CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209830Orig1s000

OTHER REVIEW(S)

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	June 8, 2018
Requesting Office or Division:	Division of Psychiatry Products (DPP)
Application Type and Number:	NDA 209830
Product Name and Strength:	Aristada Initio (aripiprazole lauroxil) extended release injectable suspension 675 mg/2.4 mL
Product Type:	Combination Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Alkermes, Inc.
FDA Received Date:	August 31, 2017, March 13, 2018 and May 25, 2018
OSE RCM #:	2018-2060
DMEPA Safety Evaluator:	Loretta Holmes, BSN, PharmD
DMEPA Team Leader:	Lolita White, PharmD

1 REASON FOR REVIEW

The Division of Psychiatry Products (DPP) consulted the Division of Medication Error Prevention and Analysis (DMEPA) to evaluate the labels, labeling and packaging submitted for NDA 209830 to determine if they are acceptable from a medication error perspective.

2 REGULATORY HISTORY

With this NDA submission, the Applicant, Alkermes, submitted human factors study results report #702-07404, entitled "Aripiprazole Lauroxil NCD Confirmatory User Study Report for Differentiation and Negative Transfer". The 662 mg strength was assessed in this study, however, the proposed strength was (b) (4) 675 mg after submission of the NDA. Therefore, the study methodology and results do not meaningfully inform this review so will not be discussed.

3 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B (N/A)
Human Factors Study	C (N/A)
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed container labels, carton labeling, Instructions for Use, Medication Guide labeling, and prescribing information for Aristada Initio (aripiprazole lauroxil) to determine if there are any areas of concern or needed improvement from a medication safety perspective. We identified the following:

1. Overlapping type fonts and similar layout contribute to the look-alike similarity between the Aristada Initio and Aristada container labels and carton labeling which may contribute to product selection medication errors.

2. On the carton labeling, the proprietary name and established name lack prominence relative to the large size of the statement of strength. Increasing the font size will increase their prominence and visibility.

3. Additional information is needed on the principal display panel (PDP) of the carton labeling and Instructions for Use leaflet in order to help clarify the timing of Aristada Initio administration.

Additionally, we compared the proposed Aristada Initio container labels and carton labeling to the currently marketed Aristada to determine whether the products lines are adequately differentiated from one another in order to minimize potential wrong product selection errors.

5 CONCLUSION & RECOMMENDATIONS

We determined that the proposed Aristada Initio and marketed Aristada product line syringe labels and carton labeling are differentiated but there is potential to do more to further differentiate the products. Additionally, we identified areas of needed improvement in the size and/or positioning of certain statements on the Aristada Initio commercial and professional sample carton labeling and the instructions for use. We provide recommendations in Section 5.1, below.

5.1 RECOMMENDATIONS FOR ALKERMES, INC.

We recommend the following be implemented prior to approval of this NDA:

A. General Comment

We find that the different colors, carton shape and clarifying information on the Aristada Initio syringe label and carton labeling help to differentiate Aristada Initio from Aristada container labels and carton labeling. However, similarities such as overlapping type fonts and similar layout contribute to the look-alike similarity between the labels and labeling of the products and may potentiate the risk for product selection medication errors. To further differentiate the Aristada Initio product from the Aristada product line, we recommend you further consider the use of different type fonts, layout, or other additional means, if feasible.

B. Carton Labeling (Commercial and Professional Sample)

1. The proprietary name and established name lack sufficient prominence relative to the large size of the statement of strength. Increase the relative font size of the proprietary name and established name to increase their prominence and visibility.

2. Additional information is needed on the principal display panel (PDP) in order to help clarify the timing of Aristada Initio administration. Add the following statement (or a similar alternative statement) to the PDP and position it below the first orange

bullet: “Give with the first Aristada dose only or to re-initiate Aristada treatment following a missed dose of Aristada”.

B. Instructions for Use Leaflet

1. See Comment B.2, above. Add the statement “Give with the first Aristada dose only or to re-initiate Aristada treatment following a missed dose of Aristada” to the cautionary statements located above Step 1.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Aristada Initio received on March 13, 2018 from Alkermes, Inc.

Table 2. Relevant Product Information for Aristada Initio	
Initial Approval Date	N/A
Active Ingredient	aripiprazole lauroxil
Indication	Indicated as a starting dose to initiate Aristada (aripiprazole lauroxil) treatment for schizophrenia (b) (4)
Route of Administration	Intramuscular
Dosage Form	Extended-release injectable suspension
Strength	675 mg
Dose and Frequency	Administer one injection of Aristada Initio and oral aripiprazole 30 mg in conjunction with the first Aristada injection (441 mg, 662 mg, 882 mg, or 1064 mg). The first Aristada injection may be administered on the same day as Aristada Initio or up to 10 days thereafter.
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 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.
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.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Aristada Initio labels and labeling submitted by Alkermes, Inc.

- Commercial Syringe Label received on March 13, 2018
- Professional Sample Syringe Label received on March 13, 2018
- Commercial Carton labeling received on March 13, 2018 received on March 13, 2018
- Professional Sample Carton Labeling received on March 13, 2018
- Instructions for Use received on May 25, 2018
- Medication Guide received on March 13, 2018
- Prescribing Information (image not shown) received on March 13, 2018

Additionally, we compared the proposed 675 mg strength container labels and carton labeling to the currently marketed 441 mg, 662 mg, 882 mg, and 1064 mg strengths of Aristada to determine whether there is adequate differentiation between the products (see Section G.3)

G.2 Label and Labeling Images (not to scale)

(b) (4)

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[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

LORETTA HOLMES
06/08/2018

LOLITA G WHITE
06/08/2018

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: June 5, 2018

To: David H. Millis, M.D., Clinical Reviewer
Division of Psychiatry Products (DPP)

Kofi Ansah, PharmD, Regulatory Project Manager, (DPP)

Kim Updegraff, PharmD, Associate Director for Labeling, (DPP)

From: Domenic D'Alessandro, PharmD, MBA, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, RN, MPH, Acting Team Leader, OPDP

Subject: OPDP Labeling Comments for ARISTADA INITIO™ (aripiprazole lauroxil) extended-release injectable suspension, for intramuscular use (Aristada Initio)

NDA: 209830

In response to DPP consult request dated October 9, 2017, OPDP has reviewed the proposed product labeling (PI), Instructions for Use (IFU), Medication Guide, and carton and container labeling for Aristada Initio.

PI:

OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DPP on May 24, 2018, and are provided below.

Medication Guide:

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under a separate cover on June 1, 2018.

IFU:

OPDP has reviewed the proposed IFU submitted by the Sponsor to the electronic document room on May 25, 2018, and we do not have any comments.

Carton and Container Labeling:

OPDP has reviewed the proposed carton and container labeling submitted by the Sponsor to the electronic document room on May 2, 2018, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Domenic D'Alessandro at (301) 796-3316 or domenic.dalessandro@fda.hhs.gov

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/s/

DOMENIC G DALESSANDRO
06/05/2018

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	June 1, 2018
To:	Mitchell Mathis, MD Director **Division of Psychiatry Products (DPP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Domenic D'Alessandro, PharmD, MBA, CDE Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	ARISTADA INITIO (aripiprazole lauroxil)
Dosage Form and Route:	extended-release injectable suspension, for intramuscular use
Application Type/Number:	NDA 209830
Applicant:	Alkermes, Inc.

1 INTRODUCTION

On August 31, 2017, Alkermes, Inc., submitted for the Agency's review an original New Drug Application (NDA) for ARISTADA INITIO (aripiprazole lauroxil) extended-release injectable suspension, for intramuscular use for the proposed indication of use as a starting dose to initiate ARISTADA (aripiprazole lauroxil) treatment for schizophrenia in adults (b) (4)

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Psychiatry Products (DPP) on October 09, 2017, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for ARISTADA INITIO (aripiprazole lauroxil) extended-release injectable suspension, for intramuscular use.

2 MATERIAL REVIEWED

- Draft ARISTADA INITIO (aripiprazole lauroxil) extended-release injectable suspension, for intramuscular use, MG received on March 13, 2018, and received by DMPP and OPDP on May 24, 2018.
- Draft ARISTADA INITIO (aripiprazole lauroxil) extended-release injectable suspension, for intramuscular use, Prescribing Information (PI) received on March 13, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 24, 2018.

3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHAWNA L HUTCHINS
06/01/2018

DOMENIC G DALESSANDRO
06/01/2018

LASHAWN M GRIFFITHS
06/01/2018

OFFICE OF DEVICE EVALUATION

DIVISION OF ANESTHESIOLOGY, GENERAL HOSPITAL,
RESPIRATORY, INFECTION CONTROL, AND DENTAL DEVICES

GENERAL HOSPITAL DEVICES BRANCH

INTERCENTER CONSULT MEMORANDUM

Date	March 07, 2018
To	Teshara Bouie, Project Manager, CDER/OPQ/OPRO/DRBPMI/RBPMBI
Requesting Division	DRBPMI
From	John McMichael, Combination Products Team Lead CDRH/ODE/DAGRID/GHDB
Through (Team Lead)	John McMichael, Combination Products Team Lead CDRH/ODE/DAGRID/GHDB
Through (Branch Chief)	CAPT Alan Stevens CDRH/ODE/DAGRID/GHDB
Subject	NDA 209830, Aripiprazole Pre-Filled Syringe ICC1700846
Recommendation	**Approvable**

Digital Signature Concurrence Table	
Reviewer	John C. Mcmichael -S 2018.03.07 09:07:01 -05'00'
Team Lead	
Branch Chief	Alan M. Stevens -S Digitally signed by Alan M. Stevens -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300189211, cn=Alan M. Stevens -S Date: 2018.03.07 12:56:11 -05'00'

1. SUBMISSION OVERVIEW

Table 1. Submission Information	
ICCR # (Lead)	ICCR2017-01793
ICCR SharePoint Link	http://sharepoint.fda.gov/orgs/OSMP/ocp/ICRR/Lists/ICRR%20Forms/DispForm.aspx?ID=2022
ICC tracking # (Lead)	ICC1700846
Submission Number	NDA 209830
Sponsor	Alkermes, Inc.
Drug/Biologic	Aripiprazole lauroxil
Indications for Use	A starting dose to initiate ARISTADA (aripiprazole lauroxil) treatment for schizophrenia (b) (4)
Device Constituent	Pre-Filled Syringe
Related Files	ICC1700844 (CDRH/OC consult)

Table 3. Important Dates	
Information Requests Sent	None
Review Checkpoints	**Meeting / Due Date**
Mid-Cycle	01/24/2018
Primary Review / Lead Device Review	05/05/2018

TABLE OF CONTENTS

2. PURPOSE/BACKGROUND

2.1. Scope

Alkermes Inc. has submitted an original NDA for a pre-filled syringe for delivery of Aripiprazole lauroxil extended-release suspension. This NDA is for the starting dose of (b) (4) mg to initiate ARISTADA treatment for schizophrenia (b) (4)

CDER/OPQ has consulted CDRH/ODE for the following:

The drug product is available in a strength of (b) (4) mg in 2.4 mL. The kit contains a 5-mL pre-filled syringe containing ARISTADA INITIO sterile aqueous suspension and safety needles. A (b) (4) mg strength kit 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. Please review.

This memo includes a review of the device constituent parts performance and design control documentation. This review does not include a review of the sterility or drug-device compatibility of the primary container closure, which is deferred to the CDER review team.

2.2. Prior Interactions

CDRH/ODE has had no prior interaction with the Sponsor regarding this NDA submission.

2.2.1. Related Files

There are no CDRH/ODE related files for this NDA.

2.3. Indications for Use

Combination Product	Indications for Use
Aripiprazole	Aripiprazole lauroxil extended-release injectable suspension: A starting dose to initiate ARISTADA (aripiprazole lauroxil) treatment for schizophrenia (b) (4)
Pre-Filled Syringe	Deliver drug product

3. ADMINISTRATIVE

3.1. Documents Reviewed

Document Title / Number	Date – Version	Location
Draft Carton Labels - (b) (4) mg Commercial Carton (Starter)	08/31/17	1.14.1.1
Draft Container Labels - (b) (4) mg Sample Syringe Label	08/31/17	1.14.1.1
proposed-pi	08/31/17	1.14.1.3
(b) (4) - Responsible for Labeling,	08/31/17	1.4.2

Kit Assembly Secondary Packaging		
Letter of Authorization - 510(k)s for (b) (4)	08/31/17	1.4.2
Container Closure System	08/31/17	3.2.P.7
700-07205 - Verification of ALKS 9072 Design Inputs Based on Leveraging Aristada Verification	08/31/17	3.2.R
702-07157 - Shipping Verification for ALKS 9072N	08/31/17	3.2.R
700-02850 - Verification of Aristada and Aripiprazole Lauroxil NCD Dead Space Design Inputs	08/31/17	3.2.R
Design Control	08/31/17	3.2.R
Method Validation Report - 702-03633 - Dose Delivery and CU	08/31/17	3.2.R
Method Validation Report - 702-07143 - Breakloose and Glide Force	08/31/17	3.2.R
Executed Batch Record - Lots 0000080673 and 83726	08/31/17	3.2.R
Stability Data	08/31/17	3.2.P.8.3
Specifications	08/31/17	3.2.P.5.1

4. DEVICE DESCRIPTION AND PERFORMANCE REQUIREMENTS

The Sponsor provided the following description of the device constituent parts of the combination product:

(b) (4)

(b) (4)

(b) (4)

• An assessment consistent with the principles highlighted in the guidance on Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products (June 2013), including an assessment of the severity of potential over- or under-dosing of the drug product (Section 4.2.3.1).

(b) (4)

• Verification of the integrity of the container closure system during manufacturing, storage, and distribution (Section 4.2.3.4).

Assessment Based on FDA's Technical Guidance for Pen, Jet, and Related Injectors

Alkermes performed an assessment (b) (4) based on the FDA guidance on Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products (June

(b) (4)

(b) (4)

Each syringe containing the AL-NCD injectable suspension is designed to deliver a single dose. It is not a multi-dose product. As a single-dose product syringe, the product is designed to deliver the labeled dose without adjustment by the user. Finally, a hazard assessment did not identify the severity of potential under- or over-dosing of the drug product as critical.

Overview of Safety Needles

AL-NCD injectable suspension may be administered by the gluteal or deltoid routes. For gluteal administration either a 1½-inch 20G or a 2-inch 20G needle is used. For the deltoid route, either a 1-inch 21G or a 1½-inch 20G needle is used. Needles of different lengths are included to provide a choice of needle based on the amount of subcutaneous tissue overlaying the injection site muscle. An overview of the safety needles is provided in Table 14.

Table 14: Overview of Safety Needles for Dose Administration

Needle Gauge	Needle Length	Route of Administration	Amount of subcutaneous tissue overlaying the injection site muscle
21G	1-inch	Deltoid	Small
20G	1½-inch	Deltoid	Large
20G	1½-inch	Gluteal	Small
20G	2-inch	Gluteal	Large

Needle components are commercially available and are supported by 510(k)'s. The 510(k) references are (b) (4). Letters of authorization are provided in Section 1.4.1.

Selection of Safety Needle Gauge and Length

Selection of the needle gauge and needle lengths for AL-NCD injectable suspension is based on the demonstrated suitability of these needles for ARISTADA. Both products are aqueous suspensions of the same drug. Since the particle size for the suspended drug in AL-NCD is smaller than the particle size of the drug in ARISTADA, transit of the AL-NCD suspension through the selected needles is expected to be at least as easy as transit associated with ARISTADA. Laboratory studies involving needles of the same or more narrow gauge (21G or 23G) than the proposed needles and AL-NCD syringes exposed to stress conditions are associated with acceptable injectability results. Suitability of the needles has been also demonstrated during clinical studies for AL-NCD.

Impact of Alternate Needle Selection on Administered Dose

A 1-inch 21G or a 2-inch 20G needle may be selected alternatively to the 1½-inch 20G needle by the user to

administer AL-NCD. The impact on the dose delivered when different needles are used has been assessed as having a minimal impact on dose accuracy based on comparison of needle volumes.

A summary of the needle volumes for the three needle types is provided in Table 15. (b) (4)

(b) (4)

Table 15: Comparison of Needle Volumes

Needle Type	ID x Length (mm)	Calculated Volume, mL[a]
1-inch 21G	(b) (4)	
1½-inch 20G		
2-inch 20G		

[a] Volume = $(\frac{1}{2}ID)^2 \times \pi \times$ length

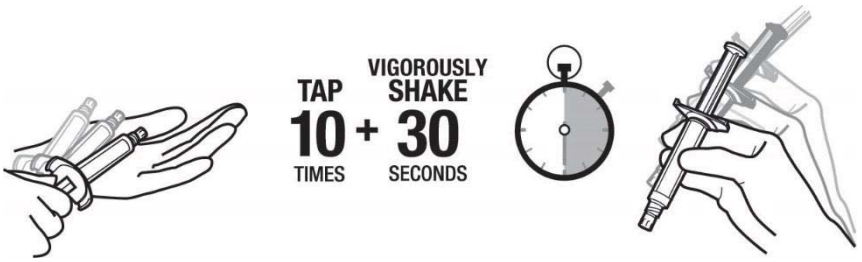
Table 16: Change in Volume Injected

Dose	Volume per unit dose (3.2.P.1)	Needle used rather than 1½-inch 20G	(b) (4)
(b) (4)	2.4 mL	1-inch 21G	
		2-inch 20G	

[a] (Change in dose volume/ volume per unit dose) * 100

The following performance requirements were derived from the Sponsor's design input and design control documentation provided within section 3.2.R of the NDA:

Device Characteristic	Description / Specification
Syringe Name	(b) (4)
Dose Accuracy	
Injection Site	Deltoid or gluteal muscle
Injection Tissue / Depth	Intramuscular (1.5 – 2 inches)
Breakloose Force	NMT (b) (4) N
Glide Force	NMT N
Visibility of Medication	Yes
Needle Specifications	1", 21G – Deltoid 1.5", 20G – Deltoid/Gluteal 2", 20G – Gluteal
Type of Use	Single (b) (4), disposable
Intended User	HCP only
Residual Medication	N/A
Drug Container Type	(b) (4)
Dose Units of Measure (e.g., mL, Units, mg,	mg/mL

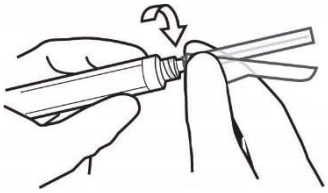
increments, etc.)	
Environments of Use	Any
Storage Conditions and Expiry	20-25 degrees Celsius with excursions 15-30 degrees Celsius DO NOT FREEZE
(b) (4)	
Preparation and Administration	**1. TAP** and vigorously **SHAKE** the syringe.  **1a. Tap** the syringe at least 10 times to dislodge any material which may have settled. **1b. Shake** the syringe **vigorously** for a minimum of 30 seconds to ensure a uniform suspension. If the syringe is not used within 15 minutes, shake again for 30 seconds. **2. SELECT** the injection needle. **2a. Select** injection site. **2b. Select** needle length based on injection site. For patients with a larger amount of subcutaneous tissue overlaying the injection site muscle, use the longer of the needles provided. **Table 1: ARISTADA INITIO: Injection Site and Associated Needle Length**

INJECTION SITE	NEEDLE LENGTH
(b) (4) **mg dose**	
Deltoid	21 GAUGE, 1-INCH or 20 GAUGE, 1½-INCH
Gluteal	20 GAUGE, 1½-INCH or 20 GAUGE, 2-INCH

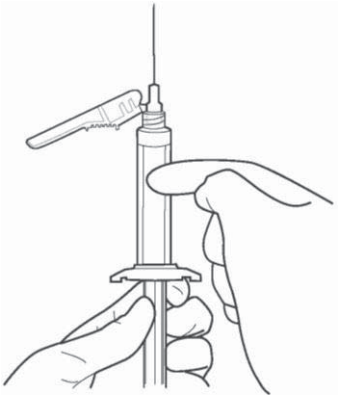
(b) (4)

(b) (4)

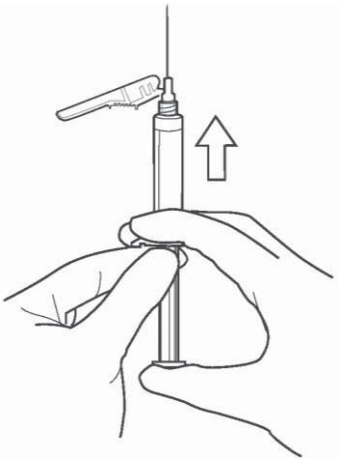
3. ATTACH the injection needle.
Attach the appropriate needle securely with a clockwise twisting motion. Do NOT overtighten. Overtightening could lead to needle hub cracking.



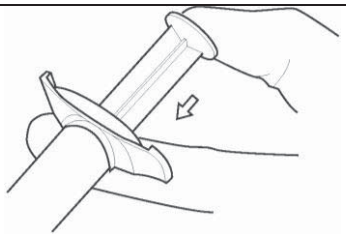
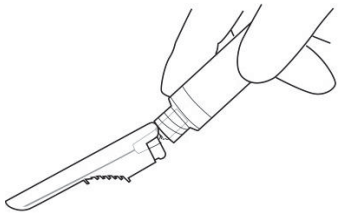
4. PRIME the syringe to remove air.
4a. Bring the syringe into upright position and **tap** the syringe to bring air to the top.



4b. Depress the plunger rod to remove air until a few drops are released. It is normal to see small air bubbles remaining in the syringe.



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.

	 **6. DISPOSE** of the needle. Cover the needle by pressing the safety device. Dispose of used and unused items in a proper waste container. 
Safety Features	Needle safety device (attached to needle and not the PFS body)

5. DESIGN CONTROL REVIEW

5.1. Design Review Summary

The Sponsor 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. All necessary information was provided within the NDA application itself, although LOAs were provided for [redacted] (b) (4) Both 510(k)s are cleared devices.

5.1.1. Design Control Documentation Check

Design Control Requirement*	**Signed/Dated Document Present**		**Submission Location**
	Yes	**No**	
Design Requirements Specifications included in the NDA by the Combination Product Developer	X		3.2.R
Design Verification Data included in the NDA or adequately cross-referenced to a master file.	X		3.2.R
Risk Analysis supplied in the NDA by the Combination Product Developer	X		3.2.R
Validation Data	X		3.2.R

• Human factors • Clinical data	X		
Traceability Documentation	X		3.2.R

***Sponsor may derive the regulatory requirements from 21 CFR 820.30 into multiple sets of documents. For example, injectors containing software may include separate software requirements and specification documents. In these circumstances, additional rows may need to be added to the table.**

6. DESIGN VERIFICATION AND VALIDATION REVIEW

6.1. Summary of Design V&V Attributes

Design Verification / Validation Attributes	**Yes**	**No**	**N/A**
Validation of essential requirements covered by clinical and human factors testing	X		
To-be-marketed device was used in the pivotal clinical trial	X*		
Verification methods relevant to specific use conditions as described in design documents and labeling	X		
Stability and simulated shipping / transport data adequately verifies device will meet essential performance requirements at expiry	X		
Traceability demonstrated for specifications to performance data	X		

*See section 6.2

Standards / Guidance Conformance		**YES**	**NO**	**N/A**
Conformance to Standards	ISO 11040-5 – Prefilled syringes Part 5: Plunger Stoppers for injectables	X		
	ISO 11040-6 - Prefilled syringes Part 6: Plastic barrels for injectables	X		
	ISO 7886-1 – Sterile hypodermic syringes for single-use	X		
	ISO 80369-7 – Small-bore connectors for liquids and gases in healthcare applications Part 7: Connectors for intravascular or hypodermic applications	X		
	ISO 23908 – Sharps injury prevention – Requirements and test methods – Sharps protections features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling	X		
	ISO 7864 – Sterile hypodermic needles for single use	X		
	ISO 10993 – Biocompatibility	X		
	ISO 11137 – Sterility	X		
	ISO 80369-20 - Small-bore connectors for liquids and gases in healthcare applications Part 20: Common test methods (leakage)	X		
	Infusion Pumps Total Product Life Cycle – Guidance for Industry and FDA Staff (2014)			X
	Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (2005)			X
	Guidance for Industry and FDA Staff – Intravascular Administration Sets Premarket Notification Submissions			X

Adherence to FDA Guidance	(2008)			
	Guidance for Industry and FDA Staff: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products (2013)			X
	Guidance for Industry Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation (2002)			X
	Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (2017)	X		
	Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff (2015)			X

*This table does NOT include discipline specific Guidances / Standards that may be applicable to the review

6.2. Design Validation Review

Design Validation Attributes	Yes	No	N/A
Phase I/II/III Study utilized the to-be-marketed device	X		
Bioequivalence Study utilized to-be-marketed device			X
Simulated Actual Use Study utilized to-be-marketed device	X		

Table 12: Comparison of Clinical and Commercial Pre-filled Syringe Container Closure Systems for AL-NCD Injectable Suspension

Attribute	Container Closure System Description	
	Clinical	Commercial
Pre-filled Syringe Primary Components (b) (4) (b) (4)	The clinical and commercial primary packaging components are the same.	
		(b) (4)

The following human factors information was provided within the NDA (although this information is not the subject of this review memo), serving as additional validation information:

Alkermes previously conducted a Summative Human Factors Study of ARISTADA prefilled syringe kits and validated that intended users (healthcare professionals) safely and effectively performed important tasks in the expected user environment. The study results were presented in the ARISTADA NDA 207,533 and confirmed that the risk mitigations implemented following formative studies successfully decreased risks associated with critical steps in the Instructions for

Use (IFU). Additionally, enhancements to the Aristada IFU were validated and submitted to the Aristada NDA 207,533 (Sequence 0065, 1.11.1 Results of Human Factors Validation). Alkermes has conducted formative user studies and risk assessment to assess functional equivalence and suitability of the ARISTADA presentation and IFU for aripiprazole lauroxil NCD pre-filled syringe kit.

Reviewer Comments:
The differences in the clinical and commercial pre-filled syringe presentations are minor dimensional differences that could not impact the functional performance of the product. The lead reviewer finds the clinical presentation validation transferrable to the proposed commercial presentation.

6.3. Design Verification Review

Essential Performance Requirement	Specification	Verification	Validation	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)	Lot Release Testing (Y/N)
Dose Accuracy	+/- 10% label claim	Yes	Yes	Yes	Yes	Yes
Break Loose Force	NMT (b) (4) N	Yes	Yes	Yes	Yes	Yes
Glide Force	NMT N	Yes	Yes	Yes	Yes	Yes
Needle Length / Gauge	1.0" / 21 Gauge 1.5" / 20 Gauge 2.0" / 20 Gauge	Yes	Yes	Yes	Yes	Yes
Injection Depth	38.1 – 50.8 mm (1.5 – 2.0 inches)	Needle Lengths	N/A	N/A	N/A	N/A

The following is a traceability matrix of the verification testing results provided by the Sponsor:

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

[redacted]

Reviewer Comments:
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.

7. RISK ANALYSIS

7.1. Risk Analysis Attributes

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	X		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	X		
Mitigations are adequate to reduce risk to health	X		
Version history demonstrates risk management throughout design / development activities	X		

7.2. Summary of Risk Analysis

The Sponsor provided the following risk-related information in the NDA:

Aripiprazole lauroxil NCD is intended to be administered with or prior to the initiation of treatment with ARISTADA. ARISTADA is comprised of an extended release injectable, micron-sized suspension, while the formulation utilized for AL-NCD is comprised of an extended release injectable, nanometer-sized suspension.

Aripiprazole lauroxil NCD utilizes the same pre-filled syringe components and kit design as ARISTADA and has similar instructions for use and presentation with the exception of label content, which is unique to the drug product. Therefore,

the aripiprazole lauroxil NCD kit used for initiation of treatment is functionally equivalent to ARISTADA kits used for maintenance of treatment. Risk mitigations that were required for ARISTADA were applied to aripiprazole lauroxil NCD kits to minimize the potential of negative transfer from the use of either product.

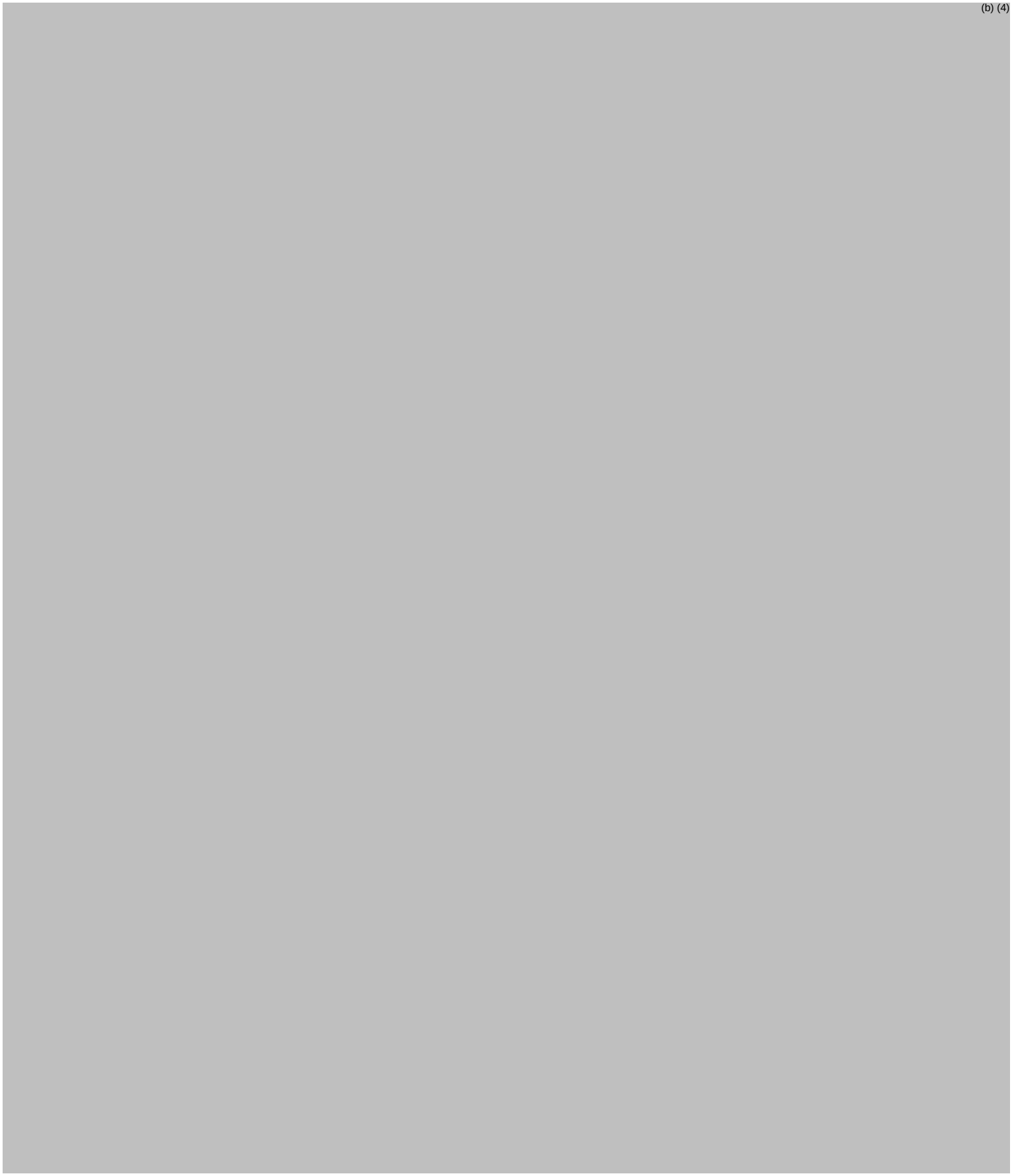
In additions to the use-related risk analysis and human factors information provided for the device constituents of the combination product, the Sponsor also referred to the FMEA performed for the same pre-filled syringe container closure under NDA 207533.

Reviewer Comments:
Through the thorough design control documentation, use-related risk assessment, adherence to standards, cleared 510(k) submissions, referenced FMEA, and risk related information held under DMF (b) (4) syringe the lead consultant believes the Sponsor has adequately mitigated the risks of the device constituent parts of the combination product for its intended use.

8. LABELING

The Sponsor provided the following proposed labeling related to the outer packaging (carton) and the pre-filled syringe on-device labeling:

(b) (4)



Reviewer Comments:

The proposed labeling is acceptable to the lead consultant reviewer. The labels include the storage conditions reflected by the stability testing, correct injection site/depth, contents of the kit, and user population.

9. DESIGN TRANSFER ACTIVITIES – RELEASE SPECIFICATION

Attribute	Specification
Dose Accuracy	(b) (4) % of label claim
Break Loose Force	NMT (b) (4) N
Glide Force	NMT N

Table 1: Proposed Specification for AL-NCD

Attribute	Test Method	Acceptance Criteria	Test Category Release: R Stability: S
Dose Delivery Assay (Label Claim)	HPLC	(b) (4) % of Label Claim	R,S
Break Loose Force	(b) (4)	NMT (b) (4) N	R, S
Glide Force		NMT N	R, S

Reviewer Comments:
The Sponsor included dose accuracy, breakloose, and glide force in their lot release specifications for the product. This is acceptable to the lead consultant reviewer.

10.INTERACTIVE REVIEW

None

11.RECOMMENDATION

CDRH/ODE recommends Approval for the device constituents parts of the combination product.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TESHARA G BOUIE
03/07/2018
T. Bouie on Behalf of John McMichael, CDRH/ODE/DAGRID/GHDB