CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209830Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 209830
Review #1

Drug Name/Dosage Form	**Aristada Initio** (aripiprazole lauroxil) Extended-Release Injectable Suspension
Strength	675 mg
Route of Administration	IM
Rx/OTC Dispensed	Rx
Applicant	Alkermes, Inc.
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
0001	8/31/2017	All
0003	10/30/2017	Facilities
0010	11/27/2017	Biopharm
0012	12/20/2017	Microbiology
0013	2/6/2018	Drug Product
0015	3/1/2018	Drug Product/Microbiology/ Biopharm/Process
0018	3/9/2018	Drug Product

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Thomas Wong	Wendy Wilson-Lee
Drug Product	Thomas Wong	Wendy Wilson-Lee
Process	Hang Guo	Peter Guerrieri
Microbiology	Helen Ngai	Erika Pfeiler
Facility	Rose Xu	Derek Smith
Biopharmaceutics	Gerlie Gieser	Ta-Chen Wu
Regulatory Business Process Manager	Teshara Bouie	
Application Technical Lead	David Claffey	

Quality Review Data Sheet

IQA Review Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		Aripiprazole lauroxil	adequate		
	Type III *(if applicable)*	various	(b) (4)	adequate		See drug product review

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
	NDA 207533	Aristada
	IND 121179	Aristada Initio studies
	NDA 21436	Aripiprazole tablets

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
CDRH Office of Compliance	complete	approval	21 MAY 2018	Bella Pelina
CDRH ODE	complete	approval	7 MAR 2018	John McMichael

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommend **approval** from a product quality perspective. Each of the OPQ team members made an approval recommendation, including CDRH ODE and CDRH OC consult reviewers

II. Summary of Quality Assessments

A. Product Overview

This application proposes the marketing of Aristada Initio (aripiprazole lauroxil) extended release injectable suspension in one dosage strength – 675 mg. It is to be used with the initial ARISTADA® dose for the treatment of schizophrenia in adults. It is designed to be a more convenient alternative to the current 21-day oral aripiprazole tablet supplementation after the first dose of Aristada. It is similar to Aristada in terms of composition, volume and dosing instructions. The main difference is the (b) (4) smaller particle size distribution in the proposed product – (b) (4) This allows the active to reach therapeutic levels by the first day following administration. Product quality information and controls support the performance of the product at room temperature storage through 24 months.

Given the nature of the product – a (b) (4) suspension – it can block the needle during administration. As the suspension displays non-newtonian behavior, faster speeds of injection were found to have better injectability due to (b) (4) . This was addressed in the application along with the means to mitigate this risk – including formulation design and the label instructions prior to dosing. Due to its smaller particle size, it appears that the risk of needle clogs is lower for this product compared to Aristada. On the other hand, the smaller particle size causes the suspension to irreversibly agglomerate on exposure to temperatures ≤ (b) (4) C. This is not likely to present a direct risk to the patient as the agglomeration will render the product uninjectable. Again, this risk is mitigated by label warnings.

Proposed Indication(s) including Intended Patient Population	Indicated for the initiation of ARISTADA® treatment of schizophrenia in adults
Duration of Treatment	*One-time treatment with initial Aristada dose*

Maximum Daily Dose	*Only one dosage strength. Entire syringe delivered.*
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Background: This application proposes the marketing of Aristada Initio (aripiprazole lauroxil) extended-release injectable suspension in one dosage strength – 675 mg. It is intended to be a more convenient alternative to the oral aripiprazole supplementation needed for the first 21 days of treatment with Aristada (NDA 207533). The supplementation is needed because aripiprazole does not reach systemic therapeutic levels until several weeks after the first Aristada injection. Aristada Initio releases aripiprazole lauroxil faster *in vivo* due to its smaller particle size distribution. This product's particle size is (b) (4) smaller than that in the Aristada (b) (4) -NOT FOI. The reduced particle size is achieved by (b) (4) submicron range.

Drug Substance: The drug substance is aripiprazole lauroxil. It is a methylene ester of aripiprazole. (b) (4). The CMC information on the drug substance was previously reviewed for NDA 207533 (Aristada) and found acceptable. All supplements related to CMC changes made in the drug substance have also been reviewed and approved. (b) (4) This was evaluated as part of the drug product review.

Drug product composition/components: 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 (1-inch 21 gauge needle, 1 ½ inch 20 gauge needle and 2-inch 20 gauge needle). (b) (4)

The syringe is filled with 2.4 ml of drug product suspension. (b) (4) (b) (4) The drug substance's aqueous insolubility ensures that no significant amounts (b) (4) are dissolved prior to administration. All other excipients are dissolved in the aqueous medium. The drug product is similar to 662 mg strength Aristada in terms of composition and suspension volume. The main difference is the greater amount of polysorbate 20 (b) (4)

Comparison of Aristada and Aristada Initio compositions:

Component	Amount expressed per unit dose (b) (4)	Amount expressed per unit dose (total volume per unit dose strength: 2.4 mL fill)*
	NDA 207533	NDA 209830
Aripiprazole lauroxil	662 mg	675.0 mg**

Sorbitan monolaurate	(b) (4)
Polysorbate 20	
Sodium citrate dihydrate	
Sodium chloride	
Monobasic sodium phosphate dihydrate	
Dibasic sodium phosphate anhydrous	
WFI	(b) (4)

Product excipients are compendial and adequately controlled. Polysorbate 20 (b) (4) (b) (4)

The commercial formulation was developed based on Phase 1 clinical PK study on three prototypes formulations with different particle size distributions. The formulation with a nominal median distribution (Dv[50]) of (b) (4) was selected for commercial formulation development.

The drug product specification adequately controls drug product quality through the expiry period. It includes tests typical of a sterile extended release suspension with device related controls (break loose force, glide force). Delivered dose, PSD, related substances, degradants and elemental impurities were adequately controlled. All analytical methods have been adequately validated.

Drug product stability: The OPQ review team found the proposed 24-months expiry period acceptable when stored at USP room temperature storage conditions. This is based on the satisfactory stability data of the registration batches on 17 months at long-term storage and 6 months at accelerated storage conditions.

Changes did occur to the product on storage – (b) (4) (b) (4) (b) (4). However, the data remained within specification when the labeled storage conditions were used. Changes within this range were not found to significantly impact drug release through the expiry period. Although, statistical analysis predicted that the median particle size may fail specification at 29 months – so this should be considered if a postmarketing expiry period extension is proposed.

(b) (4)

(b) (4)

Studies also found that the formulation aggregates (i.e., irreversibly solidifies) when the drug product was stored ≤(b) (4)C. The container labels carry a warning statement *"Do NOT freeze"*.

It was also noted that the break loose force increased linearly on storage from (b) (4) over 18 months at long-term storage conditions, but remained within the specified (b) (4) limit. Glide force did not show any changes – which is critical as the label specifies that that product be injected quickly. Shipping studies found no significant change in the CQAs.

Product Administration Issues: Data showed that the product displays (b) (4) (b) (4) faster injection speeds will have better injectability (b) (4) (b) (4). This is reflected in the labeling instructions for use.

Tap the syringe at least 10 times to dislodge any settled material and vigorously shake for 30 seconds to ensure uniform suspension. If the syringe is not used within 15 minutes, shake again for 30 seconds. Inject in a RAPID and CONTINUOUS manner. Product requires a RAPID injection. Do not hesitate.

OPQ recommends that the applicant revise the labeling to include the 10 second maximum injection time like ARISTADA.

Syringe blockages were found to be more likely if the syringe is stored in a vertical rather than a horizontal position. The secondary packaging shape is designed to discourage storage of the kit in a vertical position.

It is noted that Aristada has had a significant number of postmarketing reports of syringe blockages during administration. Formulation development in this application attempted to address this in a similar manner to Aristada- mainly through drug-load studies and (b) (4) Regardless, as the plot below demonstrates, changes in product concentration (e.g. evaporation) or changes to the (b) (4) levels have the potential to cause syringe blockages (b) (4). Although the product is designed to be within a stable region, this region appears relatively narrow. This should be considered with any postmarketing changes.

(b) (4)

Manufacturing Process: (b) (4)

(b) (4)

Microbiology: (b) (4)

he drug product process and controls were found acceptable from a microbiology perspective.

Biopharmaceutics: The accepted dissolution acceptance criteria are as follows: (b) (4)% at 10 min, (b) (4)% at 40 minutes, and NLT (b) (4)% at 240 minutes using USP Apparatus 2 (paddle) rotating at 75 rpm, 1000 grams of 50 mM phosphate buffer with 6% SDS, pH 8. The dissolution method was shown to have discriminating power for changes in finished product particle size distribution, (b) (4) and it had stability indicating potential.

The Biopharmaceutics review team found a 'weak to moderate' linear relationship between drug product particle size distribution and *in vitro* drug release, as well as the impact of storage on d_{90}, in addition to d_{10} and d_{50}. Formulation bridging was not needed because the proposed to-be-marketed drug product has the same formulation, concentration, drug product manufacturer and process steps, and API supplier as the batches evaluated in the clinical PK and the primary stability studies. The extended release claim was found acceptable.

Facilities/Compliance: OPQ team members participated in a pre-approval inspection (PAI) at the drug product manufacturing site (Alkermes, Ohio) on 4/29-5/4/2018. As the product is a drug/device combination product, it is required to comply with 21CFR Part 4, and the quality system is required to be supplemented with the applicable elements of 21 CFR 820 for the device constituent part. During the inspection, the three objectives of the pre-approval inspection were covered and the team found that the firm is in compliance with cPGM 7346.832. In addition, the device Design Quality plan, management responsibility, design controls, design history, purchasing controls, and CAPA were reviewed. CDRH OC also provided the consult memo on the device part. No FDA 483-Form was issued to the firm at the end of the inspection, and an acceptable recommendation was made. The remaining drug substance and drug product manufacturing and testing sites were found acceptable by OPQ OPF based on inspection history and manufacturing capability – giving an overall approval recommendation from OPF.

CDRH Office of Compliance recommended that the application be approved from the perspective of the applicable quality systems regulations. Although they did not carry out a systemic review of the application they concluded that the potential issues identified were covered by the OPQ team in the PAI of the drug product manufacturing site.

Device functionality: CDRH ODE recommended approval of the application from their perspective. They determined that the lack of a fill-line was acceptable. Needle components are commercially available and are supported by 510(k)s (b) (4). The needles in the kit were (b) (4). CDRH 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. They determined that there were no significant differences between the clinical and commercial product that is likely to impact the functional performance of the product. The Sponsor 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 Sponsor has successfully verified the device constituent per its requirements.

Drug product name/strength issue: Note that the proposed nominal strength of this product in the initial NDA submission was (b) (4) (b) (4) found to be a potential medication errors issue. There are severe consequences to the patient should these products be mixed up – continuous overdosing for an entire 30 day period with no possibility to remove the product. It was noted that the batches used in the pivotal clinical studies were slightly super-potent (though within specification). The possibility of changing the nominal labeled strength was raised with the applicant during the review cycle. In response, the applicant revised the nominal dosage strength of this product (b) (4) to 675 mg. Although this change is unusual, it is scientifically justified as the 675 mg strength is more in line with that used in the clinical studies. More critically, the potential harm to the patient is significantly reduced (b) (4) (b) (4) (although they still share a non proprietary name). Additional measures will be added to the labeling to distinguish these products, though the risk to the patients will be significantly higher in future generic products as they will not likely have proprietary names to distinguish the products. Additional measures will be considered by OPQ during labeling negotiations, e.g. addition under the nonproprietary name of 'submicron', 'submicronized' or (less likely) 'nano-sized'.

C. Special Product Quality Labeling Recommendations (NDA only)

- Addition of injection time.
- Increased prominence of 'do not freeze' statements.
- Addition of other labeling language to distinguish this product from Aristada (eg. Use of 'submicron' or 'submicronized' after non proprietary name).

D. Final Risk Assessment (see Attachment)

APPEARS THIS WAY ON ORIGINAL

53 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

LABELING

I. Package Insert (Seq. #0020)

1. *Highlights of Prescribing Information*

ARISTADA INITIO™ (aripiprazole lauroxil) extended-release injectable suspension, for intramuscular use
Initial U.S. Approval: 201x

DOSAGE FORMS AND STRENGTHS

(b) (4) extended-release injectable suspension: 675 mg single (b) (4) pre-filled syringe (3)

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	Proprietary name is Aristada Initio (Pending approval) Established name is aripiprazole lauroxil.
Dosage form, route of administration	To be administered by intramuscular injection in either the deltoid or gluteal muscle
Controlled drug substance symbol (if applicable)	N/A. Not a controlled substance.
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Aripiprazole lauroxil extended-release injectable suspension, 675 mg/2.4 mL

2. *Section 2 Dosage and Administration*

2 DOSAGE AND ADMINISTRATION

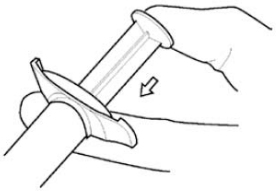
2.1 Recommended Dosage

ARISTADA INITIO is only to be used as a (b) (4) dose to initiate ARISTADA treatment or to re-initiate ARISTADA treatment following a missed dose of ARISTADA. ARISTADA INITIO is not (b) (4) for repeated dosing.

ARISTADA INITIO is (b) (4) to be administered as an intramuscular injection by a healthcare professional. For patients who have never taken aripiprazole, establish tolerability with oral aripiprazole prior to initiating treatment with ARISTADA INITIO. Due to the half-life of oral aripiprazole, it may take up to 2 weeks to fully assess tolerability. Refer to the prescribing information of oral aripiprazole for the recommended dosage and administration of the oral formulation.

2.5 Important Administration Instructions

5. Inject in a **RAPID** and **CONTINUOUS** manner. Product requires a **RAPID** injection. Do not hesitate. Administer the entire content intramuscularly. Do not inject by any other route.



Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	There is no product preparation is needed. In 2.5 – Important Administration Instructions, Setp #5, the word "rapid" should provide a time period, like 10 seconds, as stated in the ARISTADA.

3. *Section 3 Dosage Forms and Strengths*

3 DOSAGE FORMS AND STRENGTHS

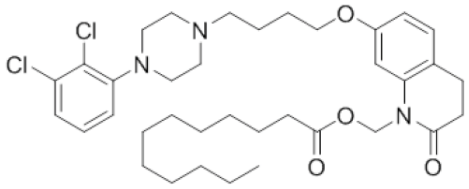
ARISTADA INITIO (b) (4) is a white to off-white aqueous extended-release suspension provided in a single- (b) (4) pre-filled syringe (b) (4) (b) (4)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Extended-release injectable suspension
Strengths: in metric system	675 mg/2.4 mL
Active moiety expression of strength with equivalence statement (if applicable)	The strength is expressed in active moiety form.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	The color of the aqueous injection suspension is white to off-white.

4. *Section 11 Description*

ARISTADA INITIO contains aripiprazole lauroxil, an atypical antipsychotic.

The chemical name of aripiprazole lauroxil is 7-{4-[4-(2,3-dichlorophenyl)-piperazin-1-yl]butoxy}-2-oxo-3,4-dihydro-2H-quinolin-1-yl)methyl dodecanoate. The empirical formula is $C_{36}H_{51}C_{l2}N_3O_4$ and its molecular weight is 660.7 g/mol. The chemical structure is:



ARISTADA INITIO is available as a white to off-white sterile aqueous extended-release suspension for intramuscular injection in the following strength of aripiprazole lauroxil (and deliverable volume from a single-(b)(4) pre-filled syringe): 675 mg (2.4 mL). The inactive ingredients include polysorbate 20 (16.2 mg/mL), sodium chloride (3.3 mg/mL), sodium citrate dihydrate (8.1 mg/mL), sodium phosphate dibasic anhydrous, sodium phosphate monobasic and water for injection.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	Proprietary name is Aristada Initio (Pending approval) Established name is aripiprazole lauroxil.
Dosage form and route of administration	Extended-release injectable suspension, for intramuscular injection.
Active moiety expression of strength with equivalence statement (if applicable)	The strength, 675 mg/2.4 mL, is expressed in active moiety form, aripiprazole lauroxil.
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Inactive ingredients with quantities are provided.
Statement of being sterile (if applicable)	Yes, it is stated.
Pharmacological/ therapeutic class	Atypical antipsychotic
Chemical name, structural formula, molecular weight	Provided.
If radioactive, statement of important nuclear characteristics.	Not applicable
Other important chemical or physical properties (such as pKa or pH)	Color is white to off-white

5. *Section 16 How Supplied/Storage and Handling*

16.1 How Supplied

ARISTADA INITIO extended-release injectable suspension is available in a strength of 675 mg in 2.4 mL. The kit contains a 5-mL pre-filled syringe containing ARISTADA INITIO sterile aqueous suspension and safety needles.

- A 675 mg strength kit (NDC 65757-500-03*; grey 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.

16.2 Storage

Store at room temperature 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C and 30°C (between 59°F and 86°F). Do not freeze.

For additional information, visit www.ARISTADA.com or call 1-866-274-7823

Manufactured and marketed by:

Alkermes, Inc.

852 Winter Street

Waltham, MA 02451-1420

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	The strength is expressed in active moiety form.
Available units (e.g., bottles of 100 tablets)	Available in a strength 675 mg/2.4 mL of aripiprazole lauroxil.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	There is no mention of color of the aqueous suspension. The color of white of off-white as described in Sectio 11 should be added to this section.
Special handling (e.g., protect from light)	Do not freeze
Storage conditions	Provided.
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Provided.

Reviewer's Assessment of Package: Adequate with comment

The expression of strength in Section 3 - Dosage Forms and Strengths is 675 mg/2.4 mL which is different from the usual expression in per mL basis. However, it is

acceptable for this product since the entire dose is 2.4 mL and the entire volume is administered in one single injection.

Addition of injection time limit in Section #2 - Dosage and Administration and the color description of the suspension in Section #16 - How Supplies will be discussed in the labeling review meetings with the full multidisciplinary team.

II. Labels:

1. ***Container and Carton Labels*** (Seq. #0022)

   Syringe label

(b) (4)

2. ***Carton Label*** (Seq. #0022)

Carton Label

(b) (4)

(b) (4)

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Proprietary name is Aristada Initio (Pending approval) Established name is aripiprazole lauroxil.	Proprietary name is Aristada Initio (Pending approval) Established name is aripiprazole lauroxil.
Dosage strength	The strength is expressed in active moiety form.	The strength is expressed in active moiety form.
Net contents	Provided	Provided
"Rx only" displayed prominently on the main panel	Yes	Yes
NDC number (21 CFR 207.35(b)(3)(i))	Provided	Provided
Lot number and expiration date (21 CFR 201.17)	Yes	Yes
Storage conditions	Provided.	Provided.
Bar code (21CFR 201.25)	Yes	Yes
Name of manufacturer/distributor	Yes	Yes
And others, if space is available	Do not freeze warning.	Inactive ingredients are provided. Do not freeze warning.

Reviewer's Initial Assessment of Labels: Inadequate

The dash symbol in the temperature conditions should be replaced with the word "to". The following IR was sent the applicant:

> To avoid confusion in reading the storage conditions in the syringe label and carton container label, replace the dash symbol in the temperature conditions with the word "to". The storage conditions should read as: Store at 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C to 30°C (59°F to 86°F).

Reviewer's Final Assessment of Labels: Adequate

On 5/2/2018, the applicant submitted an amendment # 0022 stating the acceptance of our recommendation to change the dash symbol in the temperature conditions to the word "to". The revised container lables were included in the amendment and are shown above.

Overall Assessment and Recommendation: Adequate with comment

Addition of injection time limit in Section #2 - Dosage and Administration and the color description of the suspension in Section #16 - How Supplies will be discussed in the labeling review meetings with the full multidisciplinary team.

Thomas Wong

Digitally signed by Thomas Wong
Date: 5/08/2018 11:26:04AM
GUID: 508da7230002a25bbe89865c0c14bc44

Wendy Wilson- Lee

Digitally signed by Wendy Wilson- Lee
Date: 5/08/2018 12:49:20PM
GUID: 50816dbc000085595ca3284bbca465a8

39 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

BIOPHARMACEUTICS

Product Background:

NDA: 209830; 505(b)(2) NDA

Drug Product Name / Strength: ARISTADA INITIO™ (aripiprazole lauroxil) extended-release injectable suspension; 675 mg/2.4 mL; packaged in a 5 mL single (b) (4) pre-filled syringe

Route of Administration: For intramuscular injection. ARISTADA INITIO™ is administered as a single dose on Day 1 [to initiate (which replaces the 21-day oral aripiprazole lead-in phase) or to re-initiate a missed dose] of ARISTADA™ treatment for schizophrenia.

Applicant Name: Alkermes

Review Recommendation:

From the Biopharmaceutics perspective, NDA 209830 for ARISTADA INITIO™ (aripiprazole lauroxil) extended release injectable suspension is recommended for **APPROVAL**.

Review Summary:

In Vitro Drug Release Method and Acceptance Criteria

The proposed QC *in vitro* dissolution method and dissolution acceptance criteria shown in the table below are approved for the routine QC of ARISTADA INITIO™ (aripiprazole lauroxil) extended release injectable suspension, 675 mg/2.4 mL at batch release and stability testing.

USP Apparatus	Speed	Medium	Volume	Acceptance criteria
2 (paddle)	75 rpm	50 mM Phosphate buffer, 6% SDS, 90 mM Sodium Sulfate, pH 8.0 37 ± 0.5°C	1000 grams (approximately equivalent to 1000 mL)	(b) (4) % at 10 min (b) (4) % at 40 min NLT (b) (4) % at 240 min

The proposed QC dissolution/drug release method was shown to have (1) discriminating power for changes in finished product particle size distribution, (b) (4) and (2) stability indicating potential.

Relationship of Finished Product Particle Size Distribution and In Vitro Drug Release

The results of the Reviewer's exploratory analysis suggested (1) a weak to moderate linear relationship between finished product particle size distribution and *in vitro* drug release (IVR) of ARISTADA INITIO, as well as the (2) impact of storage on d_{90}, in addition to d_{10} and d_{50}.

Formulation Bridging
Formulation bridging data are not needed because the proposed to-be-marketed drug product has the same formulation, concentration, drug product manufacturer and process steps, and API supplier as the batches evaluated in the clinical PK and the primary stability studies.

Extended Release Claim
ARISTADA INITIO™ is an extended release product because a single injection is able to prolong the dosing interval of aripiprazole to approximately 21 days (as compared to a dosing interval of 24 hours for the immediate release oral tablets).

List Submissions reviewed:
SDN-1, 08/31/2017; Original Submission
SDN-10, 11/27/2017; Response to Biopharmaceutics Information Request
SDN-15, 03/01/2018; Response to Quality Information Request

Concise Description Outstanding Issues Remaining:
None

BCS Designation

NOTE: BCS-based biowaivers are not applicable to modified release non-oral dosage forms.

ARISTADA INITIO™ (formerly known as aripiprazole lauroxil NanoCrystal® Dispersion [AL-NCD]) is a long-acting injectable drug product intended for single-dose intramuscular administration. For general information purposes, the drug substance solubility, and the drug dissolution/release characteristics of the drug product are described below.

Reviewer's Assessment:

Solubility: *Low solubility*. The solubility of aripiprazole lauroxil is < 4 ng/mL in various aqueous buffer media with pH ranging from of (b) (4) Based on (b) (4) testing, the drug substance has only one known polymorphic form (b) (4).

Permeability: *Indeterminate.* According to the NDA review of ARISTADA®, the Population PK model-predicted steady state bioavailability of intramuscularly administered aripiprazole lauroxil is (b) (4)% relative to the approved immediate release oral product.

Dissolution: *Drug not rapidly dissolving.* Per the Applicant, ARISTADA INITIO™ was designed to contain drug particles with size in the nanometer range in order to provide faster dissolution as compared to ARISTADA™ which contains drug particles in the micrometer size range. Of note, ARISTADA INITIO™ 675 mg/2.4 mL is not qualitatively and quantitatively of the same composition as the already marketed ARISTADA 675 mg/2.4 mL.

7 Pages have been Withheld In Full as B4(CCI/TS) Immediately Following This Page

(b) (4)

[redacted]

EXTENDED RELEASE DOSAGE FORMS –Extended Release Claim

Per the Applicant (and as confirmed by the Clinical Pharmacology Reviewer), PK Study B102 demonstrated that overall the plasma exposures to aripiprazole and its active metabolites are comparable (during the first 21 days) following an initiation regimen consisting of a single intramuscular dose of ARISTADA-INITIO™ 675 mg (given concomitantly with 30 mg oral aripiprazole on Day 1) and following an initiation regimen consisting of 15 mg oral aripiprazole once daily for 21 days. [As intended, AL-NCD (ARISTADA INITIO™) in Study B102 demonstrated more rapid drug release of the same drug load (and thus, an anticipated shorter duration of effect) than expected with ARISTADA given monthly (with a 21-day oral aripiprazole initiation regimen).] Thus, it is appropriate to classify ARISTADA INITIO™ as an extended release or long-acting injectable formulation of aripiprazole because its administration is able to prolong the dosing interval of aripiprazole to approximately 21 days (as compared to a dosing interval of 24 hours for the immediate release oral tablets). In other words, a single dose of ARISTADA INITIO Injection on Day 1 is able to replace the equivalent of 20 days oral aripiprazole administered to provide therapeutic drug concentrations during the lag phase following the first ARISTADA Injection on Day 1. For the relative bioavailability data and the comparative PK parameters of the test and the reference products, refer to the Clinical Pharmacology review.

Bridging of AL-NCD Formulations

Reviewer's Assessment: *ADEQUATE*

AL-NCD formulation bridging data *per se* are not needed because the proposed to-be-marketed drug product has the same formulation (i.e., Formulation B), concentration (675 mg/2.4 mL), manufacturer (Alkermes Ohio), API supplier (b) (4) [redacted] and process steps as the batches evaluated in three clinical PK studies (ALK9072-B101, ALK9072-B102, and ALK9072-B103). Note that Lot # 467-0013AA (tested in PK Studies B102 and B103) is one of three registration (primary stability) batches.

Study B101 determined the PK of three candidate AL-NCD formulations (Formulations A, B, and C) with varying particle size; Formulation B was evaluated further in the two subsequent PK studies (B102 and B103). 'Formulation' was one of the tested covariates in the Population PK (PopPK) analysis conducted by the Applicant. For the evaluation of the Clinical Study and the Population PK Analysis Reports, refer to the Clinical Pharmacology Review.

The Applicant conducted Study B102 to establish a PK bridge between the 21-day oral aripiprazole therapy and the one-time injection with ARISTADA INITIO™ (when given concomitantly with oral aripiprazole on Day 1).

Biowaiver Request

Reviewer's Assessment: *NOT APPLICABLE*

A biowaiver was not requested nor required because the PK of the proposed to-be-marketed drug product was evaluated in three clinical studies.

List of Deficiencies:

None

Primary Biopharmaceutics Reviewer Name and Date:
Gerlie Gieser, Ph.D., 5/7/2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed):
Ta-Chen Wu, Ph.D., 5/7/2018

Gerlie Gieser

Digitally signed by Gerlie Gieser
Date: 5/08/2018 09:35:35AM
GUID: 507592ba00003d190b2ea34fe8fb8ccb

Ta-Chen Wu

Digitally signed by Ta-Chen Wu
Date: 5/08/2018 12:36:40PM
GUID: 508da6df000269e151ff37cd8f4e13a1

MICROBIOLOGY

IQA Review Guide Reference

Product Background: 505(b)(2)

NDA: 209830

Drug Product Name / Strength: ARISTADA INITIO, Aripiprazole lauroxil extended-release injectable suspension. 675 mg (proposed dose).

Route of Administration: IM

Applicant Name: Alkermes, Inc.

Manufacturing Site: Alkermes Inc., 265 Olinger Circle, Wilmington, Ohio

Method of Sterilization: (b) (4)

Review Recommendation: **Adequate**

Theme (ANDA only): Choose an item.

Justification (ANDA only): Choose an item.

Review Summary: The submission **is recommended** for approval on the basis of sterility assurance.

List Submissions Being Reviewed:

Submit	Receive	Review request	Assigned to reviewer
8/31/2017	8/31/2017	N/A	9/12/2017
12/20/2017	12/20/2017	N/A	12/20/2017
2/6/2018	2/6/2018	N/A	3/9/2018
3/1/2018	3/1/2018	N/A	3/9/2018
3/9/2018	3/9/2018	N/A	3/9/2018

Highlight Key Outstanding Issues from Last Cycle: N/A

Remarks: The 74 day letter was due 11/13/2017. The mid-cycle date was 1/31/2018. The review due date was 5/23/2018. The NDA is reviewed as a standard review

(priority request was denied). Some figures were reproduced directly from the submission. IRs were issued on 11/30/2017 and 2/15/2018; responses received 12/20/2017 and 3/1/2018. The sponsor originally proposed (b) (4) (b) (4) but the Agency requested a change to the labeled strength to differentiate between the proposed Aristata Initio product from the marketed Aristata product (email dated 1/18/2018, response received 2/6/2018).

Concise Description Outstanding Issues Remaining: None identified

Supporting Documents:

Sister NDA 207533 for ARISTADA from Alkermes, Inc., and associated microbiology review 207533.pdf (recommended) dated 7/18/2015. The same buildings and facilities, EM, similar manufacturing process, equipment used to manufacture the drug product for NDA 207533 is also proposed for manufacturing NDA 209830. The drug product for NDA 207533 is ARISTADA. The subject drug product proposed is ARISTADA INITIO. ARISTADA INITIO and ARISTADA predominately differ in the particle size of aripiprazole lauroxil, the former in the nanometer range and the latter in the micrometer range. ARISTADA INITIO and ARISTADA are not interchangeable because of differing pharmacokinetic profiles.

Type V DMF (b) (4) (b) (4). LOA date 5/24/2017. Relevant information was reviewed (b) (4) (b) (4) (adequate) dated 2/28/2017.

Type V DMF (b) (4) LOA date 5/24/2017. Relevant information (b) (4) (b) (4) was reviewed (b) (4) (adequate) dated 4/4/2017.

List Number of Comparability Protocols (ANDA only): N/A.

Note to reviewer:

1. The subject drug product ARISTADA INITIO (Aripiprazole lauroxil NanoCrystal Dispersion or AL-NCD), is a new formulation of ARISTADA designed to provide faster dissolution. AL-NCD and AL predominantly differ in the particle size of AL, the former in the nanometer range and the latter in the micrometer range. ARISTADA INITIO and ARISTADA are not interchangeable because of differing pharmacokinetic profiles. The currently approved ARISTADA drug product is manufactured as a 662 mg dose. The NDA sponsor originally proposed to manufacture the ARISTADA INITIO drug product as (b) (4). In an email dated 1/18/2018, the Agency requested a change to the labeled strength to differentiate between the proposed Aristata Initio product from the marketed Aristata product. The sponsor responded on 2/6/2018 and acknowledges the potential for increased risk of prescribing and product selection errors due to the similarity in the nonproprietary name and dose strength of AL-NCD and ARISTADA. To address this issue, Alkermes proposes to change the labeled dose of AL-NCD (b) (4) to

675 mg, which reflects the actual dose strength of the clinical and registration stability batches. The target dose of 675 mg is achieved with a fill weight of (b) (4) with a calculated overfill (b) (4) (b) (4). Representative carton labeling indicating the proposed 675 mg strength is also provided. Measures including brand name modifier, distinctive artwork, a unique product code and text for the intended user that AL-NCD is only to be used for the initiation of ARISTADA treatment are proposed to ensure differentiation to reduce the risk of administration errors. The process reviewer issued a comment on 2/15/2018 regarding the overfill factor and calculations. Responses received on 3/9/2018 are reproduced and described below.

2. The same manufacturing facility, equipment, similar manufacturing process and environmental monitoring SOPs are used to manufacture the ARISTADA (Aripiprazole lauroxil, or AL) drug product described in NDA 207533.pdf (recommended) dated 7/18/2015.

P.1 Description of the Composition of the Drug Product

- **Description of drug product** – The drug product is a white to off-white aqueous extended-release suspension for IM injection provided as a single (b) (4) 5 mL pre-filled syringe combination product at mg dosage strength (2.4 mL fill). The drug product is supplied as a kit containing the pre-filled syringe and safety needles. The drug product is Aripiprazole Lauroxil NanoCrystal® dispersion or AL-NCD.

- **Drug product composition** –

Ingredient	Content per mL	Function
Aripiprazole lauroxil	(b) (4)	Drug substance
Polysorbate 20	16.2 mg	(b) (4)
Sodium citrate dehydrate	8.1 mg	
Sodium chloride	3.3 mg	
Monobasic sodium phosphate dihydrate	(b) (4)	
Dibasic sodium phosphate anhydrous		
WFI		

Note to reviewer: The formulation is slightly different from NDA 207533; compared below.

Component	Amount expressed per unit dose (b) (4)	Amount expressed per unit dose (total volume per unit dose strength: 2.4 mL fill)*
	NDA 207533	NDA 209830
Aripiprazole lauroxil	662 mg	(b) (4)
Sorbitan monolaurate	(b) (4)	
Polysorbate 20		
Sodium citrate dihydrate		
Sodium chloride		
Monobasic sodium phosphate dihydrate		
Dibasic sodium phosphate anhydrous		

WFI

(b) (4)

* (b) (4). The total volume per unit dose strength is 2.4 mL. (b) (4)

(b) (4)

** In the 2/6/2018 submission, the proposed dose of 675 mg is achieved with an overfill (b) (4)

(b) (4)

The sponsor originally proposed to manufacture the drug product as (b) (4) (b) (4) but the Agency requested a change to the labeled strength to differentiate between the proposed Aristata Initio product from the marketed Aristata product (email dated 1/18/2018, response received 2/6/2018). The proposed dose of 675 mg will be achieved with an overfill (b) (4).

(b) (4)

24 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

P.5 Control of Drug Product

P.5.1 Specification

Bacterial Endotoxins Testing: NMT (b) (4) EU/mL
Sterility Testing: No evidence of microbial growth

Reviewer's Assessment: Acceptable

P.5.2 Analytical Procedures

USP <85> Bacterial Endotoxins Test; (b) (4)
USP <71> Sterility; (b) (4)

Reviewer's Assessment: Acceptable

P.5.3 Validation of Analytical Procedures

Endotoxins

(702-06753.pdf, Method qualification for the bacterial endotoxin test for Aripiprazole Lauroxil Nano Drug Product, dated 9/3/2015).

Test Method: USP <85>; (b) (4)
Endotoxins specification: NMT (b) (4) EU/mL; USP Monograph specification: no USP endotoxin limit for this drug

(b) (4)

Inhibition/ enhancement testing was performed at a dilution of (b) (4), against three lots of filled drug product. No interfering factors were observed at the test concentration, the measured concentration of the endotoxin added to the sample solution was within (b) (4) % of the known added endotoxin concentration after subtraction of any endotoxin detected in the solution without added endotoxin. A dilution of (b) (4) will be used for routine testing.

The following finished lots all met the acceptance criteria of NMT (b) (4) EU/mL.

Batch no.	Date of manufacture	Batch size	Dosage strength	Use of batch	Endotoxin results (A.C.: NMT (b) (4) EU/mL)
467-0002AA	7/22/201	(b) (4)	662 mg	Clinical ALK9072-B101 ALK9072-B102 ALK9072-B103	(b) (4)
467-0002AB	7/22/2014		441 mg	Clinical ALK9072-B101	
467-0007AA	10/29/2014		882 mg	Clinical ALK9072-B101	
467-0013AA	8/13/2015		662 mg	Clinical and registration stability ALK9072-B102 ALK9072-B103	
0000080974	12/1/2015		662 mg	Registration stability	
0000081080	12/10/2015		662 mg	Registration stability	
0000084258	7/21/2016		662 mg	TBD	
0000084554	8/11/2016		662 mg	TBD	
0000083726	6/8/2016		662 mg	Supportive stability	
0000084883	9/8/2016		662 mg	TBD	

(batch-analyses.pdf).

Maximum dose according to the package insert: (b) (4) administered as a bolus dose. The calculated endotoxins dose at the proposed endotoxins specification ((b) (4) EU/mL) and maximum dose is: (b) (4) EU/ mg x (b) (4) / 70 kg = (b) (4) EU/ kg/ hr. The endotoxins dose at the endotoxins limit and maximum dose as calculated by this reviewer is within the USP <85> recommended maximum level of 5 EU/kg/hr.

Reviewer's Assessment: Acceptable. The BET method has been adequately validated and the maximum potential endotoxins exposure is less than or equal to the USP <85> recommended hourly amount for drug administered on a body mass (per kg) basis.

Sterility

(701-06619, Sterility test method validation of Aripiprazole Lauroxil Nano, dated 6/2/2016)

Test Method: according to USP <71>; (b) (4)

Bacteriostasis/ fungistasis testing were performed against three lots of filled drug product. The subject drug product was tested using the compendial organisms. All challenges with ATCC cultures and Alkermes environmental isolates showed no bacteriostatic or fungistatic activity in the presence of the drug product; results provided.

The following finished lots all met the acceptance criteria of, 'no evidence of microbial growth.'

Batch no.	Date of manufacture	Batch size	Dosage strength	Use of batch	Sterility results (A.C.: no evidence of microbial growth)
467-0002AA	7/22/201	(b) (4)	662 mg	Clinical ALK9072-B101 ALK9072-B102 ALK9072-B103	no evidence of microbial growth
467-0002AB	7/22/2014		441 mg	Clinical ALK9072-B101	no evidence of microbial growth
467-0007AA	10/29/2014		882 mg	Clinical ALK9072-B101	no evidence of microbial growth
467-0013AA	8/13/2015		662 mg	Clinical and registration stability ALK9072-B102 ALK9072-B103	no evidence of microbial growth
0000080974	12/1/2015		662 mg	Registration stability	no evidence of microbial growth
0000081080	12/10/2015		662 mg	Registration stability	no evidence of microbial growth
0000084258	7/21/2016		662 mg	TBD	no evidence of microbial growth
0000084554	8/11/2016		662 mg	TBD	no evidence of microbial growth
0000083726	6/8/2016		662 mg	Supportive stability	no evidence of microbial growth
0000084883	9/8/2016		662 mg	TBD	no evidence of microbial growth

The following comment was issued on 2/15/2018: *In regard to the proposed change to the labeled strength of the drug product (675 mg), provide results of suitability testing for sterility including positive controls that demonstrate growth of the challenge organisms.*

(b) (4)

Note to reviewer: The proposed 675 mg dose reflects the actual dose strength of the clinical and registration stability batches. The target label dose of 675 mg will be achieved using an overfill (b) (4). See pages 3-5 regarding overfill calculations and discussions with the process reviewer. The reviewer finds the response using an

overfill [redacted] reasonable since the target fill weight and volume of the PFS are not changed.

Reviewer's Assessment: Acceptable. The sterility test method has been adequately validated as per USP <71>.

P.7 Container Closure – see P.1

P.8 Stability

P.8.1 Stability Summary and Conclusion – see P.8.2.

P.8.2 Post-Approval Stability Protocol and Stability Commitment

Storage conditions: 25°C/ 60% RH

Stability Test	Time 0	12 month	24 month	36 month
Endotoxins	X	X	X	X
Sterility	X	X	X	X

Proposed Expiry: 24 months from the date of formulation [redacted] (stability-summary.pdf, pg. 3)

Post Approval Stability Commitment

The applicant commits to placing the first three commercial lots of the subject drug product into their stability program. Thereafter, on an annual basis, one production lot will be added to the stability program.

Reviewer's Assessment: Acceptable. The microbiological test methods, acceptance criteria and frequencies in the stability protocol are suitable for a parenteral drug product.

P.8.3 Stability Data

Batch no.	Date of manufacture	Endotoxin results- initial time point (A.C.: NMT [redacted] EU/mL)	Sterility results – initial time point (A.C.: no evidence of microbial growth)
467-0013AA	8/13/2015	[redacted]	no evidence of microbial growth
0000080974	12/1/2015		no evidence of microbial growth
0000081080	12/10/2015		no evidence of microbial growth
0000084554	8/11/2016		no evidence of microbial growth
0000083726	6/8/2016		no evidence of microbial growth

Reviewer's Assessment: Acceptable. There are no microbiology relevant concerns regarding the stability data for the exhibit batches.

A Appendices

A.2 Adventitious Agents Safety Evaluation – N/A

R Regional Information

Executed Batch Records

The batch records confirm that validated (b) (4) manufacturing processes were used for the manufacture of the exhibit batch.

Reviewer's Assessment: Acceptable. There are no microbiology relevant concerns regarding the executed batch records.

Comparability Protocols – N/A

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Package Insert

Aristada Initio is a white to off- white aqueous extended-release suspension provided in a single (b) (4) pre-filled syringe for intramuscular injection in the deltoid or gluteal muscle at the (b) (4) dose strength. Aristada Initio and Aristada are not interchangeable because of differing pharmacokinetic profiles.

Store at room temperature 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C and 30°C (between 59°F and 86°F). Do not freeze.

Reviewer's Assessment: Acceptable. There are no microbiology relevant concerns regarding the package insert.

Post-Approval Commitments: none

List of Deficiencies: none identified

Primary Microbiology Reviewer Name and Date: Helen Ngai, Ph.D., 4/4/2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Erika Pfeiler, Ph.D., *date pending*

Helen Ngai

Digitally signed by Helen Ngai
Date: 4/05/2018 12:46:59PM
GUID: 508da70b00028e6d6f228f597b070551

Erika Pfeiler

Digitally signed by Erika Pfeiler
Date: 4/05/2018 12:48:51PM
GUID: 502d1da500002b6a73a00c0e0dff6e1d

Final Risk Assessment

Product Property/Impact of Change/CQAs	Initial Risk Ranking	Final Ranking	Comment
Sterility	**H**	L	Micro review found this acceptable
Endotoxin Pyrogen	**M**	L	
Assay	**L**	L	
Uniformity of Dose	**M**	L	
Osmolality	**L**	L	Small volume parenteral
pH	**L**	L	In process controls and buffers used.
Particulate Matter	**M**	L	IM administration
Leachable/Extractable	**L**	L	Data provided to show it is not a risk
Appearance	**L**	L	Release and stability control
Name/Strength	**H**	M	Initial application (b) (4) Amendment changed the strength of the product (b) (4) to 675 mg. Differentiating the products will remain a risk to the product which can be mitigated further by labeling language.

A