CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207533Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

Product Quality Microbiology Review

JULY 18, 2015

NDA: 207533

Drug Product Name
Proprietary: ARISTADA
Non-proprietary: aripiprazole lauroxil for injection

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
August 22, 2014	August 22, 2014	September 29, 2014	October 9, 2014

Submission History (for 2nd Reviews or higher) – N/A

Applicant/Sponsor
Name: Alkermes Inc.
Address: 852 Winter Street, Waltham, MA 02451-1420
Representative: Georgianna Harris, Ph.D. Vice President R. A.
Telephone: 781-609-6516, Ann Kurowski, Assoc. Director

Name of Reviewer: Vinayak B. Pawar, Ph.D.

Conclusion: Recommend Approval

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUBMISSION:** Original NDA

2. **SUBMISSION PROVIDES FOR:** Aripiprazole lauroxil, extended-release injectable suspension.

3. **MANUFACTURING SITE:** Alkermes Inc.,
Wilmington, OH 45177-2484
FEI: 1000142940

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** A single use 5 mL pre-filled syringe combination product in dosage strengths of 441 mg, 662 mg & 882 mg for intramuscular administration.

5. **METHOD(S) OF STERILIZATION:** (b) (4)

6. **PHARMACOLOGICAL CATEGORY:** Indicated for treatment of schizophrenia.

B. **SUPPORTING/RELATED DOCUMENTS:**

C. **REMARKS:** This original NDA 207533 submission is for Aripiprazole lauroxil (ARISTADA™), is an injectable extended-release atypical antipsychotic developed by Alkermes for the treatment of schizophrenia. Oral aripiprazole is an atypical antipsychotic approved by the FDA [Abilify® NDA 021-436; 2002] and is the Reference Listed Drug (RLD) for this NDA. This is an electronic submission.

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Executive Summary

I. Recommendations

A. Recommendation on Approvability - Recommend Approval

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology - Alkermes manufactures aripiprazole lauroxil injectable suspension via (b) (4)

B. Brief Description of Microbiology Deficiencies - None

C. Contains Potential Precedent Decision(s) - ☐ Yes ☒ No

III. Product Quality Microbiology Risk Assessment

A. Initial Product Quality Microbiology Risk Assessment

CQA	Risk Factor	Prob. of Occ. (O)	Modifier for O[3, 4, 5]	Severity of Effect (S)	Detect. (D)	Risk Priority Number[6] (RPN)	Additional Review Emphasis based on Risk (in addition to normal review process)
Ster.	(b) (4)	9		5	5	225	(b) (4)
Endo		4		4	4	64	

(b) (4)

6 = RPN = O (after modification when applicable) ×S×D
RPN <50 = Low Risk; RPN 50-120 = Moderate Risk; RPN >120 = High Risk

B. Final Risk Assessment – Low

IV. Administrative

A. Reviewer's Signature _____
Vinayak B. Pawar, Ph.D., Sr. Review Microbiologist, DMA/OPQ

B. Endorsement Block _____
Stephen E. Langille, Ph.D., Acting Chief, Branch III, DMA/OPQ

C. CC Block
N/A

Product Quality Microbiology Assessment

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

S DRUG SUBSTANCE – (b) (4)

Drug Substance Specifications:

Bacterial Endotoxins: USP <85>, NMT (b) (4) EU/mg

Microbial Limits: USP <61>, TAMC at NMT (b) (4) cfu/g

TCYM at (b) (4) cfu/g

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- *Description of drug product* – Aripiprazole lauroxil injectable suspension is a white to off-white aqueous extended-release suspension for intramuscular injection provided as a single use 5 mL pre-filled syringe combination product in dosage strengths of 441 mg, 662 mg, and 882 mg.

- *Drug product composition* – The components of the drug product formulation and their functions are presented in Table 1 (copied from Table 1, Section 3.2.P.1. The quantitative and qualitative unit composition for each aripiprazole lauroxil injectable suspension dose strength was provided in Table 2, but not reproduced here.

Table 1. Quantitative Composition of Drug Product

Component	Reference to Quality Standard	Target Amount per Batch[a]	Weight Percent of Vehicle Formulation
Aripiprazole Lauroxil	Non-compendial	(b) (4)	
Sodium Phosphate, Dibasic, Anhydrous	USP		
Sodium Chloride	USP		
Sodium Phosphate, Monobasic	USP		
Polysorbate 20	NF		
Sorbitan Monolaurate	NF		
WFI	USP		
			(b) (4)

- *Description of Container Closure System* – Description of container closure system – The drug product is supplied as a kit containing the pre-filled syringe and safety needles. The 441 mg strength kit contains a 1-inch 21 gauge needle, a 1½-inch 20 gauge needle, and a 2-inch 20 gauge needle. The 662 mg and 882 mg strength kits each contain a 1½-inch 20 gauge needle and 2-inch 20 gauge needle. The product KIT consists of: Primary Packaging Components [syringe barrel, tip

cap, plunger], Secondary Packaging Components [plunger rod, finger flange, tray, carton] and safety needles.

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- Container-Closure and Package integrity –

Bulk Container Closure Integrity: Container closure integrity of the (b) (4) was qualified by microbial ingress challenges. (b) (4)

Syringe Container Closure Integrity: The integrity of the container closure system during manufacturing, storage and distribution has been demonstrated using media fill studies as summarized in Section 3.2.P.2.4.1.4.5 and reviewed in Review Section P.3.5. Microbial and dye ingress testing were performed to ensure container closure integrity (b) (4) (Report 702-03350, Section 3.2.P.2.4). (b) (4) Non-microbiological evaluation such as actual and simulated shipping studies were performed, and injectability (dose delivery) as well as visual inspection results demonstrate that the container closure integrity is robust to shipping stresses, such as temperature, vibration, and dropping.

Shipping Verification Thermal & Mechanical Stress:
The results from these shipping verification studies in combination with temperature excursion stability test results were provided in

(Section 3.2.P.8.3) and support a recommendation for (b) (4) Recommended labeling of the product includes the following: "Store at (b) (4) room temperature (20°C - 25°C) with excursions between 15°C and 30°C". Recommended additional labeling for product shipping containers indicates (b) (4)

Table 2. Dye Ingress and Microbial Ingress Test Results

(b) (4)

- (b) (4)

ADEQUATE

REVIEWER COMMENT – The applicant's verification of container closure integrity is consistent with regulatory expectations for a pharmaceutical product.

P.3 Manufacture

P.3.1 Manufacturers - Alkermes Inc., 265 Olinger Circle, Wilmington, OH 45177- 2484 FEI: 1000142940

P.3.3 Description of the Manufacturing Process and Process Controls

(b) (4)

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(b) (4)

[redacted]

ADEQUATE

REVIEWER COMMENT – The applicant has met regulatory expectations for validating the process used for (b) (4) [redacted] as well as process simulations in support of the (b) (4) manufacture of the subject drug product.

P.5 Control of Drug Product

P.5.1 Specifications

P.5.2 Analytical Procedures

- Endotoxin – Testing for bacterial endotoxins is performed according to USP <85> using the kinetic chromogenic method.

(b) (4)

[redacted]

- Sterility – Sterility Testing is performed using Harmonized USP <71> Method. Bacteriostasis and Fungistasis results were provided in Tables 4 through 14 from drug product batches ALKS 9070, ALKS 9071 and ALKS 9072 in Validation Report 701-026551,

ADEQUATE

REVIEWER COMMENT – The applicant met regulatory expectations with regard to the test method, acceptance criteria and verification of the suitability of use of the bacterial endotoxins and sterility test methods that will be performed on the drug product [redacted] (b) (4)

P.7 Container Closure System – See Review Section P.1

P.8 Stability

P.8.1 Stability Summary and Conclusion

Data currently support a [redacted] (b) (4) month expiry [redacted] (b) (4). Fifteen (15) months of stability data at the long-term condition and six (6) months at accelerated conditions are available for the pre-filled syringe registration batches and has shown little to no change over time. Seven (7) lots were manufactured and analyzed for stability: six primary registration lots and one stacked stability lot. Four (4) lots were manufactured at the high dose of 882 mg and three (3) lots were manufactured at the low dose of 441 mg. A bracketing and matrix design was utilized for most time points except for the initial, 6 month, 12 month, 24 month and 36 month time points. Stability is currently ongoing. [redacted] (b) (4) Therefore, three (3) additional aripiprazole lauroxil pre-filled syringe lots were manufactured as supportive stability for sterility. No sterility positive results so far.

P.8.2 Post-Approval Stability Protocol and Stability Commitment

The post-approval stability commitments are summarized below:

• All stability studies will be performed on the final drug product in the primary packaging components as defined in Section 3.2.P.7.

• Complete primary registration stability through at least 36 months at [redacted] (b) (4)

• Conduct long-term stability on the first three production batches per ICH Q1A (R2), *Stability Testing of New Drug Substances and Products.* The stability study design will follow the protocol for the primary registration stability batches as shown in Table 2 in Section 3.2.P.8.1.

• Annually thereafter, conduct long-term stability on the lowest and highest dose distributed according to the study design shown in Table 1, Section 3.2.P.8.1 in accordance with ICH Q1D, *Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products.* The bracketing design will support the stability of any intermediate dose by testing the lowest and the highest doses.

- Container Closure Integrity – N/A
- Sterility & Endotoxin – At release and annually thereafter.

P.8.3 Stability Data – See Review Section P.8.2

ADEQUATE

REVIEWER COMMENT – The regulatory expectations with regard to the test methods, acceptance criteria and verification of the suitability of use for release and stability time points are met.

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

A. **PACKAGE INSERT** - A single use 5 mL pre-filled syringe combination product in dosage strengths of 441 mg, 662 mg & 882 mg for intramuscular administration. No product manipulation or reconstitution is required.

ADEQUATE

REVIEWER COMMENT – The applicant has met regulatory expectations with regard to the information related to issues of product quality microbiology that is provided in the product labeling.

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS: None.

Digitally signed by Vinayak B. Pawar -A
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Stephen E. Langille -A

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