted with this NDA, the Applicant conducted various PK simulations to assess "clinically feasible scenarios" of erroneous dosing, recommended dosing under various scenarios of missed AL doses, plasma concentrations in known CYP2D6 poor metabolizers or subjects taking CYP modulators, and to demonstrate the adequacy of the

proposed dosage initiation with 675 mg AL-NCD for patients transitioning from 10-30 mg/day of oral aripiprazole to AL.

Dr. Balimane's main findings are summarized below:

1. The use of AL-NCD is acceptable for missed AL doses.
2. Adequate PK bridging was established between AL-NCD and the listed drugs (i.e., oral aripiprazole and AL).
3. Because the proposed product is available only in one dose and health care providers are not able to adjust the dose, AL-NCD is not recommended for use in patients who are known CYP2D6 poor metabolizers or are taking CYP modulators (strong inhibitors of CYP3A4 or CYP2D6 or inducer of CYP3A4).
4. AL-NCD can be administered at gluteal or deltoid muscles.
5. When initiating therapy, the first AL injection may be administered on the same day as AL-NCD, or up to 10 days thereafter.
6. AL-NCD and AL have unique and differing pharmacokinetic profiles and thus should not be used interchangeably.
7. No evidence of dose dumping was observed in pharmacokinetic data collected from around 100 individual subjects across three different clinical trials.

5. Clinical Microbiology

Not applicable.

6. Clinical/Statistical- Efficacy

No new efficacy data were submitted with this application. The efficacy of AL-NCD combined with a single oral dose of aripiprazole 30 mg was established through pharmacokinetic bridging to 21 days of oral aripiprazole 15 mg.

7. Safety

David Millis, MD, was the clinical reviewer for this application; he recommends approval.

Dr. Millis' safety review was based on the Development Safety Update Report submitted to IND 121179 for the reporting period November 25, 2016, to November 24, 2017, the safety data submitted for the three pharmacokinetic studies (i.e., ALK9072-B101, ALK9072-B102, and ALK9072-B103), and the Summary of Clinical Safety submitted with the NDA application.

There was one death reported in Study B102. This subject died secondary to being hit by multiple vehicles on a highway after exiting his vehicle to confront another driver and was not considered to be related to the study drug. There were 15 SAEs reported in six of the 212 subjects exposed to AL-NCD in the development program; eight of these were associated with the System Organ Class (SOC) of psychiatric disorders, including schizoaffective disorder (five cases), schizophrenia (one case), and psychotic disorder (one case). These are likely attributable to the subjects' underlying psychiatric illness. There was one incident of suicidal ideation. There were no completed suicides, and no attempted suicides.

There was one unexpected SAE during the development program. A 59 y/o male with no history of seizures had an incident of status epilepticus two weeks after the treatment initiation regiment of AL-NCD, AL, and oral aripiprazole. He did not respond to levetiracetam or valproic acid but was discharged on lacosamide 100mg twice a day. The subject's only concomitant medication was asenapine 5 mg daily by mouth, which he had been taking since 2013. An electroencephalogram (EEG) two days after showed isolated infrequent generalized sharp activity, possibly of epileptogenic potential, and isolated infrequent sharp activity over the left temporal region, possibly associated with partial onset seizures. It is unknown if this SAE was related to study drug.

In general, the safety data submitted with this NDA are consistent with the known safety profile of aripiprazole lauroxil. Dr. Millis' review revealed no safety findings that would require a labeling revision, preclude approval of this supplement, or necessitate other regulatory action.

8. Advisory Committee Meeting

No advisory committee meeting was held for this NDA. The evaluation of the safety data did not reveal safety issues that were unexpected for this drug (AL) and class. The design and results of the submitted trials did not pose concerns.

9. Pediatrics

The Agency waived the pediatric study requirement because necessary studies are impossible or highly impracticable in the pediatric population. In addition, oral aripiprazole is already approved for use in the pediatric population.

10. Other Relevant Regulatory Issues

Needle Clogging

During the last supplement to NDA 207533, we addressed the issue of postmarketing reports of needle clogging occurring in AL. CDRH concluded that these clogging incidents were likely related to the speed of injection (longer injection times causing more clogging). The Applicant updated the Instructions for Use (IFU) with instructions to inject (b) (4) and potential for further actions (such as a drug-product containing demonstration kit) to address this issue were discussed. As previously noted, no needle clogging incidents were observed during the AL-NCD development program. OPQ expects for needle clogging incidents to be significantly less likely with the proposed formulation because of the smaller particle size in AL-NCD. Furthermore, OPQ recommended language to specify the speed of the injection (i.e., less than 10 seconds) to further minimize the risk of clogging. This issue will continue to be monitored post-marketing.

11. Labeling

The initial label submitted with the NDA contained information on AL (Aristada) and AL-NCD (Aristada Initio). As previously noted, the (b) (4) (b) (4) Applicant did not agree with suggestions from the OPQ team to change the proprietary or the generic name of the product. However, Alkermes agreed to change the nominal strength of the proposed product to 675 mg. Nevertheless, the review team felt strongly that the proposed label could be confusing and potentially lead to medication errors, particularly in future generic products. The Applicant agreed with the review team's recommendation to separate the AL-NCD from the AL label. The Division of Medication Error Prevention and Analysis' (DMEPA) and the Office of Prescription Drug Promotion's (OPDP) recommendations were also incorporated into the label and medication guide (MG). The Applicant has agreed to these changes.

12. Recommendations/Risk Benefit Assessment

Study B102 provided an adequate pharmacokinetic bridge between the proposed new initiation of AL treatment regimen (one dose of oral aripiprazole 30mg, one dose of AL-NCD, and one dose of AL) and the previously-approved regimen (one dose of AL and 21 days of oral aripiprazole). The proposed AL-NCD regimen is expected to have similar efficacy and safety for treatment initiation of schizophrenia with AL when compared to the previously approved more extensive oral supplementation strategy. Although the Applicant did not compare medication adherence rates between the regimens, patients receiving long-acting depot antipsychotic preparations have many times had past compliance issues with their medications. Although the Applicant did not study and hence cannot claim increased treatment adherence, this new treatment initiation strategy may provide additional options for patients requiring long-acting injectable antipsychotic treatment. No new safety signals were identified in the development program that would alter the overall benefit-risk assessment for aripiprazole lauroxil.

The label and Medication Guide have been negotiated to current Division standards. This application should be approved by the PDUFA date.

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/s/

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06/29/2018

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06/29/2018