

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207533Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

| Application Information | | |
|--|--------------------------|---|
| NDA # 207533 | NDA Supplement #: S- 000 | Efficacy Supplement Type SE- N/A |
| Proprietary Name: ARISTADA Established/Proper Name: Aripiprazole Lauroxil Dosage Form: Extended-Release Injectable Suspension Strengths: 441 mg, 662 mg, and 882 mg | | |
| Applicant: Alkermes | | |
| Date of Receipt: 8/22/2014 | | |
| PDUFA Goal Date: 8/22/2015 | | Action Goal Date (if different): 10/5/15 |
| RPM: Sharonjit Sagoo, Pharm.D. | | |
| Proposed Indication: Schizophrenia | | |

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

| Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph) | Information relied-upon (e.g., specific sections of the application or labeling) |
|---|--|
| Abilify Tablets NDA 21436 | FDA's finding of safety and effectiveness for Abilify tablets as described in the labeling (e.g., section 8.1) ; See reviews for NDA and response to #3. |
| | |
| | |

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature¹.

Alkermes' Phase 3 clinical trial (ALK9072-003) was a global, multicenter, randomized, double-blind, placebo-controlled study to compare the efficacy of once monthly intramuscular aripiprazole lauroxil to a placebo over a period of 12 weeks in the treatment of schizophrenia. The study included 623 subjects who were divided into three groups, described below, at a 1:1:1 ratio:

1. A group that was injected with 441 mg of aripiprazole lauroxil suspension every four weeks and was administered aripiprazole tablets for 21 days following the first injection.
2. A group that was injected with 882 mg of aripiprazole lauroxil suspension every four weeks and was administered aripiprazole tablets for 21 days following the first injection.
3. A group that was injected with a placebo every four weeks and was administered placebo tablets for 21 days following the first injection.

A total of 360 subjects (58%) completed the 12-week treatment period. The primary efficacy endpoint was the change from baseline to day 85 in Positive and Negative Syndrome Scale (PANSS) total score, and the secondary efficacy endpoint was Clinical Global Impression of Improvement (CGI-I). A statistically significant and clinically meaningful improvement over the placebo group was observed consistently in both the 441 mg and 882 mg treatment groups.

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

In addition to conducting a Phase 3 clinical study to support approval of the Aristada NDA, Alkermes relied, in part, on FDA's finding of safety and effectiveness for the listed drug Abilify (aripiprazole) Tablets. Data from Alkermes Phase 3 clinical study and Phase 1 PK studies established the scientific bridge between its product and the listed drug, Abilify Tablets and thus demonstrated that the basis for reliance on the listed drug was scientifically justified.

Specifically, in two of its Phase 1 studies (ALK9072-001 and ALK9072-002) and one Phase 3 study (ALK9072-003), Alkermes generated data on the exposure level of aripiprazole from Abilify Tablets. In all four of Alkermes' Phase 1 studies (ALK9072-001, ALK9072-002, ALK9072-101, and ALK9072-102) and in the Phase 3 study (ALK9072-003), Alkermes generated data on the exposure level of aripiprazole from Aristada extended-release injectable suspension. The data from these studies demonstrate that the exposure levels of aripiprazole in subjects who were administered Aristada extended-release injectable suspension were similar to the exposure levels of aripiprazole in subjects who ingested Abilify Tablets. The studies conducted by Alkermes, together with the finding of safety and effectiveness for Abilify Tablets, support the conclusion that Aristada is safe and effective under the conditions of use described in the Aristada labeling.

An article by Boulton et al. was used to refine the Physiologically based PK (PBPK) model to accurately describe the historical PK of aripiprazole. The PBPK model was used to develop a model to predict the PK of Aristada and define Aristada's drug interaction potential.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES NO

If "NO," proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If "NO," proceed to question #5.

If "YES", list the listed drug(s) identified by name and answer question #4(c).

Abilify tablets

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

| Name of Listed Drug | NDA # | Did applicant specify reliance on the product? (Y/N) |
|---------------------|--------|--|
| Abilify Tablets | 021346 | Y |
| | | |

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a final OTC drug monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES NO

If “**YES**”, please list which drug(s) and answer question d) i. below.

If “**NO**”, proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

The active moiety in Abilify tablets is aripiprazole. The proposed drug product is for aripiprazole lauroxil. Aripiprazole lauroxil is a prodrug of N-hydroxymethyl aripiprazole, which itself is a prodrug of aripiprazole.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA’s “Approved Drug Products with Therapeutic Equivalence Evaluations” (the Orange Book)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES NO

If "NO" to (a) proceed to question #11.
If "YES" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?
YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?
N/A YES NO

If this application relies only on non product-specific published literature, answer "N/A"
If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.
If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO
If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?
YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?
N/A YES NO

If this application relies only on non product-specific published literature, answer "N/A"
If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If “**NO**” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): 7053092, 8017615, 8017615, 8580796, 8642600, 8642760, 8759350, 5006528, 9089576

No patents listed proceed to question #14

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If “**NO**”, list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s): 8642600, 8759350, 7053092

Method(s) of Use/Code(s): U-1492 for the “treatment of irritability associated with autistic disorder”; U-1529 for the “adjunctive treatment of major depressive disorder (MDD)”; U-839 for the “treatment of major depressive disorder (MDD)”

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s): 8017615, 8580796, 8642760

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES NO

If “NO”, please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

If “NO”, please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): 11/11/2014, 11/12/2014

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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

/s/

SHARONJIT K SAGOO
10/05/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
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Addendum to Pregnancy and Lactation Labeling Rule (PLLR) Labeling Review

Date: 9-30-2015

From: Leyla Sahin, MD
Medical Officer,
Division of Pediatric and Maternal Health, Maternal Health Team

Through: Tamara Johnson, M.D., M.S.
Acting Team Leader, Maternal Health Team
Division of Pediatric and Maternal Health

Lynne P. Yao, MD
Director,
Division of Pediatric and Maternal Health

To: Division of Psychiatry Products

Drugs: Aristada (aripiprazole lauroxil) extended release intramuscular injection; NDA 207533

Subject: Pregnancy and Lactation Labeling Rule (PLLR) Conversion

Applicant: Alkermes

Addendum: The Division of Pediatric and Maternal Health (DPMH) concurs with the Toxicology Reviewers' Nonclinical Review Addendum (dated 9-28-2015)

(b) (4)



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

/s/

LEYLA SAHIN
09/30/2015

TAMARA N JOHNSON
09/30/2015

LYNNE P YAO
10/01/2015



Memorandum

To: NDA 207533
From: Norman R. Schmuff, Ph.D., Associate Director for Science,
Office of Process and Facilities (OPF)
Date: 1 October 2015
Subject: Active moiety determination for Aripiprazole Lauroxil
(NDA 207533)

Summary

Alkermes has submitted NDA 207533 for Aristada (aripiprazole lauroxil) extended release injectable suspension. Aripiprazole lauroxil (i.e., N-lauroyloxymethyl aripiprazole) is a prodrug of N-hydroxymethyl aripiprazole, which in turn is a prodrug of and is subsequently metabolized to aripiprazole. Consistent with 21 CFR 314.108, FDA identifies the active moiety of a drug in order to determine its eligibility for 5-year new chemical entity (“NCE”) exclusivity. As I explain in detail below, I conclude that the active moiety of aripiprazole lauroxil is N-hydroxymethyl aripiprazole.

Factual Background

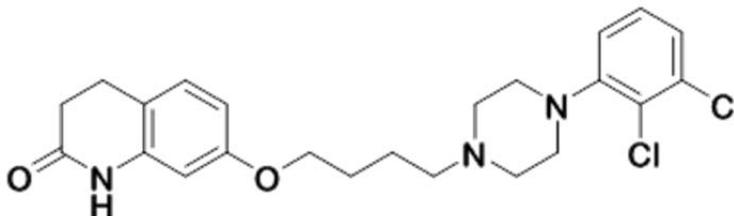
Currently pending before FDA is Alkermes’ new drug application (NDA 207533) for Aristada (aripiprazole lauroxil), extended release injectable suspension. According to Alkermes, “[d]evelopment of aripiprazole lauroxil was undertaken to improve upon the clinical profile of a depot antipsychotic injection while benefiting from the clinical and safety profile of the parent compound, aripiprazole.”¹

Aripiprazole was first approved by FDA in 2002 as the active moiety in Otsuka Pharmaceuticals’ drug product Abilify in tablet form, and has since been

¹ See Turncliff, R. et al., *Relative bioavailability and safety of aripiprazole lauroxil, a novel once-monthly, long-acting injectable atypical antipsychotic, following deltoid and gluteal administration in adult subjects with schizophrenia*, *Schizophrenia Research* 159 (2014) 404–410, at 404. The study described in this article was funded by Alkermes, Inc.

approved in numerous other dosage forms.² Aripiprazole is 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyril.³ The empirical formula is $C_{23}H_{27}Cl_2N_3O_2$ and its molecular weight is 448.38. The chemical structure is shown below in Figure 1.

Figure 1: Aripiprazole



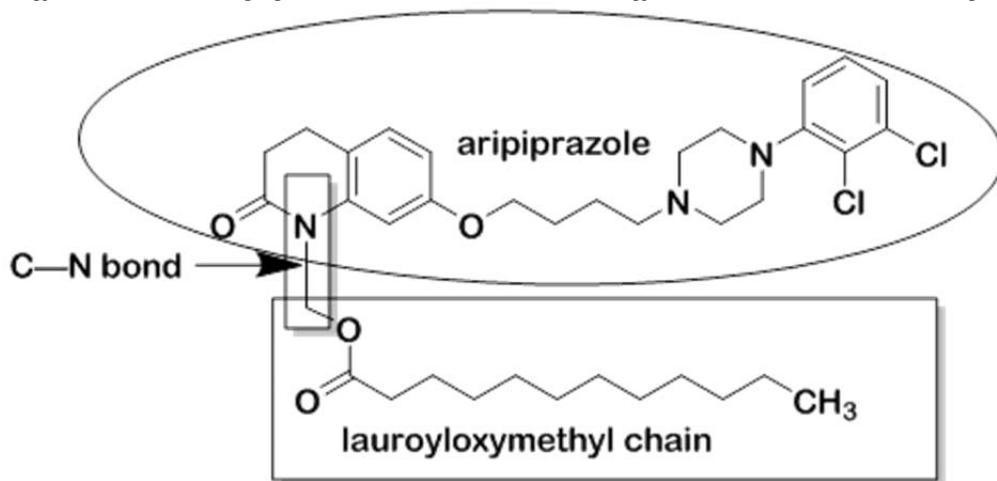
Aristada contains the active ingredient aripiprazole lauroxil (N-lauroyloxymethyl aripiprazole), or, more specifically, 7-{4-[4-(2,3-dichlorophenyl)-piperazin-1-yl]butoxy}-2-oxo-3,4-dihydro-2H-quinolin-1-yl methyl dodecanoate.⁴ The empirical formula is $C_{36}H_{51}Cl_2N_3O_4$ and its molecular weight is 660.7 g/mol. The structural differences between aripiprazole and aripiprazole lauroxil are as follows: In aripiprazole lauroxil, the aripiprazole structure is modified by the introduction of an N-hydroxymethyl group that is esterified with lauric (dodecanoic) acid such that the aripiprazole is attached to a lauroyloxymethyl chain via a carbon-nitrogen (C-N) bond. The structure of aripiprazole lauroxil where these differences from aripiprazole are highlighted is shown in Figure 2.

² Aripiprazole is the active moiety in Otsuka's Abilify line of products, which include Abilify tablets (NDA 21346), Abilify Oral Solution (NDA 21713), Abilify Discmelt Orally Disintegrating Tablets (NDA 21729), Abilify Injection for intramuscular (IM) use (NDA 21866), and Abilify Maintena for extended-release injectable suspension (NDA 202971).

³ Chemical Abstracts Service Name: 2(1H)-Quinolinone, 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydro-

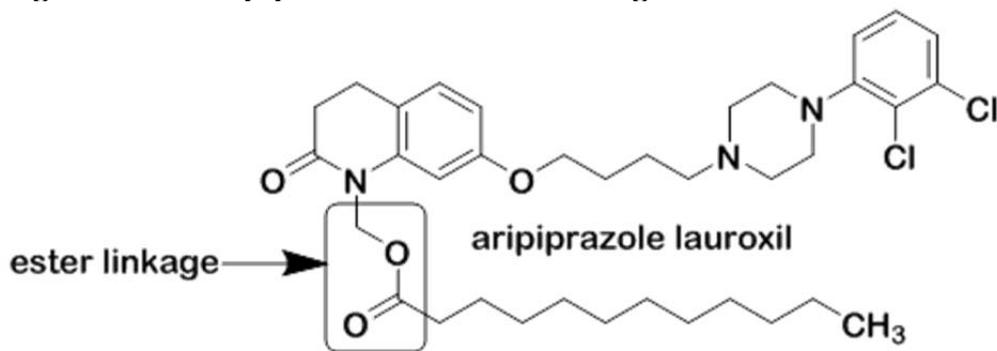
⁴ Chemical Abstracts Service Name: Dodecanoic acid, [7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydro-2-oxo-1(2H)-quinolinyl]methyl ester

Figure 2: Aripiprazole Lauroxil Showing Differences From Aripiprazole



By virtue of the ester bond in its lauroyloxymethyl chain (see Figure 3 below), aripiprazole lauroxil is also an ester. Importantly, aripiprazole lauroxil is an ester of N-hydroxymethyl aripiprazole, not aripiprazole.

Figure 3: Aripiprazole Lauroxil Showing Ester Bond



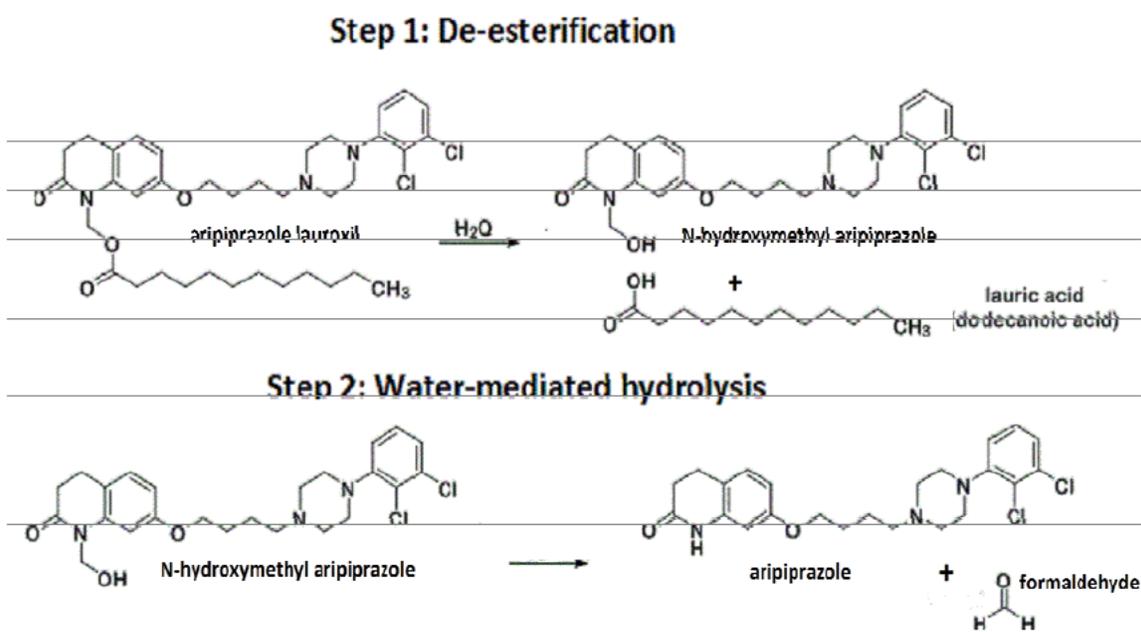
In vivo, aripiprazole lauroxil undergoes a two-step bioconversion to aripiprazole, through N-hydroxymethyl aripiprazole.⁵ The first step is de-esterification.⁶ Both in vitro and in vivo, aripiprazole lauroxil is known to be de-esterified via hydrolysis (likely enzymatic in nature) to N-hydroxymethyl

⁵ Rohde, M., et al., *Biological Conversion of Aripiprazole Lauroxil – An N-acyloxymethyl Aripiprazole Prodrug*, Results in Pharma Sciences 4 (2014)19–25; see also Turncliff R., et al. at 404. Both Rohde and Turncliff measured in vivo concentrations of N-hydroxymethyl aripiprazole after aripiprazole lauroxil was administered (Rhode et al., at 19, 23; Turncliff at 406).

⁶ *Id.*

aripiprazole, its alcohol component, and lauric acid (dodecanoic acid), its carboxylic acid component.⁷ This de-esterification is shown as step 1 in Figure 4 below. Thus, aripiprazole lauroxil is a prodrug⁸ of N-hydroxymethyl aripiprazole. In step two, the N-hydroxymethyl aripiprazole metabolite is likely non-enzymatically cleaved through water-mediated hydrolysis to aripiprazole and formaldehyde. This hydrolysis is shown in step 2 of Figure 4 below. Accordingly, N-hydroxymethyl aripiprazole is a prodrug of aripiprazole.

Figure 4: Two Step Bioconversion of Prodrug Aripiprazole Lauroxil to Aripiprazole via an N-hydroxymethyl Aripiprazole Intermediate



⁷ *Id.* In vivo hydrolysis of aripiprazole lauroxil to N-hydroxymethyl aripiprazole is likely enzymatic and preceded by dissolution of the drug particles from the injection site.

⁸ Although there does not appear to be a standard, universal definition of “prodrug,” for the purposes of this analysis, prodrugs are “[a] class of drugs, the pharmacologic action of which results from conversion by metabolic processes within the body (biotransformation)” Farlex Partner Medical Dictionary (2012), retrieved August 17, 2015 from <http://medical-dictionary.thefreedictionary.com/prodrug>. Similarly, the International Union of Pure and Applied Chemistry (IUPAC) defines a prodrug as “any compound that undergoes biotransformation before exhibiting its pharmacological effects. Prodrugs can thus be viewed as drugs containing specialized non-toxic protective groups used in a transient manner to alter or to eliminate undesirable properties in the parent molecule.” Glossary of Terms Used in Medicinal Chemistry (IUPAC Recommendations 1998). *Pure Appl. Chem.*, 70, 1129, 1141 (1998).

Analysis

Under FDA's interpretation of the relevant statutory provisions, whether a drug is eligible for 5-year NCE exclusivity involves a determination that the drug does not contain a previously approved active moiety.⁹ In order to identify the active moiety of a drug, the Agency applies a "structure-based" approach, as described in FDA's decisional letter finding that the drug lisdexamphetamine is an NCE:¹⁰

FDA interprets and applies 21 CFR 314.108 so that the relevant inquiry addresses the structure of the molecule that forms the drug substance, and whether that molecule has been previously approved as an active moiety. Whether a molecule will be considered to be responsible for the physiological or pharmacological action of the drug substance depends upon the chemical structure of that molecule, which in turn depends on certain reasonable assumptions FDA had adopted about the activity of these classes of molecules. If the molecules in the drug substance are salts or esters or other noncovalent derivatives, the active moiety will be the molecule minus the appendage. If the drug substance is composed of non-ester covalently bonded molecules, the covalently bonded molecule is considered the active moiety.

Under FDA's interpretation of its regulation described in its Vyvanse decision which was subsequently upheld by the courts,¹¹ the active moiety of a molecule where all bonds are non-ester covalent bonds is the entire molecule. This is true even if the molecule includes a non-ester covalent bond to a molecule that was itself a previously approved active moiety, and even if the molecule is subsequently metabolized to the previously approved active moiety in vivo.¹²

⁹ See 314.108(a)-(b).

¹⁰ Letter from Gary Buehler, FDA, to Chad A. Landmon, Axinn Veltrop & Harkrider LLP, Docket No. FDA-2009-N-0184 (Oct. 23, 2009) (FDA's Vyvanse decision) at 11.

¹¹ *Actavis Elizabeth LLC v. FDA*, 689 F. Supp. 2d 174 (D.D.C. 2010), *aff'd* by *Actavis Elizabeth LLC v. FDA*, 625 F.3d 760 (D.C. Cir. 2010).

¹² See FDA's Vyvanse decision at 12. Vyvanse (lisdexamphetamine), a prodrug of dexamphetamine, a previously approved active moiety, comprises dexamphetamine covalently bonded to lysine by an amide bond.

Applying this interpretation to aripiprazole lauroxil, I note that aripiprazole lauroxil is an ester of N-hydroxymethyl aripiprazole. Under the regulation, the active moiety excludes “those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule.”¹³ N-hydroxymethyl aripiprazole is the molecule excluding the appended portion of aripiprazole lauroxil that causes it to be an ester. Therefore, I conclude that N-hydroxymethyl aripiprazole is the active moiety of aripiprazole lauroxil.

I further note that N-hydroxymethyl aripiprazole comprises aripiprazole, a previously approved active moiety, covalently bonded to a hydroxymethyl group via a non-ester covalent bond. Although N-hydroxymethyl aripiprazole includes aripiprazole, it is not an ester of aripiprazole — aripiprazole is attached to its hydroxymethyl group by a covalent C—N bond.¹⁴ Under FDA’s “structure-based” approach, because of the covalent C—N bond, I take into account the hydroxymethyl group of N-hydroxymethyl aripiprazole in determining the active moiety of aripiprazole lauroxil.

Thus, N-hydroxymethyl aripiprazole is the active moiety of aripiprazole lauroxil, despite its subsequent conversion to aripiprazole.

¹³ See 21 CFR 314.108(a).

¹⁴ Similarly, in Vyvanse, although lisdexamfetamine includes amphetamine, a molecule that was itself previously an active moiety, it is not an ester of amphetamine, but instead covalently bonded to lysine by an amide bond.

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

/s/

NORMAN R SCHMUFF

10/01/2015

Active moiety determination for Aripiprazole Lauroxil



Food and Drug Administration
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Ave.
Silver Spring, MD 20993

Intercenter Consult Memorandum – COVER LETTER MEMO

ICC1400644/NDA207533

Date: 7/7/2015

To: Sharonjit Sagoo
Division of Psychiatry Products (DPP),
Office of Drug Evaluation I (ODEI),
Office of New Drugs (OND),
Center for Drug Evaluation and Research (CDER)

From: Ryan McGowan
General Hospital Devices Branch (GHDB),
Division of Anesthesiology, General Hospital, Respiratory,
Infection Control, & Dental Devices (DAGRID),
Office of Device Evaluation (ODE),
Center for Devices and Radiological Health (CDRH)

Ryan J.
McGowan -S

Digitally signed by Ryan J. McGowan - S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=20003524
62, cn=Ryan J. McGowan -S
Date: 2015.07.09 13:04:22 -04'00'

Subject: Device Design Review – COVER LETTER MEMO
ARISTADA (aripiprazole lauroxil) extended release injectable suspension for schizophrenia
NDA 207533; CDRH ICC1400644

Recommendation: NDA Approval for Considerations of Device Design

Within the consulting reviewer's 5/4/2015 memorandum, a recommendation for approval was made with one post-approval comment:

Within NDA207533 Supplement 0015, submitted on April 1, 2015, the sponsor committed to performing ongoing stability analysis to assess mechanical reliability of the fully assembled device through the expiration date of the drug product using primary registration stability batches. The sponsor should submit evidence of completion of these activities to NDA annual reports.

After discussion with CMC reviewer Dr. Wendy Wilson, it was determined that this concern could be provided to the sponsor within a conventional information request. On May 8, 2015, the following information request was issued to the sponsor:

We acknowledge your commitment to continue performing on-going stability analysis to assess the mechanical reliability of the fully assembled device through the expiration date of the drug product using primary registration stability batches (Amendment 0015, submitted April 1, 2015). We would also like your commitment to submit evidence of completion of these activities to NDA annual reports.

On May 15, 2015, the sponsor provided the following response:

We will include in the NDA annual reports results from the on-going stability analysis to assess the mechanical reliability of the fully assembled device through the expiration date of the drug.

This response is considered acceptable and the outstanding concern is resolved. Recommend approval.



Food and Drug Administration
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Ave.
Silver Spring, MD 20993

Intercenter Consult Memorandum

ICC1400644/NDA207533

Date: 5/4/2015

To: Sharonjit Sagoo
Division of Psychiatry Products (DPP),
Office of Drug Evaluation I (ODEI),
Office of New Drugs (OND),
Center for Drug Evaluation and Research (CDER)

From: Ryan McGowan
General Hospital Devices Branch (GHDB),
Division of Anesthesiology, General Hospital, Respiratory,
Infection Control, & Dental Devices (DAGRID),
Office of Device Evaluation (ODE),
Center for Devices and Radiological Health (CDRH)

Subject: Device Design Review
ARISTADA (aripiprazole lauroxil) extended release injectable suspension for schizophrenia
NDA 207533; CDRH ICC1400644

Recommendation: NDA Approval for Considerations of Device Design
(1) Post approval comment

I. Recommendation

The device consultant authoring this review memorandum has performed a design review of submission materials intended to support the safety and functionality of the of the device constituent parts of the subject combination product. This review covered review of design documentation for the final finished pre-filled syringe combination product as well as cross-referenced 510(k) clearance documentation supporting use of safety needle devices with the subject pre-filled syringe. This review did not cover manufacturing of the device constituent parts, sterility or biocompatibility of the pre-filled syringe, or usability of the device constituent parts.

The review of submission documentation by CDRH/ODE found that the product components are of acceptable pedigree and that essential performance of the final fished device can be assured with a reasonable degree of certainty. Essential performance elements of the device under review by the consultants were considered to be:

- Dose accuracy of each dose presentation
- Connection and compatibility of components
- Sterility and biocompatibility of non-primary closure components
- Functionality of the syringe and needle safety device component
- Stability after exposure to aging and shipping conditions

Review of this information found that there are sufficient design control documentation and verification activities for the device constituent part of the combination product to recommend approval.

Additionally, the reviewer has one post approval comment (additional information located at the end of this memo).

II. Consult Purpose

The Center for Drugs Evaluation and Research (CDER) requested a consult from CDRH/ODE for device constituent part design review of NDA 207533, which is a combination product consisting of a syringe safety system that delivers ARISTADA (aripiprazole lauroxil) extended release injectable suspension for schizophrenia. This NDA has been submitted by Alkermes.

III. Coverage of Review

CDRH/ODE reviews content related to the design of device constituent parts for combination product submissions. This review is limited to design requirements and verification/validation information to support the device constituent part, including essential performance of the device constituent part and reliability of the device constituent part over time and after expected environmental exposures.

IV. Device Description

Section 3.2.P.7 of the submission contains summary information on the design of the drug delivery system selected to administer the subject medication. The sponsor states that the device constituent part of the combination product is a pre-filled syringe delivery system. The “primary packaging” system is composed of the following components:

| Primary Packaging Components ^a | | | |
|---|--|--------------|-----------------|
| Kit Component | Description | Manufacturer | Reference/ DMF# |
| Syringe barrel ^b |  | | |
| Tip cap ^b | | | |
| Plunger ^d | | | |

The sponsor references several drug master files (DMFs) for the primary package. The “second packaging” system of the combination product is composed of the following components. Note that there are 3 unique plunger rods (1 for each dose configuration).

| Secondary Packaging Components | | |
|---------------------------------------|---|--------------|
| Kit Component | Description | Manufacturer |
| Plunger rod ^a | 5 mL plunger rod for the 441-mg dose strength | (b) (4) |
| Plunger rod ^a | 5 mL plunger rod for the 662-mg dose strength | |
| Plunger rod ^a | 5 mL plunger rod for the 882-mg dose strength | |
| Finger flange (backstop) ^a | 5 mL finger flange | |
| Tray ^b | Syringe kitting tray | |
| Carton ^b | Carton | |

The sponsor further defines additional “kit components” which will reside within the system packaging.

| Associated Packaging Components ^a | | |
|--|-------------|--------------|
| Kit Component | Description | Manufacturer |
| 21G X 1” needle | | (b) (4) |
| 20G X 1½” needle | | |
| 20 G X 2” needle | | |

The needles to be included within the kit are “safety needles” – meaning they have a flexible needle cover which is capable of covering the needle after the injection takes place.

V. Device Constituent Part – Design Review

This review covers the following critical attributes related to functionality and safety of the device constituent parts of the combination product:

- 1) Statement of device inputs (system requirements and specifications), including:
 - a. Dimensional characteristics
 - b. Functional characteristics
 - c. Stability of dimension and functional characteristics

- 2) Evidence of verification of device inputs (device testing/design output)
 - a. Dimensional characteristics
 - b. Functional characteristics
 - c. Connectivity of components
 - d. Sterility and biocompatibility of fluid path (deferred to CDER)
 - e. Stability and shipping

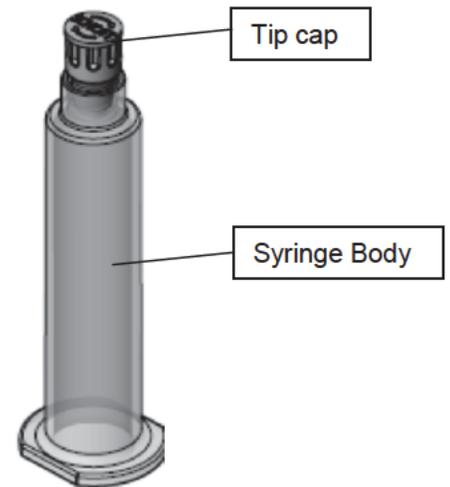
Combination Product Design Inputs

Attributes Covered Under NDA-207533:

Section 3.2.P.7 of the submission contains a document titled “Container Closure System [Aripiprazole Lauroxil, Injectable Suspension]. This document contains a listing of combination product system-level specifications. Select specifications are reproduced below:

Syringe Barrel with Mounted Tip Cap:

| Test | Method | Acceptance Criteria |
|--|-----------|--|
| Particulates | USP <788> | (b) (4) μm: max (b) (4) per syringe (b) (4) μm: max (b) (4) per syringe |
| Sterility | (b) (4) | Meets the (b) (4) requirements listed on the certificate |
| Bacterial Endotoxins | 110-01416 | < (b) (4) EU/mL (per (b) (4) syringes) |
| Identification (syringe barrel) | 110-02183 | IR spectrum conforms to reference spectrum (b) (4) |
| Identification (tip cap) | 110-02183 | IR spectrum conforms to reference spectrum (b) (4) |
| Visual Inspection, intermixing | 110-01268 | No foreign syringes or parts |
| Visual Inspection Cleanliness Cosmetic defect, syringe barrel Molding defects | 110-01268 | Meets AQL ^a |
| Dimensional Testing | 110-01268 | Meets AQL ^a for the following: Internal syringe body diameter: (b) (4) mm – (b) (4) mm Overall length (with tip cap): (b) (4) mm ± (b) (4) mm |



Syringe Plunger:

| Test | Method Description | Acceptance Criteria |
|--------------------------|--------------------|---|
| Identification | 110-02183 | IR spectrum conforms to reference spectrum (b) (4) |
| Sterility | (b) (4) | Meets the (b) (4) requirements listed on the certificate |
| Bacterial Endotoxins | 110-01416 | < (b) (4) EU/ plunger |
| Visual inspection | 110-01268 | Meets AQL ^a |
| Dimensional testing | 110-01268 | Meets AQL ^a for the following: Overall height: (b) (4) mm ± (b) (4) mm |
| Opalescence | USP <381> | ≤6 NTU (Nephelometric Turbidity Units) |
| Color | USP <381> | Solution S is not more intensely colored than the colored standard. |
| Acidity or Alkalinity | USP <381> | Not more than 0.3 mL of 0.01N sodium hydroxide produces a blue color, or not more than 0.8 mL of 0.01 N hydrochloric acid produces a yellow color, or no titration is required. |
| Absorbance | USP <381> | Absorbance of filtrate is ≤0.2 |
| Reducing Substances | USP <381> | The difference between the titration volumes is ≤3 mL. |
| Ammonia | USP <381> | ≤2 ppm |
| Extractable zinc | USP <381> | ≤5 ppm |
| Extractable heavy metals | USP <381> | ≤2 ppm |
| Volatile sulfides | USP <381> | Any black stain on the paper produced by the test solution is not more intense than that produced by the control substance. |
| Residue on evaporation | Ph. Eur. 3.2.9. | ≤ (b) (4) mg |



Plunger Rods:

Three plunger rods have been developed for the system, as there are three dosing options for the subject NDA. Each of the plunger rods are shown below:

Table 6: Specification for the 5 mL Plunger Rod, 441-mg Dose Strength

| Test ^a | Acceptance Criteria |
|---------------------|---|
| Visual inspection | Meets the visual inspection criteria (AQL ^b) listed on the certificate |
| Dimensional testing | Meets AQL ^b for the following: Rod diameter: (b) (4) mm ± (b) (4) mm Total length: (b) (4) mm ± (b) (4) mm Clipping distance: (b) (4) mm ± (b) (4) mm |

Table 7: Specification for the 5 mL Plunger Rod, 662-mg Dose Strength

| Test ^a | Acceptance Criteria |
|---------------------|---|
| Visual inspection | Meets the visual inspection criteria (AQL ^b) listed on the certificate |
| Dimensional testing | Meets AQL ^b for the following: Rod diameter: (b) (4) mm ± (b) (4) mm Total length: (b) (4) mm ± (b) (4) mm Clipping distance: (b) (4) mm ± (b) (4) mm |

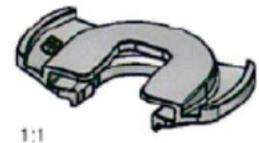
Table 8: Specification for the 5 mL Plunger Rod, 882-mg Dose Strength

| Test ^a | Acceptance Criteria |
|---------------------|---|
| Visual inspection | Meets the visual inspection criteria (AQL ^b) listed on the certificate |
| Dimensional testing | Meets AQL ^b for the following: Rod diameter: (b) (4) mm ± (b) (4) mm Total length: (b) (4) mm ± (b) (4) mm Clipping distance: (b) (4) mm ± (b) (4) mm |



Finger Flange Backstop:

| Test ^a | Acceptance Criteria |
|---------------------|---|
| Visual inspection | Meets the visual inspection criteria (AQL ^b) listed on the certificate |
| Dimensional testing | Meets AQL ^b for the following: Total length: (b) (4) mm ± (b) (4) mm Total height: (b) (4) mm ± (b) (4) mm Notch width: (b) (4) mm ± (b) (4) mm |



The above listing of component dimensional specifications is considered to be acceptable. Based on the dimensional descriptions provided, the system components are compatible. The firm has not, however, provided a description of functional characteristics of the combination product. The following functional attributes were not explicitly provided within the listing of combination product specifications/requirements:

- ISO594 compliance of the syringe luer fitting
- Connectivity without leakage or burst between the syringe and needle
- Burst resistance of the sealed primary container closure
- Activation force and glide force with each needle configuration
- Dose delivered for each dose configuration with each needle configuration
- Initial sterility of the system and prevention of microbial ingress

The above listing will be requested of the sponsor within an information request.

Review Update: Functional Specifications

Within a 1/20/2015 information request, the sponsor was asked to provide a description of system functional requirements and specifications for the combination product, including dose accuracy, glide force, break-loose force, compatibility between syringe/needle components, freedom from leakage, component sterility, and component biocompatibility. The sponsor was asked to provide a comprehensive description of system design requirements and specifications for device constituent parts of the combination product.

Within a 2/2/2015 response, the sponsor provided a table of combination product performance inputs. These requirements and specifications were reviewed and found to be acceptable. For a full listing of the design inputs cited within the IR response, please see the "design verification" section of this memorandum, as the sponsor combined their response with design output information in the form of traceability documentation.

Attributes Covered Under DMFs or 510(k) Files

For the needles which will be co-packaged within the system, 510(k) clearance records were obtained under CDRH 510(k) (b) (4). The 510(k) was cleared by the Agency on March 5, 2012 and was found to have the following attributes:

Intended Use:

(b) (4)

Technical Characteristics:

- Supplied sterile (b) (4)
- Conformant to ISO 10993-1: Biological Evaluation of Medical Devices
- Conformant to ISO 6009: Hypodermic needles for single use: color coding
- ISO 594-1: Conical Fittings
- A simulated use study in accordance with the FDA Medical Devices with Sharps Injury Prevention Features Guidance
- Expiration (b) (4)
- Pyrogen-free

The content provided within the 510(k) is supportive of use of the (b) (4) Safety Needle Device within the subject NDA if the following concerns can be resolved by the NDA sponsor:

- The syringe component supplied within the kit has not been shown to conform to ISO594
- The NDA sponsor has not provided a cross-reference form for the 510(k)
- The 510(k) is cited as having an expiration date (b) (4); the subject kit is labeled (b) (4)

The above concerns will be expressed within an information request to the sponsor.

Review Update: Needle Specifications

Within a 1/20/2015 information request, the sponsor was asked to provide information on how the co-packaged needles were verified to perform as intended with the pre-filled syringe component as well as how needle expiration would be factored into larger kit expiration. Within a 2-2-15 submission, the

sponsor responded to both questions and also provided letter of authorization to reference the needle 510(k) submissions:

For the functional assessment and connectivity, the sponsor provided assessments of dose accuracy for each needle length per each dose. The sponsor reported that, over 18 lots of tests, mean and standard deviation results for dose delivery are 99.3% and 1.137%, respectively. Additionally, testing was conducted per ISO594-2 for the syringe-needle interface and provided test reports demonstrating that the interface met the acceptance criteria outlined within the standard for liquid and air leakage, separation force, unscrewing torque, ease of assembly, resistance to overriding, and stress cracking. This is considered acceptable.

For the expiration date concern, the sponsor stated that there are in-process procedures in place to assure that a kit will not be labeled with an expiration date which is greater than that of the needles which are present within the package. This is considered acceptable.

Review of non-functional attributes of the primary and secondary container closure (i.e. syringe barrel, plunger, plunger rod, and flange components) including sterility and biocompatibility, is considered as differed to CDER's Office of Product Quality per a 3/24/15 email discussion with Wendy I. Wilson-Lee, Ph.D., Branch Chief (Actg), Branch 1, FDA/OMPT/CDER/OPQ/ONDP/DNDP1.

Combination Product Verification Activities

Initial System Verification:

Within the submission, the sponsor has not provided explicit evidence that combination product functional and dimensional characteristics are verified. Following from the section above, at this time, there are no clearly established system level device product requirements. This information will be requested of the sponsor within an information request.

Review Update: System Verification

Within a 1/20/2015 information request, the sponsor was asked to provide information which explicitly verifies functional requirements and specifications. The sponsor responded on 2-2-15 with the detailed design control information, including requirements and verification methods. Each requirement and corresponding verification method is shown below:

| Requirement Category | Ref. No. | Requirement Clause | Verification Method | Result |
|-----------------------|----------|--|---|--|
| Functional | A1 | The PFS with needle attached Shall deliver aripiprazole lauroxil drug product with an accuracy of $\pm (b)(4)\%$ as measured by HPLC or gravimetrically after a resuspension of not more than 10 taps and 30 seconds shaking. | Lab Test (T) | Requirement Met |
| Functional | A2 | The break loose force of the aripiprazole lauroxil PFS with needle attached Shall be $(b)(4)N$ when tested at a speed of $(b)(4)mm/min$ | Lab Test (T) Verification against more stringent drug product specification | Requirement Met |
| Functional | A3 | The glide force of the PFS Shall be $< (b)(4)N$ when tested at a speed of $(b)(4)mm/min$ | Lab Test (T) Verification against more stringent drug product specification | Requirement Met |
| Functional | A4 | The plunger rod Shall not become detached from the plunger when plunger is withdrawn at a rate of $(b)(4)mm/min$ | Lab Test (T) | Did Not Meet Requirement (see Section 2.1.1) |
| Functional | A5 | If the dose is equal to or greater than 662 mg the PFS Shall be able to inject $(b)(4)\%$ of the intended dose (gravimetric weight) into a resistance model using a 20G needle after a resuspension of not more than 10 taps and 30 seconds shaking. | Lab Test (T) | Requirement Met |
| Functional | A6 | If the dose is equal to or less than 441 mg the PFS Shall be able to inject $(b)(4)\%$ of the intended dose (gravimetric weight) into a resistance model using a 21G needle after a resuspension of not more than 10 taps and 30 seconds shaking. | Lab Test (T) | Requirement Met |
| Functional | A7 | The plunger of the PFS Shall not move greater than $(b)(4)mm$ from its initial position | Lab Test (T) | Requirement Met |
| Functional | A8 | The PFS when filled with media Shall not exhibit microbial growth for $(b)(4)$ days | Lab Test (T) | Requirement Met |
| Functional | A9 | The PFS when filled with media Shall not exhibit microbial growth for $(b)(4)$ days after exposure to a challenge organism suspension | Lab Test (T) | Requirement Met |
| Functional | A10 | The contents of the PFS Shall be sterile when tested by USP <71> | Lab Test (T) | Requirement Met |
| | A11 | The detachment torque of the needle from the syringe barrel when attached according to ISO 594-2 Shall be less than $(b)(4)Nm$. | Lab Test (T) | Requirement Met |
| User | B1 | The aripiprazole lauroxil PFS with needle attached Should be suitable for single-handed injection. | "Should" requirements intended for guidance only. | Verification not required. |
| | B2 | The aripiprazole lauroxil PFS with needle attached Shall be operable by both left-handed and right-handed healthcare professionals. | User Study (T) | Requirement Met |
| | B3 | Healthcare professionals Should be able to use the aripiprazole lauroxil kit without training. | User Study (T) | Requirement Met |
| | B4 | Healthcare professionals Shall be able to differentiate needles for deltoid injection from needles for gluteal injection. | User Study (T) | Requirement Met |
| Interface | C1 | Connection of the needle and syringe barrel Shall be achieved by means of a Luer lock connection in accordance with ISO 594. | Vendor component specification indicating ISO 594 compliance (R) | Requirement Met |
| | C2 | Connection of the plunger and plunger rod Shall be achieved by means of a threaded connection in accordance with ISO 11040-5. | Vendor component specification compared to ISO 11040-5 (R) | Requirement Met |
| Regulatory and Safety | D1 | Any leachables $(b)(4)$ from the aripiprazole lauroxil Primary Container Closure Shall not present a human safety risk. | Lab Test (T) | Requirement Met |
| | D2 | The adsorption of drug product or excipients onto aripiprazole lauroxil Primary Container Closure components Shall be such that drug product specifications are met. | Lab Test (T) Verification of drug product specifications after exposure to primary container closure components | Requirement Met |
| | D3 | The adsorption of drug product or excipients onto aripiprazole lauroxil Primary Container Closure components Shall be such that aripiprazole lauroxil PFS operates to specification | Lab Test (T) Verification of A1, A2, A3, A5, A6 after exposure of primary container closure components to drug product | Requirement Met |

| | | | | |
|-----------------------|-----|--|--|-----------------|
| Regulatory and Safety | D4 | The aripiprazole lauroxil Primary Container Closure Shall show no signs of corrosion when in contact with drug product for duration of at least (b) (4) months. | Inspection of combination product to verify product has no metal components and cannot corrode (I) | Requirement Met |
| | D5 | The aripiprazole lauroxil Primary Container Closure Should show no signs of corrosion when in contact with drug product for duration of at least (b) (4) months. | Inspection of combination product to verify product has no metal components and cannot corrode (I) | Requirement Met |
| | D6 | All drug contacting surfaces of the aripiprazole lauroxil Primary Container Closure components Shall be essentially free of particles and extraneous matter. | Review of vendor documentation (R) | Requirement Met |
| | D7 | The plunger Shall conform to dimensional constraints outlined in ISO 11040-5. | Dimensional inspection compared to ISO 11040-5 (R) | Requirement Met |
| | D8 | The plunger Shall conform to USP <381> | Vendor component specification indicating USP <381> compliance (R) | Requirement Met |
| | D9 | The syringe barrel Shall conform to dimensional constraints outlined in ISO 11040-6. | Dimensional inspection compared to ISO 11040-6 (R) | Requirement Met |
| | D10 | The syringe barrel Shall conform to USP <661> | Vendor component specification indicating USP <661> compliance (R) | Requirement Met |
| | D11 | The needles contained in the aripiprazole lauroxil kit Shall each employ a needle safety guard in accordance with ISO 23908. | Vendor component specification indicating ISO 23908 compliance (R) | Requirement Met |
| | D12 | The aripiprazole lauroxil tip cap Shall conform to USP <381>. | Vendor component specification indicating USP <381> compliance (R) | Requirement Met |
| | D13 | The needle Shall conform to ISO 7864. | Vendor component specification indicating ISO 7864 compliance (R) | Requirement Met |

| Requirement Category | Ref. No. | Requirement Clause | Verification Method | Result |
|--------------------------|-----------------------|--|--|---|
| Regulatory and Safety | D14 | Any color coding elements of the needle Shall conform to ISO 6009. | Vendor component specification indicating ISO 6009 compliance (R) | Requirement Met |
| | D15 | All administration needles Shall by complaint with ISO 10993 | Review 510k indicating ISO 10933 compliance (R) | Requirement Met |
| | D16 | The dead space of the aripiprazole lauroxil PFS Shall be less than (b) (4) mL. | Lab Test (T) ISO 7886-1 Annex C | Requirement Met |
| | D17 | The PFS Shall prevent liquid leakage past the plunger and tip cap when pressurized to (b) (4) kPa for a period of (b) (4) seconds. | Lab Test (T) ISO 7886-1 Annex D | Requirement Met |
| | D18 | The PFS with needle attached Shall prevent liquid leakage at the needle/syringe interface when pressurized to (b) (4) kPa for a period of (b) (4) seconds. | Lab Test (T) ISO 594-2, section 5.2 | Requirement Met |
| | D19 | The needle and syringe barrel Shall have a separation force of at least (b) (4) N. | Lab Test (T) ISO 594-2, section 5.4 | Requirement Met |
| | D20 | The torque required to correctly attach the needle and syringe barrel Shall be less than (b) (4) Nm. | Lab Test (T) ISO 594-2, section 5.6 | Requirement Met |
| | D21 | The needle Shall remain attached to the syringe barrel after application of an unscrewing torque of (b) (4) Nm for (b) (4) seconds. | Lab Test (T) ISO 594-2, section 5.5 | Requirement Met |
| | D22 | Application of a torque of (b) (4) Nm for (b) (4) seconds on the needle of the aripiprazole lauroxil PFS with needle attached Shall not override the threads of the syringe or the lugs of the needle. | Lab Test (T) ISO 594-2, section 5.7 | Requirement Met |
| | D23 | There Shall be no evidence of stress cracking when the needle is attached with a torque of at least (b) (4) Nm. | Lab Test (T) ISO 594-2 section 5.7 | Requirement Met |
| | D24 | All drug contacting components of the aripiprazole lauroxil PFS with needle attached Shall be sterile (b) (4) per ISO 11135 or ISO 11137. | Vendor component specification indicating sterility of components (R) | Requirement Met |
| | Operation Environment | E1 | The aripiprazole lauroxil PFS Shall operate to specification at a temperature range of 15°C to 30°C. | Lab Test (T) Verification of A1, A2, A3, A4, A5, A6 at 15°C and 30°C |
| Operation Lifetime | F1 | The aripiprazole lauroxil PFS with needle attached Shall be suitable for single use. | Review of drug product fill weight targets to confirm PFS contains only one dose of drug (R) | Requirement Met |
| Maintenance and Disposal | G1 | The aripiprazole lauroxil PFS with needle attached Shall be able to be disposed of according to standard medical waste sharps disposal procedures in the clinical setting. | User Study (T) | Requirement Met |
| Manufacturability | H1 | The aripiprazole lauroxil Primary Container Closure Shall be suitable (b) (4) | Review of process validation for syringe filling (R) | Requirement Met |
| | H2 | The syringe barrels Shall be provided (b) (4) | Vendor component specification indicating packaging method (R) | Requirement Met |
| | H3 | The syringe barrel and label Shall be suitable (b) (4) | Lab test of units (b) (4) (T) | Requirement Met |
| | H4 | The plunger rod Shall be suitable (b) (4) to the plunger. | Lab test of units (b) (4) (T) | Did Not Meet Requirement (see Section 2.1.1) |
| Labeling | J1 | All aripiprazole lauroxil kit labeling Shall be printed in English. | Visual inspection of labeling language (I) | Requirement Met |
| | J2 | Any leachables from the aripiprazole lauroxil (b) (4) Shall not present a human safety risk. | Lab Test (T) | Requirement Met |
| | J3 | Healthcare professionals Shall be able to visually distinguish between aripiprazole lauroxil dosages. | User Study (T) | Requirement Met |
| | J4 | The aripiprazole lauroxil kit DFU Shall include needle selection criteria based on injection site. | Visual inspection of DFU information (I) | Requirement Met |
| | J5 | Contents of aripiprazole lauroxil labeling Shall be compliant with relevant code of federal regulations | Labeling compliance review document (R) | Requirement Met |

| Requirement Category | Ref. No. | Requirement Clause | Verification Method | Result |
|----------------------|----------|---|---|---|
| Labeling | J6 | The aripiprazole lauroxil PFS label will remain intact and legible post removal from the tray. | Visual assessment of label post removal from tray (T) | Did Not Meet Requirement (see Section 2.1.2) |
| Packaging | K1 | All needle components Shall be packaged to maintain sterility until opened by the clinician. | Vendor component specification review indicating sterility (R) | Requirement Met |
| | K2 | The aripiprazole lauroxil kit external packaging Shall allow for the inclusion of the following components: Aripiprazole lauroxil PFS (2) or (3) Needles Labeling/ Printed Components | Visual confirmation of items in kit (I) | Requirement Met |
| | K3 | The aripiprazole lauroxil kit external packaging Shall include (b) (4) | Visual confirmation (b) (4) (I) | Requirement Met |
| | K4 | The aripiprazole lauroxil kit packaging Shall secure the PFS in a horizontal orientation when the kit is in its intended orientation. | Visual confirmation of PFS orientation (I) | Requirement Met |
| | K5 | The aripiprazole lauroxil kit external packaging will function to protect the aripiprazole lauroxil PFS from visually apparent damage after being subjected to simulated shipping as outlined in ASTM D4169 in intended shipping packaging. | Visual assessment of damage post simulated shipping (T) | Requirement Met |
| | K6 | Syringe will remain in correct position within tray after aripiprazole lauroxil kit external packaging is subjected to simulated shipping as outlined in ASTM D4169 in intended shipping packaging. | Visual assessment of syringe position post simulated shipping (T) | Requirement Met |
| | K7 | Tray insert will remain in correct position above syringe after aripiprazole lauroxil kit external packaging is subjected to simulated shipping as outlined in ASTM D4169 in intended shipping packaging. | Visual assessment of tray insert position post simulated shipping (T) | Requirement Met |
| Requirement Category | Ref. No. | Requirement Clause | Verification Method | Result |
| Storage | L1 | The aripiprazole lauroxil PFS Shall operate to specification after a kit shelf life of (b) (4) months at USP controlled room temperature. | Verify A1, A2, A3, A4, A10, D1, D2 and J2 after storage condition (T) | A1, D1, J2, D2, A10 Requirements Met A2, A3, and A4 Requirements - In Progress (see Section 2.1.3) |
| | L2 | The aripiprazole lauroxil PFS Should operate to specification after a kit shelf life of (b) (4) months at USP controlled room temperature. | Verify A1, A2, A3, A4, A10, D1, D2 and J2 after storage condition (T) | A1, D1, J2, D2, A10 Requirements Met A2, A3, and A4 Requirements - In Progress (see Section 2.1.3) |
| | L3 | The aripiprazole lauroxil PFS Shall operate to specification after kit storage at a temperature range (b) (4) | Verify A1, A2, A3, A4, A5, A6, D1, D2, and J2 after exposure to (b) (4) (T) | A1, A2, A3, A5, A6, D1, D2, J2 requirements met. Did not meet A4 requirement. (see Section 2.1.4) |
| Transport | M1 | The aripiprazole lauroxil PFS Shall operate to specification after being subjected to vibration conditions outlined in ASTM D4169 in intended shipping packaging. | Verify A1, A2, A3, A4, A5, A6, and A8 after post simulated shipping (T) | Requirement Met |
| | M2 | The aripiprazole lauroxil PFS Shall operate to specification after being subjected to drop conditions outlined in ASTM D4169 in intended shipping packaging. | Verify A1, A2, A3, A4, and A8 after post simulated shipping (T) | Requirement Met |
| | M3 | The aripiprazole lauroxil PFS Shall operate to specification after exposure of the PFS to an absolute pressure range (b) (4) | Verify A8 and A9 after exposure to reduced pressure (T) | Requirement Met |

The above listing was considered to be acceptable for a summary/abbreviated trace table, however the reviewer noted that no test reports were presented to support the conclusions made. The reviewer also noted that several table elements referenced verification as not being satisfied. Within a 4-1-15 response, the sponsor addressed both reviewer concerns.

Verification Test Reports

The sponsor provided an updated trace table within their 4-1-15 supplement which included reference to test reports (included within the response record) as well as an enhanced summary of acceptance criteria and results. This table is included below:

| Design Input Requirement | Test Report | Test Method | Criteria | Result |
|--|-----------------------------|--------------------|--|--|
| The PFS with needle attached Shall be able to deliver (b) (4) % of intended aripiprazole lauroxil drug product dose as measured by HPLC or gravimetrically after a resuspension of not more than 10 taps and 30 seconds shaking. | 702-03671/ Section 7.2.1 | Lab Test (T) | (b) (4) % nominal g per dose 441 mg: (b) (4) g (b) (4) g 662 mg: (b) (4) g (b) (4) g 882 mg: (b) (4) g (b) (4) g | All doses verified with 95/95% reliability and confidence. Calculated intervals: 441 mg: (b) (4) g 662 mg: (b) (4) g 882 mg: (b) (4) g |
| The break loose force of the PFS with needle attached Shall be (b) (4) N when tested at a speed of (b) (4) mm/min (b) (4) (b) (4) | 702-03671/ Section 7.2.2 | Lab Test (T) | No more than (NMT) (b) (4) N Verification against more stringent drug product specification | All doses verified with 95/95% reliability and confidence. Calculated Intervals: 441 mg: (b) (4) N 662 mg: (b) (4) N 882 mg: (b) (4) N |
| The glide force of the PFS Shall be (b) (4) N when tested (b) (4) (b) (4) at a speed of (b) (4) mm/min (b) (4) (b) (4) | 702-03671/ Section 7.2.2 | Lab Test (T) | NMT (b) (4) N Verification against more stringent drug product specification | All doses verified with 95/95% reliability and confidence. Calculated upper intervals: 441 mg: (b) (4) N 662 mg: (b) (4) N 882 mg: (b) (4) N |
| The plunger rod Shall not become detached from the plunger when plunger is withdrawn (b) (4) mm at a rate of (b) (4) mm/min. | 702-03671/ Section 6.5 | Lab Test (T) | The plunger rod may not detach from the plunger with an AQL of (b) (4) % per special inspection (b) (4) (b) (4) (b) (4) | No detachment with an AQL of (b) (4) % per special inspection (b) (4) (0 failures/ (b) (4) samples) |
| Design Input Requirement | Test Report | Test Method | Criteria | Result |
| If the dose is equal to or greater than 662 mg the PFS Shall be able to inject (b) (4) (b) (4) % of the intended aripiprazole lauroxil drug product dose (gravimetric weight) into a resistance model using a 20G needle after a resuspension of not more than 10 taps and 30 seconds shaking. | 702-03671/ Section 7.2.1 | Lab Test (T) | (b) (4) % nominal g per dose 662 mg: (b) (4) g (b) (4) g 882 mg: (b) (4) g (b) (4) g | 662 and 882 mg doses verified with 95/95% reliability and confidence. Calculated intervals: 662 mg: (b) (4) g 882 mg: (b) (4) g |
| If the dose is equal to or less than 441 mg the PFS Shall be able to inject (b) (4) (b) (4) % of the intended aripiprazole lauroxil drug product dose (gravimetric weight) into a resistance model using a 21G needle after a resuspension of not more than 10 taps and 30 seconds shaking. | 702-03671/ Section 7.2.1 | Lab Test (T) | (b) (4) % nominal g per dose 441 mg: (b) (4) g (b) (4) g | 441 mg doses verified with 95/95% reliability and confidence. Calculated interval: 441 mg: (b) (4) g |
| The plunger of the PFS Shall not move greater than (b) (4) mm from its initial position (b) (4) (b) (4) | 702-06599/ Section 4.0 | Lab Test (T) | Plunger movement NMT (b) (4) mm from its initial position. | All doses verified with 90/95% reliability and confidence. (0 failures/ (b) (4) or 0 failures/ (b) (4) samples) |
| The PFS when filled with media Shall not exhibit microbial growth for (b) (4) days | 702-03670/ Section 6.0 | Lab Test (T) | Media must show no signs of microbial growth. | No microbial growth (0 failures/ (b) (4) samples) |

| Design Input Requirement | Test Report | Test Method | Criteria | Result |
|--|--|--|---|---|
| The PFS when filled with media Shall not exhibit microbial growth for (b) (4) days after exposure to a challenge organism suspension | 702-03619/ Section 7.2 | Lab Test (T) | No detectable microbial growth | Verified with 90/95% reliability and confidence. No microbial (b) (4) growth (0 failures (b) (4) samples) |
| The contents of the PFS Shall be sterile when tested by USP <71> | 700-02634/ Table 7-8 | Lab Test (T) | No microbial growth (sample size \geq (b) (4) tested per USP <71> guidance) | No microbial growth at (b) (4) months. (0 failures (b) (4) samples) |
| The detachment torque of the needle from the syringe barrel when attached according to ISO 594-2 Shall be less than (b) (4) Nm. | 700-02850/ Section 5.0 | Lab Test (T) Per ISO 594-2 | Detachment torque <(b) (4) Nm | All needles verified with 95/95% reliability and confidence. Calculated upper intervals: 20G×2-inch: (b) (4) Nm 20G×1.5-inch: (b) (4) Nm 21G×1-inch: (b) (4) Nm |
| The PFS with needle attached Should be suitable for single-handed injection. | No data collected | N/A | N/A | Verification not required for "Should" requirement. |
| The PFS with needle attached Shall be operable by both left-handed and right-handed healthcare professionals. | Sequence 0000 702-03645/ Section 6.2 | User Study (T) | Acceptable user performance demonstrated on critical tasks by representative end user population. | Risk assessment evaluation of performance indicates residual risk outweighed by benefits of device (per summative report). |
| Healthcare professionals Should be able to use the aripiprazole lauroxil kit without training. | Sequence 0000 702-03645/ Section 1.4 | User Study (T) | Acceptable user performance demonstrated on critical tasks without training. | Risk assessment evaluation of performance indicates residual risk outweighed by benefits of device (per summative report). |
| Design Input Requirement | Test Report | Test Method | Criteria | Result |
| Healthcare professionals Shall be able to differentiate needles for deltoid injection from needles for gluteal injection | Sequence 0000 702-03645/ Section 6.6 | User Study (T) | Acceptable user performance on needle and site selection. | Risk assessment evaluation of performance indicates residual risk outweighed by benefits of device (per summative report). |
| Connection of the needle and syringe barrel Shall be achieved by means of a Luer lock connection in accordance with ISO 594. | 700-02866/ Table 7 | Review (R) Vendor component specification | Confirmation of ISO 594 components selected. | ISO 594 compliant components confirmed via vendor specification. |
| Connection of the plunger and plunger rod Shall be achieved by means of a threaded connection in accordance with ISO 11040-5. | 700-02866/ Table 7 | Review (R) Vendor component specification | Confirmation of ISO 11040-5 components selected. | ISO 11040-5 compliant components confirmed via vendor specification. |
| Any leachables, including head space volatile compounds, from the Primary Container Closure Shall not present a human safety risk. | 702-03314/ Section 5.4– 5.6 | Lab Test (T) | All observed leachables are considered safe at the measured concentrations | The observed leachable species are not considered to pose any human safety risk at the anticipated levels. |
| The adsorption of drug product or excipients onto Primary Container Closure components Shall be such that drug product specifications are met. | 700-02634/ Table 5-22 | Lab Test (T) Verification of drug product specifications after exposure to primary container closure components | All drug product specifications meet requirements at T0. | All drug product specifications meet requirements at T0. |

| Design Input Requirement | Test Report | Test Method | Criteria | Result |
|--|-----------------------------|---|--|--|
| The adsorption of drug product or excipients onto Primary Container Closure components Shall be such that PFS operates to specification | 702-03671/ Section 7.2.3 | Lab Test (T) Verification of A1, A2, A3, A5, A6 after exposure of primary container closure components to drug product | Verification of A1, A2, A3, A5, A6 per individual test criteria | A1, A2, A3, A5, and A6 meet requirements. |
| The Primary Container Closure Shall show no signs of corrosion when in contact with drug product for duration of at least (b) (4) months. | 700-02849/ Table 2 | Inspection (I) Verify product has no metal components and cannot corrode | No metal components in contact with drug product | No metal components in contact with drug product |
| The Primary Container Closure Should show no signs of corrosion when in contact with drug product for duration of at least (b) (4) months. | 700-02849/ Table 2 | Inspection (I) Verify product has no metal components and cannot corrode | No metal components in contact with drug product | No metal components in contact with drug product |
| All drug contacting surfaces of the Primary Container Closure components Shall be essentially free of particles and extraneous matter. | 700-02866/ Table 6 | Review (R) Vendor Certificate of Analysis (C of A) | Confirmation of acceptable level of particles per vendor C of A. | Vendor C of A confirmed to check for acceptable level of particles. |
| Design Input Requirement | Test Report | Test Method | Criteria | Result |
| The plunger Shall conform to dimensional constraints outlined in ISO 11040-5. | 700-02866/ Table 4 | Review (R) Dimensional inspection | Confirmation of ISO 11040-5 compliant plunger dimensions. | All plunger dimensions except height in compliance with ISO 11040-5. Height requirement waived due to confirmation of plunger to syringe compatibility through dead space testing as documented in 700-02850 Section 4.0 |
| The plunger Shall conform to USP <381> | 700-02866/ Table 4 | Review (R) Vendor component specification | Confirmation of USP <381> compliant plunger selected. | USP <381> compliance confirmed via vendor specification. |
| The syringe barrel Shall conform to dimensional constraints outlined in ISO 11040-6. | 700-02866/ Table 3 | Review (R) Dimensional inspection | Confirmation of ISO 11040-6 compliant syringe barrel dimensions. | ISO 11040-6 compliance confirmed via vendor specification. |
| The syringe barrel Shall conform to USP <661> | 700-02866/ Table 3 | Review (R) Vendor component specification | Confirmation of USP <661> compliant syringe barrel selected. | USP <661> compliance confirmed via vendor specification. |
| The needles contained in the aripiprazole lauroxil kit Shall each employ a needle safety guard in accordance with ISO 23908. | 700-02866/ Table 5 | Review (R) Vendor component specification | Confirmation of ISO 23908 needle safety guard. | ISO 23908 compliance confirmed via vendor specification. |
| The aripiprazole lauroxil tip cap Shall conform to USP <381> | 700-02866/ Table 3 | Review (R) Vendor component specification | Confirmation of USP <381> compliant tip cap. | USP <381> compliance confirmed via vendor specification. |

| Design Input Requirement | Test Report | Test Method | Criteria | Result |
|---|----------------------------------|---|--|--|
| The needle Shall conform to ISO 7864. | 700-02866/ Table 5 | Review (R) Vendor component specification | Confirmation of ISO 7864 compliance for needle. | ISO 7864 compliance confirmed via vendor specification. |
| Any color coding elements of the needle Shall conform to ISO 6009. | 700-02866/ Table 5 | Review (R) Vendor component specification | Confirmation of ISO 6009 color coding on needle components. | ISO 6009 compliance confirmed via vendor specification. |
| All administration needles Shall be compliant with ISO 10933 | 700-02866/ Table 5 | Review (R) Vendor component specification | Confirmation of ISO 10933 compliant needles. | ISO 10993 compliance confirmed via vendor specification. |
| The dead space of the PFS Shall be less than (b) (4) mL. | 700-02850/ Section 4.0 | Lab Test (T) Per ISO 7886-1 | Dead space < (b) (4) mL. | Verified with 95/95% reliability and confidence. Calculated upper interval: (b) (4) mL. |
| The PFS Shall prevent liquid leakage past the plunger and tip cap when pressurized to (b) (4) kPa for a period of (b) (4) seconds. | 700-02780/ Table 11 | Lab Test (T) Per ISO 7886-1 | No leakage past the (b) (4) seal. | Verified with 90/95% reliability and confidence. (0 failures/ (b) (4) samples) |
| The PFS with needle attached Shall prevent liquid leakage at the needle/syringe interface when pressurized to (b) (4) kPa for a period of (b) (4) seconds. | 700-02780/ Table 4 | Lab Test (T) Per ISO 594-2 | No leakage through the Luer interface | All needles verified with 90/95% reliability and confidence. (0 failures/ (b) (4) samples) |
| The needle and syringe barrel Shall have a separation force of at least (b) (4) N. | 700-02780/ Table 6 | Lab Test (T) Per ISO 594-2 | No detachment of needle from syringe | All needles verified with 90/95% reliability and confidence. (0 failures/ (b) (4) samples) |
| Design Input Requirement | Test Report | Test Method | Criteria | Result |
| The torque required to correctly attach the needle to syringe barrel Shall be less than (b) (4) Nm. | 700-02780/ Table 8 | Lab Test (T) Per ISO 594-2 | Luer interface fully engaged | All needles verified with 90/95% reliability and confidence. (0 failures/ (b) (4) samples) |
| The needle Shall remain attached to the syringe barrel after application of an unscrewing torque of (b) (4) Nm for (b) (4) seconds | 700-02780/ Table 7 | Lab Test (T) Per ISO 594-2 | No detachment of needle from syringe during (b) (4) sec exposure to (b) (4) Nm unscrewing torque | All needles verified with 90/95% reliability and confidence. (0 failures/ (b) (4) samples) |
| Application of a torque of (b) (4) Nm for (b) (4) seconds on the needle or the PFS Shall not override the threads of the syringe or the lugs of the needle. | (b) (4) 700-02780/ Table 9 | Lab Test (T) Per ISO 594-2 | No override of threads or lugs within Luer interface | All needles verified with 90/95% reliability and confidence. (0 failures/ (b) (4) samples) |
| There shall be no evidence of stress cracking after the needle is attached with a torque of at least (b) (4) Nm | 700-02780/ Table 10 | Lab Test (T) Per ISO 594-2 | No stress cracking within Luer interface | All needles verified with 90/95% reliability and confidence. (0 failures/ (b) (4) samples) |
| All drug contacting components of the PFS Shall be sterile (b) (4) per ISO 11135 or ISO 11137. | 700-02866/ Table 6 | Review (R) Vendor component specification | Confirmation of sterility of drug contacting components. | ISO 11137 compliance confirmed via vendor specification. |
| The PFS Shall operate to specification at a temperature range of 15°C to 30°C. | 702-03679/ Section 7.0 | Lab Test (T) Verification of A1, A2, A3, A5, A6 at 15°C and 30°C | Verification of A1, A2, A3, A5, A6 per individual test criteria | A1, A2, A3, A5, and A6 verified with 95/95% reliability and confidence. |
| The PFS Shall be suitable for single use. | 700-02866/ Table 9 | Review (R) Drug product fill weights | Confirmation that mg/dose and mg/PFS are the same. | Confirmed mg/dose and mg/PFS match (single dose in each PFS). |

| Design Input Requirement | Test Report | Test Method | Criteria | Result |
|---|--|---|--|--|
| The PFS Shall be able to be disposed of according to standard medical waste sharps disposal procedures in the clinical setting. | Sequence 0000 702-03645/ Section 6.6 | User Study (T) | Acceptable user performance on disposal task. | Risk assessment evaluation of performance indicates residual risk outweighed by benefits of device (per summative report). |
| The Primary Container Closure Shall be suitable (b) (4) | 700-02866/ Table 10 | Review (R) Process Validation | PQ validation complete for all doses on filling line. | Confirmed PQ validation complete for all doses. |
| The syringe barrels Shall be provided (b) (4) | 700-02866/ Table 3 | Review (R) Vendor component specification | Confirmation of (b) (4) shipping configuration. | Confirmed (b) (4) shipping configuration. |
| The syringe barrel and syringe label Shall be suitable (b) (4) | 702-03671/ Section 7.2.4 | Lab Test (T) of units (b) (4) | Visual inspection per acceptable quality levels (AQL): Critical - AQL = (b) (4) % Major - AQL = (b) (4) % Minor - AQL = (b) (4) % | Verified to acceptable AQLs. |
| The plunger rod Shall be suitable (b) (4) | 702-03671/ Section 7.2.4 | Lab Test (T) of units (b) (4) | The plunger rod may not detach from the plunger with an AQL of (b) (4) % per special inspection (b) (4) | No detachment with an AQL of (b) (4) % per special inspection (b) (4) (0 failures/ (b) (4) samples) |
| All aripiprazole lauroxil kit labeling Shall be printed in English. | 700-02866/ Table 8 | Inspection (I) Label | Confirmation of labels printed in English. | Confirmed labels printed in English. |
| Design Input Requirement | Test Report | Test Method | Criteria | Result |
| Any leachables from the aripiprazole lauroxil (b) (4) Shall not present a human safety risk. | 702-03314/ Section 5.7 | Lab Test (T) | All observed leachables are considered safe at the measured concentrations | The observed leachable species are not considered to pose any human safety risk at the anticipated levels. |
| Healthcare professionals Shall be able to visually distinguish between aripiprazole lauroxil dosages. | Sequence 0000 702-03645/ Section 6.6 | User Study (T) | Acceptable user performance on dose selection task. | Risk assessment evaluation of performance indicates residual risk outweighed by benefits of device (per summative report). |
| The aripiprazole lauroxil kit DFU Shall include needle selection criteria based on injection site. | 700-02866/ Table 8 | Inspection (I) DFU | Confirmation of presence of needle selection criteria in DFU. | Confirmed DFU includes needle selection criteria. |
| Contents of aripiprazole lauroxil labeling Shall be compliant with relevant code of federal regulations | 700-02866/ Table 8 | Review (R) Label compliance document | Confirmation of regulatory approval of labeling documents. | Confirmed regulatory approval of all labeling documents. |
| The PFS label Shall remain intact and legible post removal from the tray, | 702-03671/ Section 7.2.5 | Lab Test (T) of units assembled on automated line | Visual inspection per acceptable quality levels (AQL): Critical - AQL = (b) (4) % Major - AQL = (b) (4) % Minor - AQL = (b) (4) % | Verified to acceptable AQLs. |
| All needle components Shall be packaged to maintain sterility until opened by the clinician. | 700-02866/ Table 5 | Review (R) Vendor component specification | Confirmation needles are sterile and individually packaged. | Confirmed needles are sterile and individually packaged. |

| Design Input Requirement | Test Report | Test Method | Criteria | Result |
|---|-------------------------------|--|---|---|
| The aripiprazole lauroxil kit external packaging Shall allow for the inclusion of the following components: - (1) Aripiprazole lauroxil PFS - (2) or (3) Needles - Labeling/ Printed Components | 700-02849/ Table 3 | Inspection (I) Kit contents | Kit contains 1 aripiprazole lauroxil PFS (of the dose indicated on the carton), needles (2 or 3), and labeling/ printed components. | Kit contents are as specified. |
| The aripiprazole lauroxil kit external packaging Shall include (b) (4) | 700-02849/ Table 3 | Inspection (I) (b) (4) | Kit includes (b) (4) (b) (4) | Kit includes (b) (4) (b) (4) |
| The aripiprazole lauroxil kit packaging Shall secure the PFS in a horizontal orientation when the kit is in its intended orientation. | 700-02849/ Table 3 | Inspection (I) PFS orientation | The kitted PFS is in a horizontal orientation when the package is in the intended orientation. | The kitted PFS is in a horizontal orientation when the package is in the intended orientation. |
| The aripiprazole lauroxil kit external packaging will function to protect the PFS from visually apparent damage after being subjected to simulated shipping as outlined in ASTM D4169 in intended shipping packaging. | 702-06590/ Section 7.1 | Lab Test (T) Visual assessment post shipping | No visually apparent damage such as discoloration, swelling, shrinking, leakage, or cracking associated with the syringe | Verified with 90.95% reliability and confidence. (0 failures/ (b) (4) samples) |
| Syringe will remain in correct position within tray after aripiprazole lauroxil kit external packaging is subjected to simulated shipping as outlined in ASTM D4169 in intended shipping packaging. | 702-06590/ Section 7.2 | Lab Test (T) Visual assessment post shipping | Syringe secure and aligned in tray after shipping | Verified with 90.95% reliability and confidence. (0 failures/ (b) (4) samples) |
| Design Input Requirement | Test Report | Test Method | Criteria | Result |
| Tray insert will remain in correct position above syringe after aripiprazole lauroxil kit external packaging is subjected to simulated shipping as outlined in ASTM D4169 in intended shipping packaging. | 702-06590/ Section 7.2 | Lab Test (T) Visual assessment post shipping | Tray insert aligned in tray after shipping | Verified with 90.95% reliability and confidence. (0 failures/ (b) (4) samples) |
| The PFS Shall operate to specification after a kit shelf life of (b) (4) months at USP controlled room temperature. | 700-02634/ Section 7.0 | Lab Test (T) Verify A1, A10, and D2 after storage condition | Verification of A1, A10, and D2 per individual test criteria | A1, A10, and D2 meet requirements after 15 months storage. Statistical extrapolation of data per ICH supports a (b) (4) month shelf life. |
| | 702-03314/ Section 5.4-5.7 | Lab Test (T) Verify D1 and J2 after storage condition | All observed leachables are considered safe at the measured concentrations | The observed leachable species after 6 month storage at (b) (4) C are not considered to pose any human safety risk at the anticipated levels. |
| | A2, A3, A4 - In Progress | Lab Test (T) Verify A2, A3, A4 after storage condition | Verification of A2, A3, and A4 per individual test criteria | In progress |
| The PFS Should operate to specification after a kit shelf life of (b) (4) months at USP controlled room temperature. | 700-02634/ Section 7.0 | Lab Test (T) Verify A1, A10, and D2 after storage condition | Verification of A1, A10, and D2 per individual test criteria | A1, A10, and D2 meet requirements after 15 months storage. Statistical extrapolation of data per ICH supports a (b) (4) month shelf life. |

| Design Input Requirement | Test Report | Test Method | Criteria | Result |
|--|-------------------------------|--|---|---|
| | 702-03314/ Section 5.4-5.7 | Lab Test (T) Verify D1 and J2 after storage condition | All observed leachables are considered safe at the measured concentrations | The observed leachable species after 6 months storage at (b) (4)°C are not considered to pose any human safety risk at the anticipated levels. |
| | A2, A3, A4 - In Progress | Lab Test (T) Verify A2, A3, A4 after storage condition | Verification of A2, A3, and A4 per individual test criteria | In progress |
| The PFS Shall operate to specification after kit storage at a temperature range (b) (4) | 702-06512/ Section 7.0 | Lab Test (T) Verify A1, A2, A3, A4, A5, and A6 after temperature exposure | Verification of A1, A2, A3, A4, A5, and A6 per individual test criteria | A1, A2, A3, A5, and A6 verified with 95/95% reliability and confidence. A4 verified to an AQL of (b) (4) per special inspection (b) (4) (0 failures/ (b) (4) samples) |
| | 700-02634/ Table 28-29 | Lab Test (T) Verify D2 after temperature exposure | All drug product specifications meet individual requirements after (b) (4) day temperature storage. | All drug product specifications meet requirements after (b) (4) (b) (4) |
| | 702-03314/ Section 5.4-5.7 | Lab Test (T) Verify D1 and J2 after temperature exposure | All observed leachables are considered safe at the measured concentrations | The observed leachable species after (b) (4) day storage at (b) (4)°C are not considered to pose any human safety risk at the anticipated levels. |
| Design Input Requirement | Test Report | Test Method | Criteria | Result |
| The PFS Shall operate to specification after being subjected to vibration conditions outlined in ASTM D4169 in intended shipping packaging. | 702-06599/ Section 4.3 | Lab Test (T) Verify A1, A2, A3, A4, A5 and A8 after simulated shipping | Verification of A1, A2, A3, A4, A5, and A8 per individual test criteria | A1, A2, A3, and A5 verified with 95/95% reliability and confidence. A4 and A8 verified with 90/95% reliability and confidence. (0 failures/ (b) (4) samples) |
| The PFS Shall operate to specification after being subjected to drop conditions outlined in ASTM D4169 in intended shipping packaging. | 702-06599/ Section 4.0 | Lab Test (T) Verify A1, A2, A3, A4, A5, and A8 after simulated shipping. | Verification of A1, A2, A3, A4, A5, and A8 per individual test criteria | A1, A2, A3, and A5 verified with 95/95% reliability and confidence. A4 and A8 verified with 90/95% reliability and confidence. (0 failures/ (b) (4) samples) |
| | 702-03619/ Section 6.0-7.0 | Lab Test (T) Verify A9 after exposure to (b) (4) pressure | No detectable microbial growth | Verified with 90/95% reliability and confidence. (0 failures/ (b) (4) samples) |
| The PFS Shall operate to specification after exposure of the PFS to an absolute pressure range (b) (4) (b) (4) | 702-06599/ Section 4.0 | Lab Test (T) Verify A8 after exposure to (b) (4) pressure | Media must show no signs of microbial growth. | Verified with 90/95% reliability and confidence. (0 failures/ (b) (4) samples) |

Each design requirement and its applicability acceptance criteria, and finally the outcome of each test were reviewed. Considerations for sterility, biocompatibility, and drug product quality were not

reviewed. All other attributes are considered acceptable with the exception of: "The PFS Shall operate to specification after a kit shelf life of (b) (4) months at USP controlled room temperature" and "The PFS Should operate to specification after a kit shelf life of (b) (4) months at USP controlled room temperature.", each of which are addressed within the next section of this memorandum.

Each of the above test reports were examined for the presence of evidence supporting the summary conclusions included within the trace table. Each test report or general report was found to be acceptable.

Outstanding Verification Activities

Within the verification documentation submitted on 2-2-15, the sponsor referenced several verification tests which were not representative of "pass" results. The sponsor was asked to provide evidence that these failures had been corrected or provide risk-based rationale for their acceptability.

In response, for two of the non-complaint observation, the sponsor made product corrections. These items were "The aripiprazole lauroxil PFS label will remain intact and legible post removal from the tray" and "The plunger rod shall not become detached from the plunger when plunger is withdrawn at a rate of (b) (4) mm/min".

For the intact label requirement, the sponsor (b) (4) According to test report document 702-03671, the change was implemented and verified in February 2015. This is considered acceptable.

For the plunger rod removal requirement, the sponsor attributes the prior failed product to (b) (4) No failures were observed after the process improvement as summarized within test summaries included in document 702-03671. This is considered acceptable.

Two verification activities that continue to be outstanding relate to functional assessment of the assembled system (plunger rod and needle affixed to the bulk PFS) after aging to period of (b) (4) months. The sponsor states that systems will be placed on aging protocols to satisfy this requirement, but that assessments completed to date on the fully assembled system (dose accuracy) along with complete aging studies, including glide force of the syringe, are sufficient to demonstrate aging stability for the fully assembled product.

The reviewer considers this position acceptable, but requests that post-marketing commitments be established to receive aging information for the fully-assembled system.

Verification after Aging and Shipping:

Aging:

To support functionality of the combination product after aging, the sponsor has completed an assessment of system attributes (b) (4) by shipping and (b) (4) by aging.

The sponsor believes that aging data currently available supports a (b) (4) month expiry (b) (4) They have provided fifteen (15) months of stability data at the long-term condition and six (6) months at accelerated conditions for the pre-filled syringe Registration Batches, and state that this information (b) (4)

To support functionality of the device constituent part over time, the sponsor has conducted three assessments of system functionality.

- Dose delivered
- Glide force
- Break loose force

Specifically, the sponsor plotted the specifications against with actual results of each functional test and performed regression analysis in order to demonstrate how much time it would take to exceed the stated specifications.

Figure 1: Dose Delivery Assay, % Label Claim



Figure 9: Glide Force

(b) (4)



The approach described within the submission appears acceptable; however the following information appears to be missing for shelf life/aging ^{(b) (4)}:

- Within Aripiprazole Lauroxil PFS Stability Summary, Statistical Analysis, and Shelf Life Estimation, the reviewer cannot locate stability algorithm/curve information for break loose force.

Review Update:

Within a 2-2-15 response, the sponsor provided a plot of break loose force versus natural log of time. This figure is shown below:

The sponsor also updated technical report 700-02634 to reflect this addition, which they state supports a shelf life of (b) (4) months for break loose force. This is considered acceptable to support the device attribute of break loose force.

- The sponsor has not clearly stated what device requirements are considered essential to monitor after aging.

Review Update:

Stability documentation submitted by the sponsor within section 3.2.P.8 indicate that device-relevant attributes of Dose Delivery Accuracy, Glide Force and Break Loose Force will be assessed under a real time aging program of (b) (4) months. This is acceptable.

- The sponsor states that device functionality assessments have been completed after artificial aging, but does not report the real-time equivalent reached in these studies.

Review Update:

Within a 2-2-15 response to the Agency, the sponsor stated that their accelerated aging protocols follow guidelines established under ICH Q1D Harmonized Tripartite guideline on Bracketing and Matrixing Design for Stability Testing of New Drug Substances and Products and that the study design was discussed during the 25 March 2013 Type C Meeting (IND 107,249, Seq. 0043). The sponsor states that the consistency of data received at each accelerated time point is indicative of reliable accelerated study parameters. The reviewer finds this acceptable from a device perspective, but notes that review of stability of the PFS is ultimately deferred to CDER.

Review Update:

Per the section of this memorandum describing design verification activities, the sponsor has committed to performing additional stability studies to examine the compatibility and fitment of package components. This will be requested under a post-approval commitment.

Shipping:

To support functionality of the combination product after aging, the sponsor has completed an assessment of excursion temperatures in shipping. Results of this testing, including freeze/thaw cycles and (b)(4) degree C exposure appear acceptable. The sponsor will be requested to provide evidence that the system is capable of withstanding the vibrational and atmospheric effects associated with shipping.

Review Update:

Within a 2-2-15 response to the Agency, the sponsor stated that they subjected the PFS to vibrational and atmospheric effects typically associated with shipping. They state that actual and simulated shipping studies were performed, and inject-ability (dose delivery) as well as visual inspection results demonstrated that the container closure integrity is robust to shipping stresses, such as temperature, vibration, and dropping (Section 4.3.4.3). They also state that (b)(4) testing involving media-filled syringes shown in section 3.2.P.2 further demonstrates container closure integrity following exposure to simulated (b)(4) shipment.

The reviewer finds this information acceptable

VI. Recommendation

The consulting reviewer recommends approval of the NDA in the context of device constituent parts for the combination product. The reviewer recommends one post-approval commitment, as described below:

Within NDA207533 Supplement 0015, submitted on April 1, 2015, the sponsor committed to performing ongoing stability analysis to assess mechanical reliability of the fully assembled device through the expiration date of the drug product using primary registration stability batches. The sponsor should submit evidence of completion of these activities to NDA annual reports.

VII. Concurrence Table

| Digital Signature Concurrence Table | |
|-------------------------------------|--|
| Reviewer Sign-Off | |
| Team Lead Sign-Off | |
| Branch Sign-Off | |

APPEARS THIS WAY ON ORIGINAL

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/s/

RYAN J MCGOWAN
07/09/2015



Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Pregnancy and Lactation Labeling Rule (PLLR) Labeling Review

Date: 7-6-2015

From: Leyla Sahin, MD
Medical Officer,
Division of Pediatric and Maternal Health, Maternal Health Team

Through: Tamara Johnson, M.D., M.S.
Acting Team Leader, Maternal Health Team
Division of Pediatric and Maternal Health

Lynne P. Yao, MD
Acting Director,
Division of Pediatric and Maternal Health

To: Division of Psychiatry Products

Drugs: Aristada (aripiprazole lauroxil) extended release intramuscular injection; NDA 207533

Subject: Pregnancy and Lactation Labeling Rule (PLLR) Conversion

Applicant: Alkermes

Materials Reviewed: • Applicant's proposed labeling
• Approved labeling for Abilify (reference listed drug)

Consult Question: Please advise regarding Pregnancy and Lactation Labeling Rule (PLLR) Conversion

INTRODUCTION

On August 22, 2014, the applicant submitted a 505(b)(2) application for Aristada (aripiprazole lauroxil), an atypical antipsychotic with a covalent modification of aripiprazole, for the treatment of schizophrenia. It has been developed as a new delivery system, in single dose pre-filled syringes, for intramuscular injection every 4-6 weeks. DPP consulted the Division of Pediatric and Maternal Health (DPMH) on January 15, 2015, to assist with reviewing the Pregnancy and Nursing Mothers subsections of labeling.

BACKGROUND

Product Background

Aristada (aripiprazole lauroxil) is a prodrug of aripiprazole. *In vivo* conversion of aripiprazole lauroxil to aripiprazole occurs by dissolution of the drug particles from the injection site. The referenced innovator drug, Abilify (aripiprazole), was approved in 2002, and is available as an oral tablet, oral disintegrating tablet, oral solution, and intramuscular injection. The oral formulations are indicated for treatment of schizophrenia, acute treatment of manic and mixed episodes associated with bipolar I, adjunctive treatment of major depressive disorder, irritability associated with autistic disorder, and treatment of Tourette's disorder. The injection is indicated for agitation associated with schizophrenia or bipolar mania.

Currently approved Abilify pregnancy labeling is in a hybrid format, modeled after the proposed Pregnancy and Lactation Labeling Rule, and includes developmental toxicity data in rats and rabbits at doses up to 10 times the maximum recommended oral dose, based on body surface area. Pregnancy labeling for Abilify also includes class labeling for antipsychotics regarding risks related to third trimester use and development of extrapyramidal and/or withdrawal symptoms in the neonate. This class labeling information was added by DPP in 2011.¹

Pregnancy and Lactation Labeling Rule (PLLR)

On December 4, 2014, the Food and Drug Administration (FDA) published the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,” also known as the Pregnancy and Lactation Labeling Rule (PLLR).² The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and a new subsection for information with regard to females and males of reproductive potential (if applicable). Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule, to include information about the risks and benefits of using these products during pregnancy and lactation. The PLLR officially took effect on June 30, 2015. The recommendations in this review are consistent with the PLLR format.

¹ <http://www.fda.gov/Drugs/DrugSafety/ucm243903.htm>

² Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling (79 FR 72063, December 4, 2014).

APPLICANT'S REVIEW OF PUBLISHED PREGNANCY AND LACTATION LITERATURE

The published literature on the safety of aripiprazole in pregnancy is limited to case reports and two small prospective cohort studies.³ A prospective cohort study of 56 pregnant women exposed to aripiprazole in the first trimester of pregnancy showed no increase in major malformations compared to an unexposed cohort of pregnant women in France.⁴

A prospective cohort study of pregnancy exposure to eight atypical antipsychotics conducted in Germany (44 pregnant women exposed to aripiprazole in the first trimester) showed an increase in major malformations compared to an unexposed cohort of pregnant women (adjusted odds ratio for aggregate data, 2.17; 95% confidence interval, 1.20-3.91).⁵ No statistical analysis was conducted for individual drugs, including aripiprazole.

Reviewer's comment

Available data are limited and conflicting, and not sufficient to allow any conclusions; it is the applicant's opinion that these data should not be added to labeling.

There are four published case reports of aripiprazole levels in human milk following oral intake of aripiprazole.^{6,7,8,9} Based on a published review of these case reports and a review by the National Library of Medicine's LactMed database, an exclusively breastfed infant would receive between 0.7%-8.3% of the maternal weight-adjusted dosage.^{3,10} No adverse reactions were observed in these infants at day 6⁸, 3 months⁷, and 4 months⁹ of exposure.

Reviewer's comment

Based on 4 case reports following oral intake of aripiprazole, the estimated amount of aripiprazole in milk is less than the limit of 10% of the maternal weight adjusted dose that is commonly used as the acceptable level.¹¹ Because the data are very limited and not sufficient to allow any conclusions, it is the applicant's opinion that these data should not be added to labeling. DPMH concurs. DPMH recommends the addition of a risk statement that there are insufficient data to assess the amount of drug in human milk, the effects on the breastfed infant,

³ Gentile S. A safety evaluation of aripiprazole for treating schizophrenia during pregnancy and puerperium. *Expert Opin Drug Saf.* 2014;13(12):1733-42.

⁴ Bellet F, Beyens MN, Bernard N, Beghin D, Elefant E, Vial T. Exposure to aripiprazole during embryogenesis: a prospective multicenter cohort study. *Pharmacoevidenciol Drug Saf.* 2015 Apr; 24(4):368-80.

⁵ Habermann F, Fritzsche J, Fuhlbrück F, Wacker E, Allignol A, Weber-Schoendorfer C, et al. Atypical antipsychotic drugs and pregnancy outcome: a prospective, cohort study. *J Clin Psychopharmacol.* 2013;33(4):453-62.

⁶ Schlotterbeck P, Leube D, Kircher T, Hiemke C, Grunder G. Aripiprazole in human milk. *Int J Neuropsychopharmacol.* 2007;10 : 433.

⁷ Lutz UC, Hiemke C, Wiatr G et al. Aripiprazole in pregnancy and lactation a case report. *J Clin Psychopharmacol.* 2010; 30:204-5. Letter.

⁸ Watanabe N, Kasahara M, Sugibayashi R et al. Perinatal use of aripiprazole : a case report. *J Clin Psychopharmacol.* 2011; 31:377-9.

⁹ Nordeng H, Gjerdalen G, Brede WR et al. Transfer of aripiprazole to breast milk: A case report. *J Clin Psychopharmacol.* 2014; 34:272-5.

¹⁰ United States National Library of Medicine. TOXNET Toxicology Data Network. *Drugs and Lactation Database (LactMed)*. <http://www.toxnet.nlm.nih.gov/cgi-bin/sis/search2>

¹¹ Hale T. *Medications and Mothers' Milk*. 2014. Sixteenth Edition.

or the effects on milk production. In addition, DPMH recommends that the following statement be included:

“The development and health benefits of breastfeeding should be considered along with the mother’s clinical need for ARISTADA and any potential adverse effects on the breastfed infant from ARISTADA or from the underlying maternal condition.”

DISCUSSION

DPMH concurs with the applicant’s assessment that available published pregnancy and lactation data are very limited and are insufficient to draw any specific conclusions about risks during pregnancy and lactation; therefore available data should not be added to labeling at the present time.

CONCLUSION

The Pregnancy and Lactation subsections of labeling were structured to be consistent with the PLLR.

DPMH LABELING RECOMMENDATIONS

DPMH discussed our labeling recommendations with DPP at labeling meetings. DPMH recommendations are below and reflect the discussions with DPP. Labeling for Aristada was modeled after the referenced innovator drug, Abilify, with additions that include Pregnancy and Lactation risk statements based on available human data, and removal of the recommendation to not breastfeed.

See final labeling for all of the labeling revisions negotiated with the applicant.

HIGHLIGHTS OF PRESCRIBING INFORMATION USE IN SPECIFIC POPULATIONS

Reviewer Comments: The purpose of Highlights is to highlight important information for the safe and effective use of a product. Because of potential for neonatal extrapyramidal/withdrawal symptoms following administration in the third trimester of pregnancy, DPMH recommends adding the following concise statement:

- **Pregnancy:** May cause extrapyramidal and/or withdrawal symptoms in neonates in women exposed during their third trimester of pregnancy. (8.1)

8.1 Pregnancy

Pregnancy Exposure Registry

Reviewer comment:

The National Pregnancy Registry for Atypical Antipsychotics collects data and monitors pregnancy outcomes in women exposed to atypical antipsychotics during pregnancy. The contact information for this registry should be added.

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to

ARISTADA during pregnancy. For more information contact the National Pregnancy Registry Registry for Atypical Antipsychotics at 1-866-961-2388 or visit <http://womensmentalhealth.org/clinical-andresearch-programs/pregnancyregistry/>.

Risk Summary

Reviewer comment:

In addition to the risk statement on extrapyramidal and/or withdrawal symptoms following delivery, the Risk Summary should include a risk statement based on available human data.

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. Limited published data on aripiprazole use in pregnant women are not sufficient to inform any drug-associated risks for birth defects or miscarriage. No teratogenicity was observed in animal reproductive studies with intramuscular administration of aripiprazole lauroxil to rats and rabbits during organogenesis at doses up to 6 and 18 times, respectively, the maximum recommended human dose (MRHD) of 882 mg on body surface area (mg/m² basis). However, these doses of aripiprazole lauroxil did not result in exposures to aripiprazole as high as those achieved following oral and intravenous administration of aripiprazole which caused developmental toxicity and possible teratogenic effects in rats and rabbits [see Data].

The background risk of major birth defects and miscarriage for the indicated population are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. Advise pregnant women of the potential risk to a fetus.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder have been reported in neonates who were exposed to antipsychotic drugs during the third trimester of pregnancy. These symptoms have varied in severity. Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately. Some neonates recover within hours or days without specific treatment; others may require prolonged hospitalization.

Data

Animal Data for Aripiprazole Lauroxil

Aripiprazole lauroxil did not cause adverse developmental or maternal effects in rats or rabbits when administered intramuscularly during the period of organogenesis at doses of 17.6, 48.5, or 144.1 mg/animal in pregnant rats which are approximately 0.7 to 6 times the maximum recommended human dose (MRHD) of 882 mg on mg/m² basis, and at doses of 241, 723, and 2893 mg/animal in pregnant rabbits which are approximately 1 to 18 times the MRHD on mg/m² basis.

Animal Data for Aripiprazole

Pregnant rats were treated with oral doses of 3, 10, and 30 mg/kg/day which are approximately 1 to 10 times the oral maximum recommended human dose [MRHD] of 30 mg/day on mg/m² basis

of aripiprazole during the period of organogenesis. Treatment at the highest dose caused a slight prolongation of gestation and delay in fetal development, as evidenced by decreased fetal weight, and undescended testes. Delayed skeletal ossification was observed at 3 and 10 times the oral MRHD on mg/m^2 basis.

At 3 and 10 times the oral MRHD on mg/m^2 basis, delivered offspring had decreased body weights. Increased incidences of hepatodiaphragmatic nodules and diaphragmatic hernia were observed in offspring from the highest dose group (the other dose groups were not examined for these findings). A low incidence of diaphragmatic hernia was also seen in the fetuses exposed to the highest dose. Postnatally, delayed vaginal opening was seen at 3 and 10 times the oral MRHD on mg/m^2 basis and impaired reproductive performance (decreased fertility rate, corpora lutea, implants, live fetuses, and increased post-implantation loss, likely mediated through effects on female offspring) along with some maternal toxicity were seen at the highest dose; however, there was no evidence to suggest that these developmental effects were secondary to maternal toxicity.

(b) (4)

In pregnant rabbits treated with oral doses of 10, 30, and 100 $\text{mg}/\text{kg}/\text{day}$ which are 2 to 11 times human exposure at the oral MRHD based on AUC and 6 to 65 times the oral MRHD on mg/m^2 basis of aripiprazole during the period of organogenesis decreased maternal food consumption and increased abortions were seen at the highest dose as well as increased fetal mortality. Decreased fetal weight and increased incidence of fused sternbrae were observed at 3 and 11 times the oral MRHD based on AUC.

(b) (4)

In rats treated with oral doses of 3, 10, and 30 $\text{mg}/\text{kg}/\text{day}$ which are 1 to 10 times the oral MRHD on mg/m^2 basis of aripiprazole perinatally and postnatally (from day 17 of gestation through day 21 postpartum), slight maternal toxicity and slightly prolonged gestation were seen at the highest dose. An increase in stillbirths and decreases in pup weight (persisting into adulthood) and survival were also seen at this dose.

(b) (4)

8.2 Lactation

Reviewer comment:

Under PLLR this subsection is renamed “Lactation” and renumbered 8.2. The Risk Summary should include a risk statement based on available human data and the standard PLLR risk-benefit statement.

Risk Summary

Aripiprazole is present in human breast milk; however there are insufficient data to assess the amount in human milk, the effects on the breastfed infant, or the effects on milk production. The development and health benefits of breastfeeding should be considered along with the mother’s clinical need for ARISTADA and any potential adverse effects on the breastfed infant from ARISTADA or from the underlying maternal condition.

17 PATIENT COUNSELING INFORMATION

Pregnancy

Advise patients that ARISTADA may cause extrapyramidal and/or withdrawal symptoms in a neonate and to notify their healthcare provider with a known or suspected pregnancy. Advise patients that there is a pregnancy registry that monitors pregnancy outcomes in women exposed to ARISTADA during pregnancy [*see Use in Specific Populations (8.1)*].

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/s/

LEYLA SAHIN
07/06/2015

TAMARA N JOHNSON
07/07/2015

LYNNE P YAO
07/07/2015

MEMORANDUM

REVIEW OF REVISED LABELS AND LABELING

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)

Date of This Memorandum: July 1, 2015
Requesting Office or Division: Division of Psychiatry Products (DPP)
Application Type and Number: NDA 207533
Product Name and Strength: Aristada (aripiprazole lauroxil) Extended-release Injectable Suspension
441 mg/1.6 mL, 662 mg/2.4 mL and 882 mg/3.2 mL
Submission Date: June 26, 2015
Applicant/Sponsor Name: Alkermes, Inc.
OSE RCM #: 2014-1850 and 2014-1974
DMEPA Primary Reviewer: Loretta Holmes, BSN, PharmD
DMEPA Team Leader: Danielle Harris, PharmD, BCPS

1 PURPOSE OF MEMO

The Division of Psychiatry Products (DPP) requested that we review the revised container labels, carton labeling and Instructions for Use (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSIONS

The revised container labels, carton labeling and Instructions for Use are acceptable from a medication error perspective.

¹ Brahmbhatt, M. Human Factors Study, Label and Labeling Review for Aristada (NDA 207533). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 Jan 21. 28 p. OSE RCM No.: 2014-1850 and 2014-1974.

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/s/

LORETTA HOLMES
07/01/2015

DANIELLE M HARRIS
07/01/2015

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

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

Memorandum

Date: June 26, 2015

To: Sharonjit Sagoo, PharmD, Regulatory Project Manager
Division of Psychiatry Products

From: Jessica Fox, PharmD, RAC, Regulatory Review Officer
Office of Prescription Drug Promotion

Subject: NDA 207533 – ARISTADA (aripiprazole lauroxil) extended-
release injectable suspension, for intramuscular use

As requested in the Division of Psychiatric Products' (DPP) consult dated October 22, 2014, the Office of Prescription Drug Promotion (OPDP) has reviewed the ARISTADA prescribing information, Medication Guide, carton/container labeling, and instructions for use.

OPDP reviewed the proposed substantially complete version of the prescribing information obtained via SharePoint on June 22, 2015, and has provided comments in the attached labeling.

The Division of Medical Policy Programs and OPDP provided a single, consolidated review of the Medication Guide on June 12, 2015.

OPDP reviewed the proposed carton/container labeling and instructions for use obtained from the EDR on June 26, 2015, and has no comments at this time.

Thank you for your consult. OPDP appreciates the opportunity to provide comments. If you have any questions, please contact Jessica Fox at (301) 796-5329 or Jessica.Fox@fda.hhs.gov.

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/s/

JESSICA M FOX
06/26/2015

**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 12, 2015

To: Mitchell Mathis, M.D.
Acting Director
Division of Psychiatry Products (DPP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Melissa Hulett, MSBA, MSN, FNP-BC, RN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon W. Williams, MSN, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Susannah O'Donnell, MPH
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): ARISTIDA (aripiprazole lauroxil)

Dosage Form and Route: extended release injectable suspension

Application Type/Number: NDA 20-7533

Applicant: Alkermes

1 INTRODUCTION

On August 22, 2014, Alkermes submitted for the Agency's review an original New Drug Application (NDA) for ARISTIDA (aripiprazole lauroxil) extended-release injectable suspension for the treatment of schizophrenia.

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 January 15, 2015, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for ARISTIDA (aripiprazole lauroxil) extended-release injectable suspension.

2 MATERIAL REVIEWED

- Draft ARISTIDA (aripiprazole lauroxil) extended-release injectable suspension MG received on August 22, 2014, and received by DMPP on June 9, 2015.
- Draft ARISTIDA (aripiprazole lauroxil) extended-release injectable suspension MG received on August 22, 2014, and received by OPDP on June 9, 2015.
- Draft ARISTIDA (aripiprazole lauroxil) extended-release injectable suspension Prescribing Information (PI) received on August 22, 2014 revised by the Review Division throughout the review cycle, and received by DMPP on June 9, 2015.
- Draft ARISTIDA (aripiprazole lauroxil) extended-release injectable suspension Prescribing Information (PI) received on August 22, 2014 revised by the Review Division throughout the review cycle, and received by OPDP on June 9, 2015.
- Approved ABILIFY MAINTENA (aripiprazole) comparator labeling dated December 5, 2014.
- ABILIFY MAINTENA (aripiprazole) DMPP focused review provided to DPP on June 8, 2015 pending approval.

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. We have reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- 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 is consistent with the approved comparator labeling where applicable.
- 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/

SHARON W WILLIAMS
06/12/2015

SUSANNAH O'DONNELL
06/12/2015

MELISSA I HULETT
06/12/2015

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: 06/02/2015

TO: Sharonjit Sagoo, Regulatory Project Manager
Lucas Kempf, M.D., Clinical Reviewer and Acting Team Leader
Division of Psychiatry Products (DPP)

FROM: Jenn W. Sellers, M.D., Ph.D. F.A.A.P.
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SUBJECT: Evaluation of Clinical Inspections

NDA: 207533

APPLICANT: Alkermes

DRUG: Aristada (Aripiprazole lauroxil extended-release injectable suspension)

NME: Yes

REVIEW: Standard Review

INDICATION: Schizophrenia

CONSULTATION REQUEST DATE: 10/29/14

INSPECTION SUMMARY GOAL DATE: 06/22/2015

DIVISION ACTION GOAL DATES: 08/22/2015

PDUFA DATES: 08/22/2015

I. BACKGROUND

This application (NDA #207533) included a 12-week randomized, double-blind, placebo-controlled efficacy and safety clinical trial of Aristada in the treatment of schizophrenia (Protocol ALK9072-003) and the open label extension study of Protocol ALK9072-003 (Protocol ALK9072-003EXT). Aristada is aripiprazole lauroxil extended-release injectable suspension. Aripiprazole lauroxil is a covalent non-ester modification of aripiprazole to form N-lauroyloxymethyl aripiprazole. It is converted into aripiprazole once in the body. Oral aripiprazole is an atypical antipsychotic initially approved by FDA in 2002 (brand name Abilify) and is the Reference Listed Drug for this NDA.

The study design of Protocol ALK9072-003 is briefly described as follows. All eligible subjects were randomized 2:2:1:1 into one of the four following intramuscular (IM) injection treatment groups: aripiprazole lauroxil 882 mg, aripiprazole lauroxil 441 mg, high volume placebo (Intralipid, a sterile fat emulsion containing soy oil, egg lecithin, and glycerol), and low volume placebo. After administration of the first dose of IM study drug, subjects remained in the inpatient study unit for at least two weeks and were then discharged when considered stable and appropriate. The second dose of IM study drug was administered on study Day 29. The third (and final) dose of IM study drug was administered on study Day 57. In addition to IM study drug, subjects received oral study drug (aripiprazole 15 mg or placebo) once daily from study Day 1 through the Day 21. Subjects randomized to an aripiprazole lauroxil IM treatment group received oral aripiprazole 15 mg, and subjects randomized to the placebo group received matching oral placebo. The study primary efficacy measurement was the change from baseline to endpoint in the Positive and Negative Syndrome Scale (PANSS) total score. The sponsor's result analyses showed that both the Aristada 441 mg and 882 mg treatment groups were statistically superior to placebo in improving PANSS total score.

The Division of Psychiatry Products (DPP) requested inspections of the following clinical investigator sites based primarily on large subject enrollment. For Protocol ALK9072-003EXT, an open label long-term extension study of Protocol ALK9072-003, DPP would like to know whether there was any evidence of under-reporting of local reactions at the injection site. Study ALK9072-003EXT was still on-going when the inspection consult was requested.

II. RESULTS (by Site):

| Name of Clinical Investigator Location | Protocol Study Site Number of Subjects Enrolled (n) | Inspection Date | Classification* |
|--|---|---|------------------------|
| Jim Aukstuolis, M.D. Woodland International Research Group 910 Autumn Road Little Rock, AR 72211 | ALK9072-003 Site #101 N = 45 | 01/26/2015 to 01/29/2015 | NAI |
| Robert Riesenber, M.D. Atlanta Center for Medical Research 501 Fairburn Rd, SW Atlanta, GA 30331 | ALK9072-003 Site #101 N = 24 | 01/26/2015 to 02/02/2015 | NAI |
| David Walling, Ph.D. Collaborative Neuroscience Network, Inc. 12772 Valley View St, Suite 3 Garden Grove, CA 92845 | ALK9072-003 Site # 121 N = 38 ALK9072-003EXT Site # 121 N = 30 | 03/02/2015 to 03/06/2015 and 03/09/2015 to 03/11/2015 | NAI |

***Key to Classifications**

NAI = No deviation from regulations. Data acceptable

VAI = Deviation(s) from regulations. Data acceptable

OAI = Significant deviations from regulations. Data unreliable

Pending = Preliminary classification based on information in 483 or preliminary communication with the field;

EIR has not been received from the field and complete review of EIR is pending.

CLINICAL INVESTIGATOR (CI)

1. **Jim Aukstuolis, M.D.**
910 Autumn Road, Little Rock, AR 72211
 - a. **What was inspected:** At this site, for Study ALK9072-003, 59 subjects were screened, 45 subjects were enrolled, and 17 subjects completed the study. An audit of the informed consent forms of all 59 screened subjects and complete records of 30 out of 45 enrolled subjects was conducted. The records of Study ALK9072-003EXT were not reviewed at this site since the study was incomplete.
 - b. **General observations/commentary:** No significant regulatory violations were noted, and no Form FDA 483 (List of Inspectional Observations) was issued. The primary endpoint PANSS total score data were verified. All source data matched the line listing data provided. There was no evidence of under-reporting of AEs.

- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and data generated by this site appear acceptable in support of the respective indication.

2. **Robert Riesenber, M.D.**

501 Fairburn Rd, SW, Atlanta, GA 30331

- a. **What was inspected:** At this site, for Study ALK9072-003, 36 subjects were screened, 12 subjects were considered screen failures, 24 were enrolled, and 7 completed the study. An audit of the informed consent form of all 36 screened subjects including the 14 enrolled subjects' records was conducted. The records of Study ALK9072-003EXT were not reviewed at this site since the study was not complete.
- b. **General observations/commentary:** General observations/commentary: No significant regulatory violations were noted, and no Form FDA 483 was issued. The primary endpoint PANSS total score data were verified. There was no evidence of under or non-reporting of adverse events including injection reactions.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

3. **David Walling, Ph.D.**

24275 Jefferson Ave., Oak Grove Institute, Murrieta, CA, 92562

- a. **What was inspected:**
For Study ALK9072-003, 65 subjects were screened, 38 were enrolled and 24 completed the study. A complete review of 15 subject records was conducted. The PANSS Total Scores for all enrolled subjects were reviewed, and an audit of other subject records was conducted.

For Study ALK9072-003EXT, a total of 30 subjects enrolled (eight were rolled over from Protocol ALK9072-003) and 9 subjects completed the study. A complete review of these 9 records was conducted.

- b. **General observations/commentary:**
For Study ALK9072-003, the data listing of all subjects reviewed were verified at the clinical site. The primary efficacy endpoint (PANSS Total Scores) was verifiable. There was no evidence of under-reporting of AEs. No significant regulatory violations were noted and no Form FDA 483 was issued.

For Study ALK9072-003EXT, two subjects (#121060 and #121060) each had a single documented injection site reaction. The reactions were limited to "pain" or "soreness" and resolved spontaneously. The subjects experienced no injection site reactions with subsequent doses. Both of these reactions were

recorded as adverse events. There was no evidence of under-reporting of injection site reactions.

- c. **Assessment of data integrity:** The study appears to have been conducted adequately and data generated by this site appear acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three clinical investigator sites were inspected in support of this NDA and no significant regulatory violations were noted at these sites.

Based on results of these inspections, it appears that the data submitted by the Applicant in support of the requested indication are acceptable and the studies appear to have been conducted adequately.

{See appended electronic signature page}

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

/s/

JENN W SELLERS
06/03/2015

SUSAN D THOMPSON
06/03/2015

KASSA AYALEW
06/05/2015

HUMAN FACTORS STUDY, 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: January 21, 2015
Requesting Office or Division: Division of Psychiatry Products (DPP)
Application Type and Number: NDA 207533
Product Name and Strength: Aristada (aripiprazole lauroxil) extended-release injectable suspension, 441 mg, 662 mg, and 882 mg
Product Type: Single ingredient
Rx or OTC: Rx
Applicant/Sponsor Name: Alkermes, Inc.
Submission Date: August 22, 2014
OSE RCM #: 2014-1850; 2014-1974
DMEPA Primary Reviewer: Millie Brahmhatt, PharmD, BCPS
DMEPA Acting Team Leader: Vicky Borders-Hemphill, PharmD
DMEPA Associate Director: Irene Chan, PharmD, BCPS

1 REASON FOR REVIEW

The Division of Psychiatry Products (DPP) requested DMEPA evaluate results of the human factors summative study results for Aristada (aripiprazole lauroxil) extended-release injectable suspension, to ensure the intended population is able to use the product correctly and safely. In addition, we evaluated the container label, carton and insert labeling for areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

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

| Material Reviewed | Appendix Section (for Methods and Results) |
|---|---|
| Product Information/Prescribing Information | A |
| Previous DMEPA Reviews | B |
| Human Factors Study | C |
| Labels and Labeling | D |
| Dosage and Administration Section in Highlights of Prescribing Information and Full Prescribing Information | E |

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Human Factors Summative Study Assessment

Aristada (aripiprazole lauroxil) extended-release injectable suspension will be supplied in pre-filled syringes for three dose strengths (441 mg, 662 mg, and 882 mg). The pre-filled syringe must first be prepared using specific instructions in the Directions for Use (DFU) prior to administration to the patient via deltoid (441 mg) or gluteal intramuscular (441 mg, 662 mg, and 882 mg) injection by a healthcare professional (HCP).

The results of the human factors summative study show that 12 of 15 participants (80%) were able to use the product successfully without a failure on any critical task, which was not attributable to a study artifact. All participants selected the correct dose kit, correctly prepared the medication prior to injecting, selected the correct needle, and administered the entire contents of the syringe in less than 10 seconds.

One critical task error that occurred was incorrect site of administration (n=1). The participant incorrectly chose the deltoid site for administration for the 882 mg dose instead of the gluteal

site. The participant indicated she usually injects into the deltoid and did not notice the instructions in the DFU or on the outer package. Thus, the researchers attributed this error to the participant's previous experience with injecting into the deltoid. The researchers do not expect the risk associated with incorrect administration of the 662 mg or 882 mg dose into the deltoid to be beyond transient injection site pain and swelling. Per the Clinical Reviewer, there is the potential for overdose if the dose is administered at the incorrect site. Our review determined that the carton labeling and DFU clearly state information on the correct site of administration. Thus, we believe the risk for wrong site of administration errors is mitigated to an acceptable level and no further changes to the user interface are likely to further mitigate the risk.

The other type of critical task error that occurred was over tightening of the needle and cracking of the needle hub (n=2). Both participants identified the error immediately and prepared a second syringe. One said that for the needles they typically use at her facility the nurses "really have to tighten them" and the other said she likely over tightened because she was nervous. No further design or instructional mitigation was suggested by the participants. The researchers do not suggest any further design changes to mitigate the risk of these errors from occurring. Our review determined that the DFU clearly states not to over tighten the needle. Thus, we believe the risk for over tightening the needle is mitigated to an acceptable level and no further changes to the user interface are likely to further mitigate the risk.

The two types of errors that occurred among non-critical tasks were failure to prime the syringe (n=7) and incorrect disposal of the needle (n=2). The researchers indicated that failure to prime the syringe would result in mild transient injection site pain. The researchers indicated that use of safety needles and needle disposal is common practice for HCPs, and they do not suggest any further design or instructional changes to mitigate the risk of these errors from occurring. We believe these errors cannot be further mitigated through changes to the user interface, and we do not recommend further changes to the DFU.

Labels and Labeling Assessment

DMEPA reviewed the proposed labels and labeling to determine whether there are any significant concerns that could result in medication errors. Our review of the insert labeling and DFU identified error-prone symbols and missing units of measure following numbers used to express dose. Our review of the proposed syringe labels and carton labeling identified areas for improvement to increase clarity and prominence of important information to promote safe use of the product. Thus, we make recommendations in Sections 4.1 and 4.2. We do not believe these changes to the user interface require additional human factor studies for validation.

4 CONCLUSION & RECOMMENDATIONS

Our review of the results of the human factors summative study determined that Aristada (aripiprazole lauroxil) extended-release injectable suspension is safe for use by healthcare providers, the intended user group.

We identified areas in the proposed labels and labeling that can be improved to increase clarity and prominence of important information to promote the safe use of this product. We do not believe these changes to the user interface require additional human factor studies for validation.

If you have further questions or need clarifications, please contact Vasantha Ayalasomayajula, OSE Project Manager, at 240-402-5035.

4.1 RECOMMENDATIONS FOR THE DIVISION

We have revised the Highlights of Prescribing Information and Full Prescribing Information (See Appendix E) and have provided a detailed summary below for review and consideration by DPP.

A. Highlights of Prescribing Information

1. Under the *Dosage and Administration* section, we recommend revising the dosing information from a bulleted format to a table format to improve readability and ensure important information is not overlooked as follows:

| Dose | Frequency | Site of Intramuscular Administration |
|--------|--------------------------|--------------------------------------|
| 441 mg | Monthly | Deltoid Muscle or Gluteal Muscle |
| 662 mg | Monthly | Gluteal Muscle |
| 882 mg | Monthly or every 6 weeks | Gluteal Muscle |

2. Add the following title to the table under the *Dosage and Administration* section:

[REDACTED] (b) (4)

3. Add a unit of measure immediately following all numbers in the table under the *Dosage and Administration* section. (For example, add “mg” following “441” and “662” to read “441 mg” and “662 mg”).

B. Full Prescribing Information

1. See A.1
2. Replace the error-prone symbol “>” in *Section 2.3, Table 1: Recommendation for Re-initiation of Concomitant Oral Aripiprazole Supplementation* under *Section 2.3 (Dosage and Administration)* with the appropriate full meaning “greater than.”

Presence of the error-prone symbol “>” is dangerous because this symbol can be mistaken as the opposite of the intended meaning.¹

3. Revise the statement [REDACTED] (b) (4) to read, “Do not inject by any other route” in *Step 5 of Section 2.5 Directions for Use*. We recommend revising this statement because DMEPA has identified several medication error cases that report wrong route of administration with other long-acting injectable antipsychotic products [REDACTED] (b) (4) statements such as [REDACTED] (b) (4) [REDACTED] (b) (4) should not be used [REDACTED] (b) (4) [REDACTED] even when it is emphasized by bolding, underlining, or other means.² Thus, revising this statement [REDACTED] (b) (4) [REDACTED] may help minimize the risk of wrong route of administration error.
4. Add a unit of measure immediately following all numbers in *Table 2*: [REDACTED] (b) (4) [REDACTED] [REDACTED] [REDACTED] (For example, add “mg” following “441” and “662” to read “441 mg” and “662 mg”).
5. Revise the typo in the sentence that reads, “Advise patients to inform their physicians [REDACTED] (b) (4) they are taking...” to read, “Advise patients to inform their physicians **if** they are taking...” in *Section 17.9 (Patient Counseling)*.

C. Medication Guide

1. Add the statement “Each Aristada injection must be administered by a healthcare professional only” to the section *What is the most important information I should know about Aristada*. We recommend adding this statement because DMEPA has identified several medication error cases that report patients self-administering other long-acting injectable antipsychotic products that are intended to be administered by a healthcare professional.

¹ ISMP’s List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2013 [cited 2014 October 29]. Available from: <http://www.ismp.org/tools/errorproneabbreviations.pdf>.

[REDACTED] (b) (4)

4.2 RECOMMENDATIONS FOR ALKERMES, INC.

We request the Applicant implement the recommendations in Section 4.2 prior to approval of the NDA.

A. Syringe Labels and Carton Labeling (all strengths, including Professional Sample Syringe Labels and Carton Labeling)

1. Revise the presentation of the proprietary name from all upper case letters “ARISTADA” to title case letters “Aristada” to improve readability. Words set in title case form recognizable shapes, making them easier to read than the rectangular shape formed by words set in all upper case letters.³

B. Carton Labeling (all strengths, including Professional Sample Carton Labeling)

1. Revise the statement (b) (4) to “Single-use injection - Entire Content of Syringe Must Be Administered by Healthcare Professional Only” to clarify that the syringe contains one dose that must be administered in a single dose by a healthcare professional. We recommend to add this statement because DMEPA has identified several medication error cases that report patients self-administering other long-acting injectable antipsychotic products that are intended to be administered by a healthcare professional. Relocate this statement to appear underneath the statement “For deltoid or gluteal intramuscular injection only” on the principal display panel to increase its prominence.
2. Revise (b) (4) the statements “For deltoid or gluteal intramuscular injection only” and “For gluteal intramuscular injection only” to black font to improve the readability and prominence of these statements.

3. (b) (4)

³Food and Drug Administration. *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, April 2013. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

Therefore, we recommend you move the barcode that does not contain the NDC number to the back panel of the carton labeling, (b) (4) and in a size that does not compete with, or distract from the presentation of other required or recommended information on the labeling.⁴

C. Syringe Labels (all strengths, including Professional Sample Syringe Labels)

1. Replace (b) (4) with the drug barcode. Healthcare practitioners often use the drug barcode as additional verification before drug administration in the inpatient setting; therefore, it is an important safety feature that should be part of the label whenever possible. We request adding the drug barcode to each individual syringe label as required per 21 CFR 201.25(b)(1).
2. Relocate the “Rx Only” statement to the bottom right section of the label to ensure adequate space for more important information. Add the statement “Single –use injection” above the strength on the principal display panel. Decrease the size of the strength presentation to accommodate the addition of this statement. Add the statement “Must Be Administered by Healthcare Professional Only” following the statement “Use entire content of syringe.” We recommend adding this statement because DMEPA has identified several medication error cases that report patients self-administering other long-acting injectable antipsychotic products. Consider decreasing the size of the lot and expiration date to accommodate the additional statements.

D. Directions for Use (all strengths)

1. Replace the error-prone symbol “<” in *Step 5* with the appropriate full meaning of “less than.” Presence of the error-prone symbol “<” is dangerous because this symbol can be mistaken as the opposite of the intended meaning.⁵
2. Revise the statement (b) (4) to read, “Do not inject by any other route” in *Step 5*. We recommend revising this statement because DMEPA has identified several medication error cases that report wrong route of administration with other long-acting injectable antipsychotic products. (b) (4) statements such as (b) (4) should not be used (b) (4)

⁴ Food and Drug Administration. *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, April 2013. Available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

⁵ ISMP’s List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2013 [cited 2014 October 29]. Available from: <http://www.ismp.org/tools/errorproneabbreviations.pdf>.

(b) (4) 6 Thus, revising this statement

(b) (4)

may help minimize the risk of wrong route of administration error.

6

(b) (4)

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Aristada (aripiprazole lauroxil) extended-release injectable suspension that Alkermes, Inc. submitted on August 22, 2014.

| Table 2. Relevant Product Information for Aristada (aripiprazole lauroxil) extended-release injectable suspension | |
|--|---|
| Initial Approval Date | Not Applicable |
| Active Ingredient | aripiprazole lauroxil |
| Indication | Atypical antipsychotic indicated for the treatment of schizophrenia |
| Route of Administration | intramuscular |
| Dosage Form | injectable suspension |
| Strength | 441 mg, 662 mg, and 882 mg |
| Dose and Frequency | 441 mg, 662 mg, or 882 mg intramuscularly monthly or 882 mg intramuscularly every 6 weeks |
| How Supplied | 5 mL pre-filled syringe packaged in a tray within a carton also containing safety needles, use instructions, a package insert, and a medication guide |
| Storage | Room temperature 20°C to 25°C (68°F to 77°F) with brief excursions permitted between 15°C and 30°C (between 59°F and 86°F) |
| Container Closure | 5 mL pre-filled syringe |

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

We searched the L:drive on October 31, 2014 using the term, Aristada, to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified one previous review⁷ relevant to this review. We confirmed that our previous recommendations were implemented or considered.

APPENDIX C. HUMAN FACTORS STUDY

C.1 Study Design

We evaluated the Human Factor Study Results submitted on August 8, 2014. Below is a brief overview of the study objectives, descriptions of the study participants, study design, data collection, and data analysis.

Study Objective:

Assess the safe and effective use of the aripiprazole lauroxil extended-release pre-filled syringe kits and their associated instructional materials.

| ID | Objective | Description |
|----------------------------|---|---|
| Primary Objective 1 (P1) | Performance assessment | Through observation, identify steps in the use process that result in performance difficulties or failures. |
| Primary Objective 2 (P2) | Investigation of performance failures | Through targeted discussion with the participant, determine causes of any observed performance failures |
| Secondary Objective 1 (S1) | Investigation of ease of understanding of DFU | Through targeted discussion with participant, determine areas of confusion or misunderstanding of the Directions for Use. |

Study Participants:

Fifteen participants, representative of the intended user population, were assessed in the study. Participants included health care professionals (HCPs) who are responsible for providing injections to schizophrenia patients with a range of experience with long-acting injectable antipsychotics (LAIs).

Tasks:

| Step # | User Task | Use-Risk Classification | Rationale |
|--------|---|-------------------------|---|
| - | Select the correct dose (441 mg, 662 mg, or 882 mg) | C | <i>Updated to C per FDA feedback (Section 5.3.1)</i> Could result in over- or under dose |

⁷Holmes, L. Human Factors Study Protocol Review for Aristada (IND 107249). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US);2013 Nov. 06. 8 p. OSE RCM No.: 2013-1304.

| | | | |
|---|---|---|--|
| 1 | <p>Tap and Shake the syringe.</p> <p>a. Tap the syringe at least 10 times to dislodge any material which may have settled</p> <p>b. Shake the prefilled syringe vigorously for a minimum of 30 seconds to ensure a uniform suspension.</p> | C | Failure to properly resuspend could result in a needle clog and subsequent under dose |
| 2 | <p>Select the injection needle.</p> <p>a. Select the injection site (based on dose)</p> <p>b. Select the needle (based on injection site)</p> | C | <p><i>Updated to C per FDA feedback (Section 5.3.1)</i></p> <p>Incorrect selection of injection site or needle could result in injection site reaction (e.g. pain)</p> |
| 3 | <p>Attach the injection needle</p> <p>Attach the appropriate needle securely with a clockwise twisting motion. DO NOT over tighten. Over tightening could lead to needle hub cracking.</p> | C | <p><i>Updated to C per findings in simulated use study III (Section 5.2)</i></p> <p>Needle attachment is common practice for HCP but over tightening could lead to a needle hub crack and leakage which could result in an under dose.</p> |
| 4 | <p>Prime the syringe to remove air</p> <p>a. Bring syringe upright and tap</p> <p>b. Remove air by depressing plunger rod</p> | D | Priming is common practice for HCPs and there is nothing unique about this product that would require priming. Failure to prime would not result in harm to the patient as drug product is administered intramuscularly. |
| 5 | Administer the entire contents intramuscularly in a rapid continuous manner less than 10 seconds | C | Very slow injections could result in a needle clog and possible subsequent under dose |
| 6 | <p>Dispose of the needle</p> <p>a. Cover the needle by pressing safety device</p> <p>b. Dispose of items in proper waste container</p> | D | Use of safety needles and needle disposal is common practice for HCPs. |

C: Critical

D: Desirable

Scenarios of Use:

Correct performance of critical tasks was dependent on the order prescribed to the patient as well as the profile of the patient receiving the injection. Several use scenarios were assessed in the study:

- Participants were given a patient profile that described the relevant characteristics of a patient. The patient profile included a picture of the patient, gender, weight, and height.
- The participant was also provided the prescriber’s order, including the drug name, dose, quantity, and refill number, and corresponded to one of the three kits.
- Using the patient profile and order, each participant was asked to go through a simulated use sequence of selecting the correct kit and administering the aripiprazole lauroxil drug product into an injection mannequin. The orders were used to simulate the various use scenarios that require selection of the correct kit, the correct needle, and the correct injection site. No additional instructions or prompting was provided to the participant.

Definition of Performance Standards:

| Step # | User Task | Performance Standard |
|--------|---------------------------|--|
| -- | Select the correct kit | <p>For Participants provided Patient Profile & Order ‘A’, selection of 441 mg low dose kit will be recorded as ‘Correct’ performance.</p> <p>For Participants provided Patient Profile & Order ‘B’, selection of the 662 mg high dose kit will be recorded as ‘Correct Performance’.</p> <p>For Participants provided Patient Profile & Order ‘C’, selection of the 882 mg high dose kit will be recorded as ‘Correct Performance’.</p> <p>Selection of any other kit for either A, B, or C scenarios will result in ‘Failed’ performance.</p> |
| 1 | Tap and shake the syringe | <p>If the participant taps the syringe for at least 25 or more taps this will be recorded as ‘Correct Performance’*</p> <p>If the participant shakes the syringe for at least 10 or more seconds this will be recorded as ‘Correct Performance’.*</p> <p>Failure performance of this step will be assessed if the participant:</p> <ul style="list-style-type: none"> – taps the syringe less than 25 times AND shakes 0 seconds <i>or</i> – does not tap the syringe AND shakes the syringe for less than 10 seconds <p><i>* Performance standard based on rationale provided in Section 5.3.2.2.</i></p> |
| 2a | Select injection site | <p>Correct performance of ‘intramuscularly’ will be assessed according to the participant’s selection of the correct site on the injection mannequin.</p> <p>For Participants provided Patient Profile & Order ‘A’ (low dose kit), selection of Deltoid or Gluteal site will be recorded as ‘Correct’.</p> <p>For Participants provided Patient Profile & Order ‘B’ (mid dose kit) or Order ‘C’ (high dose kit), selection of Gluteal site will be recorded as ‘Correct’.</p> <p>Selection of any other site for either kit will result in ‘Failed’ performance.</p> |

| | | |
|----|--|---|
| 2b | Select needle length | <p>For Participants who chose the Gluteal Site (A, B, or C):</p> <ul style="list-style-type: none"> - 20 gauge, 1 1/2 inch needle <i>or</i> - 20 gauge, 2 inch needle <p>will result in 'Correct' performance.</p> <p>For Participants who chose the Deltoid Site (A only):</p> <ul style="list-style-type: none"> - 21 gauge, 1 inch <i>or</i> - 20 gauge, 1 1/2 inch <p>will result in 'Correct' performance.</p> <p>Selection of Deltoid Site AND 20 gauge, 2-inch needle <i>or</i> selection of Gluteal Site AND 21 gauge, 1-inch needle will result in 'Failed Performance'.</p> |
| 3 | Attach the injection needle | <p>'Correct' performance will be determined by the moderator's subjective visual assessment of the force being applied by the participant in attaching the needle.</p> <p>'Failed' performance will be assigned for participants who "over tighten" the needle, as determined by the moderator's subjective visual assessment of the force being applied by the participant in attaching the needle. A cracked needle hub evident by leakage will be considered evidence of over tightening.</p> <p>'Failed' performance will be assigned for participants who "under tighten" the needle, as determined by the moderator's subjective visual assessment of the force being applied by the participant in attaching the needle. Leakage due to the needle coming loose will be considered evidence of under tightening.</p> |
| 4 | Prime the syringe to remove air | <p>'Correct' performance of removing air is defined by pressing the plunger rod to remove air.</p> <p>If the participants "overprime," or remove more than a few drops of product in addition to air as determined by the moderator's subjective visual assessment, 'Failed' performance will be assigned.</p> |
| 5 | Administer the entire contents intramuscularly | <p>If the participant presses the entire length of the plunger down in 10 or less seconds after aspirating this will be recorded as 'Correct Performance'.</p> <p>If the participant presses the entire length of the plunger down in 11 or more seconds after aspirating, this will be recorded as a 'Failure'.</p> |

C.2 Results

Of 15 participants, 12 (80%) were able to use the product successfully without a failure on any critical task, which was not attributable to a study artifact.

Key risks identified with the use of this product include the critical tasks of dose selection, resuspension, needle and injection site selection, needle attachment, and administration.

- 15/15 (100%) participants selected the correct dose kit
- 15/15 (100%) participants correctly prepared the medication prior to injecting (Step 1)

- 14/15 (93%) participants selected the correct injection site. One participant selected the incorrect injection site (Step 2).
 - She said she usually injects into the deltoid and did not notice the instructions in the DFU or on the outer package even though “For gluteal injection only” is stated on the front cover of the carton as well as the first page of the DFU that is apparent upon first opening the carton. All other participants selected the correct site for the injection, indicating that the labeling was clear on this point.
- 15/15 (100%) participants selected the correct needle (Step 2)
- 13/15 (87%) participants correctly attached the injection needle. Two participants over tightened the needle, causing the needle hub to crack. Both participants immediately identified the crack and correctly prepared a second syringe and injected the medication. (Step 3).
 - Both participants who experienced a needle hub crack indicated they saw the instruction not to over tighten, one even stated, “it says in big red do not over tighten.” One said that for the needles they typically use at her facility the nurses “really have to tighten them” and the other said she likely over tightened because she was nervous. No further design or instructional mitigation was suggested by the participants.
- 12/12 (100%) participants administered the entire contents intramuscularly within 10 seconds (Step 5).
 - Although 12/15 participants administered a complete injection into the mannequin, after inspection of the mannequin’s injection pads, the investigators identified a root cause for the three failures associated with the material inside the injection pad. These failures are attributed to a study artifact and those participants were removed from the success calculation for this step.

Failures on non-critical tasks were observed but these are unlikely to lead to harm and pose little risk. Additionally, these tasks are not unique to this product design and are part of normal HCP practice.

- 8/15 (53%) participants correctly primed the syringe (Step 4)
 - Failure to prime was attributed to a variety of reasons including forgetfulness, nervousness, and incorrect visual assessment of the amount of air in the syringe. No further instructional mitigation was suggested and priming instructions in this DFU are consistent with other similar products. No one seemed overly concerned that the syringe was not primed and one even stated that clinically it does not matter if air remains as it would not cause an air embolism and that often they add air to drive the solution in.
- 13/15 (87%) participants disposed of the needle correctly (Step 6).
 - One participant failed to fully engage the needle safety. She knew what she was supposed to do, she performed the correct motions of engaging the safety shield and thought she had pushed the safety down all the way. No further design or instructional mitigation was suggested by the participant and disposal instructions are consistent with other similar products.

- One participant failed to dispose of the syringe into a sharps container (Step 6) but this failure was attributed to the test environment, not to the PFS design.

APPENDIX D. LABELS AND LABELING

D.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,⁸ along with postmarket medication error data, we reviewed the following Aristada (aripiprazole lauroxil) extended-release injectable suspension labels and labeling submitted by Alkermes, Inc. on August 22, 2014.

- Syringe label
- Carton labeling
- Professional Sample Syringe label
- Professional Sample Carton labeling
- Tray Insert Card
- Directions for Use
- Medication Guide
- Full Prescribing Information

D.2 Label and Labeling Images

Syringe Label: 441 mg



⁸ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

12 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

MILLIE C BRAHMBHATT
01/21/2015

BRENDA V BORDERS-HEMPHILL
01/21/2015

IRENE Z CHAN
01/21/2015

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 207533

Application Type: New NDA

Name of Drug/Dosage Form: Aristada (aripiprazole lauroxil) extended release injectable suspension 441 mg, 662 mg, and 882 mg

Applicant: Alkermes

Receipt Date: August 22, 2014

Goal Date: August 22, 2015

1. Regulatory History and Applicant's Main Proposals

Alkermes has submitted a 505(b)(2) submission for ARISTADA (aripiprazole lauroxil) extended release injectable suspension for schizophrenia. The IND associated with this NDA is 107249. Alkermes had the following meetings with the Division prior to submitting this application:

End-of-Phase 2 CMC: 9/12/11

End-of-Phase 2 Clinical/Non-clinical: 9/15/11

Type C Guidance: 3/25/13

Pre-NDA: 5/19/14

In a communication dated 4/3/13 the Division stated that we consider this drug a New Molecular Entity. However, final determination as well as corresponding exclusivity will be made at the time of drug approval.

This application is an NME to be reviewed under the PDUFA V Program.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by November 25, 2014. The resubmitted PI will be used for further labeling review.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment: *Waiver requested*

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

- NO** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment: *White space needed before "Contraindications" and" Warnings and Precautions"*

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

| Section | Required/Optional |
|-----------------------------------|---|
| • Highlights Heading | Required |
| • Highlights Limitation Statement | Required |
| • Product Title | Required |
| • Initial U.S. Approval | Required |
| • Boxed Warning | Required if a BOXED WARNING is in the FPI |

Selected Requirements of Prescribing Information

| | |
|---|---|
| • Recent Major Changes | Required for only certain changes to PI* |
| • Indications and Usage | Required |
| • Dosage and Administration | Required |
| • Dosage Forms and Strengths | Required |
| • Contraindications | Required (if no contraindications must state "None.") |
| • Warnings and Precautions | Not required by regulation, but should be present |
| • Adverse Reactions | Required |
| • Drug Interactions | Optional |
| • Use in Specific Populations | Optional |
| • Patient Counseling Information Statement | Required |
| • Revision Date | Required |

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

- NO** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment: *Statement needs to be bolded*

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- YES** 12. All text in the BW must be **bolded**.

Comment:

- YES** 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

Selected Requirements of Prescribing Information

- YES** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

- YES** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment: *Original NDA - no RMC*

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES

Selected Requirements of Prescribing Information

21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

- NO** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment: *Statement should also include the Medication Guide*

Revision Date in Highlights

- NO** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment: *Include revision date*

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- NO** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment: Include the heading for the BW
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- NO** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

| |
|--|
| BOXED WARNING |
| 1 INDICATIONS AND USAGE |
| 2 DOSAGE AND ADMINISTRATION |
| 3 DOSAGE FORMS AND STRENGTHS |
| 4 CONTRAINDICATIONS |
| 5 WARNINGS AND PRECAUTIONS |
| 6 ADVERSE REACTIONS |
| 7 DRUG INTERACTIONS |
| 8 USE IN SPECIFIC POPULATIONS |
| 8.1 Pregnancy |
| 8.2 Labor and Delivery |
| 8.3 Nursing Mothers |
| 8.4 Pediatric Use |
| 8.5 Geriatric Use |
| 9 DRUG ABUSE AND DEPENDENCE |
| 9.1 Controlled Substance |
| 9.2 Abuse |
| 9.3 Dependence |
| 10 OVERDOSAGE |
| 11 DESCRIPTION |
| 12 CLINICAL PHARMACOLOGY |
| 12.1 Mechanism of Action |
| 12.2 Pharmacodynamics |
| 12.3 Pharmacokinetics |
| 12.4 Microbiology (by guidance) |
| 12.5 Pharmacogenomics (by guidance) |
| 13 NONCLINICAL TOXICOLOGY |
| 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility |
| 13.2 Animal Toxicology and/or Pharmacology |
| 14 CLINICAL STUDIES |
| 15 REFERENCES |
| 16 HOW SUPPLIED/STORAGE AND HANDLING |
| 17 PATIENT COUNSELING INFORMATION |

Comment: Subsection 12.4 not named/numbered in accordance with the regulations. Drug interaction information should be presented in Section 7.

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Selected Requirements of Prescribing Information

Comment:

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- YES** 36. In the BW, all text should be **bolded**.

Comment:

- YES** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- YES** 38. If no Contraindications are known, this section must state “None.”

Comment: *Contraindications listed*

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment: *There is no postmarketing experience with Aristada.*

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

[text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

36 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

SHARONJIT K SAGOO
10/29/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

| Application Information | | |
|--|--|---|
| NDA # 207533 BLA# | NDA Supplement #:S- 000 BLA Supplement # | Efficacy Supplement Type SE- |
| Proprietary Name: Aristada Established/Proper Name: Aripiprazole lauroxil Dosage Form: Extended-release injectable suspension Strengths: 441 mg, 662 mg, and 882 mg | | |
| Applicant: Alkermes Agent for Applicant (if applicable): N/A | | |
| Date of Application: August 22, 2014 Date of Receipt: August 22, 2014 Date clock started after UN: | | |
| PDUFA Goal Date: August 22, 2015 | | Action Goal Date (if different): |
| Filing Date: October 24, 2014 | | Date of Filing Meeting: October 7, 2014 |
| Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 1 | | |
| Proposed indication: Schizophrenia | | |
| Type of Original NDA: AND (if applicable) Type of NDA Supplement: | <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) | |
| <i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 | | |
| Type of BLA | <input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k) | |
| <i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i> | | |
| Review Classification: | <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher submitted | |
| <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.</i> | | |
| Resubmission after withdrawal? <input type="checkbox"/> | | Resubmission after refuse to file? <input type="checkbox"/> |
| Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i> | <input type="checkbox"/> Convenience kit/Co-package <input checked="" type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product) | |

| | | | | |
|---|--|-------------------------------------|--------------------------|----------------|
| <input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other: | <input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42) | | | |
| Collaborative Review Division (if OTC product): | | | | |
| List referenced IND Number(s): 107249 | | | | |
| Goal Dates/Product Names/Classification Properties | YES | NO | NA | Comment |
| PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| Application Integrity Policy | YES | NO | NA | Comment |
| Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | | |
| If yes, explain in comment column. | | | NA | |
| If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified: | <input type="checkbox"/> | <input type="checkbox"/> | NA | |
| User Fees | YES | NO | NA | Comment |
| Is Form 3397 (User Fee Cover Sheet) included with authorized signature? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |

| | | | | | |
|---|-----------------------|--|-------------------------------------|--------------------------|----------------|
| User Fee Status <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i> | | Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required | | | |
| <i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i> | | Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears | | | |
| 505(b)(2) (NDAs/NDA Efficacy Supplements only) | | YES | NO | NA | Comment |
| Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? | | <input type="checkbox"/> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | |
| Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)]. | | <input type="checkbox"/> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | |
| Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? | | <input type="checkbox"/> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | |
| <i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i> | | | | | |
| Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? | | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| <i>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm </i> | | | | | |
| If yes, please list below: | | | | | |
| Application No. | Drug Name | Exclusivity Code | | Exclusivity Expiration | |
| 202971 | Abilify Maintenna Kit | NDF | | Feb 28, 2016 | |
| 21866 | Abilify IM injection | M – 137 | | Jun 9, 2017 | |
| 21713 | Abilify oral solution | M – 137 | | Jun 9, 2017 | |
| 21729 | Abilify ODT | M – 137 | | Jun 9, 2017 | |
| 21436 | Abilify tablet | M – 137 | | Jun 9, 2017 | |
| <i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i> | | | | | |
| Exclusivity | | YES | NO | NA | Comment |

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|--|-------------------------------------|-------------------------------------|-------------------------------------|--|
| Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</i> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | | |
| If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i> | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |
| Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: 5-year and 3-year <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)? | <input type="checkbox"/> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | |
| If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i> | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |
| For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i> | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |

| Format and Content | |
|---|---|
| <i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i> | <input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD) |

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| If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format? | | | | |
| Overall Format/Content | YES | NO | NA | Comment |
| If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted). | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| Index : Does the submission contain an accurate comprehensive index? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no , explain. | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| BLAs only : Companion application received if a shared or divided manufacturing arrangement? If yes , BLA # | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |
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| Forms and Certifications | | | | |
| <i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i> | | | | |
| Application Form | YES | NO | NA | Comment |
| Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| Are all establishments and their registration numbers listed on the form/attached to the form? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| Patent Information (NDAs/NDA efficacy supplements only) | YES | NO | NA | Comment |
| Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

| Financial Disclosure | YES | NO | NA | Comment |
|---|-------------------------------------|--------------------------|-------------------------------------|----------------|
| <p>Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?</p> <p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| Clinical Trials Database | YES | NO | NA | Comment |
| <p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| Debarment Certification | YES | NO | NA | Comment |
| <p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| Field Copy Certification (NDAs/NDA efficacy supplements only) | YES | NO | NA | Comment |
| <p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p> | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |
| Controlled Substance/Product with Abuse Potential | YES | NO | NA | Comment |

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|--|-------------------------------------|--------------------------|-------------------------------------|----------------|
| <u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> Date of consult sent to Controlled Substance Staff: | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |
| Pediatrics | YES | NO | NA | Comment |
| <u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i> | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |
| If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| <u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i> | <input type="checkbox"/> | <input type="checkbox"/> | | NA |
| Proprietary Name | YES | NO | NA | Comment |
| Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| REMS | YES | NO | NA | Comment |

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

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| Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | |
| Prescription Labeling | <input type="checkbox"/> Not applicable | | | |
| Check all types of labeling submitted. | <input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify) | | | |
| | YES | NO | NA | Comment |
| Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| Is the PI submitted in PLR format? ⁴ | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i> | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |
| All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| OTC Labeling | <input checked="" type="checkbox"/> Not Applicable | | | |
| Check all types of labeling submitted. | <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify) | | | |
| | YES | NO | NA | Comment |
| Is electronic content of labeling (COL) submitted? | <input type="checkbox"/> | <input type="checkbox"/> | | |

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

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| <i>If no, request in 74-day letter.</i> | | | | |
| Are annotated specifications submitted for all stock keeping units (SKUs)? | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |
| <i>If no, request in 74-day letter.</i> | | | | |
| If representative labeling is submitted, are all represented SKUs defined? | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |
| <i>If no, request in 74-day letter.</i> | | | | |
| All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA? | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |
| Other Consults | YES | NO | NA | Comment |
| Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| <i>If yes, specify consult(s) and date(s) sent:</i> CDRH, 10/9/14 | | | | |
| Meeting Minutes/SPAs | YES | NO | NA | Comment |
| End-of Phase 2 meeting(s)? Date(s): 9/15/11 | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| <i>If yes, distribute minutes before filing meeting</i> | | | | |
| Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 5/19/14 | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| <i>If yes, distribute minutes before filing meeting</i> | | | | |
| Any Special Protocol Assessments (SPAs)? Date(s): NA | <input type="checkbox"/> | <input checked="" type="checkbox"/> | | |
| <i>If yes, distribute letter and/or relevant minutes before filing meeting</i> | | | | |

ATTACHMENT

MEMO OF FILING MEETING

DATE: 10/7/14 & 10/15/14

BLA/NDA/Supp #: 207533

PROPRIETARY NAME: ARISTADA

ESTABLISHED/PROPER NAME: Aripiprazole lauroxil

DOSAGE FORM/STRENGTH: Extended-release suspension for IM injection 441 mg, 662 mg, and 882 mg

APPLICANT: Alkermes

PROPOSED INDICATION: Schizophrenia

BACKGROUND: Alkermes has submitted a 505(b)(2) submission for ARISTADA (aripiprazole lauroxil) extended release injectable suspension for schizophrenia. The IND associated with this NDA is 107249. Alkermes had the following meetings with the Division prior to submitting this application:

End-of-Phase 2 CMC: 9/12/11

End-of-Phase 2 Clinical/Non-clinical: 9/15/11

Type C Guidance: 3/25/13

Pre-NDA: 5/19/14

In a communication dated 4/3/13 the Division stated that we consider this drug a New Molecular Entity. However, final determination as well as corresponding exclusivity will be made at the time of drug approval.

This application is an NME to be reviewed under the PDUFA V Program.

REVIEW TEAM:

| Discipline/Organization | Names | | Present at filing meeting? (Y or N) |
|-------------------------------------|--------------|---|--|
| Regulatory Project Management | RPM: | Sharonjit Sagoo | Y |
| | CPMS/TL: | Steve Hardeman (CPMS) Keith Kiedrow (TL) | Y N |
| Cross-Discipline Team Leader (CDTL) | Mark Ritter | | Y |
| Clinical | Reviewer: | Lucas Kempf | Y |
| | TL: | Mark Ritter | Y |

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|--|-------------------------|---------------------|---|
| Clinical Pharmacology | Reviewer: | Praveen Balimane | Y |
| | TL: | Hao Zhu | Y |
| Biostatistics | Reviewer: | Jinglin Zhong | Y |
| | TL: | Peiling Yang | Y |
| Nonclinical (Pharmacology/Toxicology) | Reviewer: | Amy Avila | Y |
| | TL: | Aisar Atrakchi | Y |
| Product Quality (CMC) | Reviewer: | Shastri Bhamidipati | |
| | TL: | David Claffey | Y |
| Quality Microbiology (<i>for sterile products</i>) | Reviewer: | Vinayak Pawar | N |
| | TL: | Stephen Langille | N |
| Facility Review/Inspection | Reviewer: | John Lee | N |
| | TL: | | |
| OSE/DMEPA | Reviewer: | Loretta Holmes | Y |
| | TL: | Rhiannon Leutner | |
| OSE/DRISK | Reviewer: | Cathy Miller | |
| | TL: | Kim Lehrfeld | |
| ONDQA Biopharmaceutics | Elsbeth Chikhale | | |
| OCP Pharmacometrics | Reviewer: | Xiaofeng Wang | Y |
| | TL: | Kevin Krudys | Y |
| Other attendees | Melissa Matles – ORP | | Y |
| | Colleen Locicero - ODEI | | Y |

FILING MEETING DISCUSSION:

| | |
|--|--|
| <p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? | <input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO |
|--|--|

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| <ul style="list-style-type: none"> ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p> | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| <ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p> | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| <ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p> | <input checked="" type="checkbox"/> Not Applicable |
| <p>CLINICAL</p> <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p> | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| <ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> | <input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: This drug is not the first in its class |
| <ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p> | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES |

| | |
|--|--|
| <p>or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</p> <p>Comments:</p> | <input type="checkbox"/> NO |
| <p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? | <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <p>BIOSTATISTICS</p> <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO |

| | |
|--|--|
| Comments: | |
| <p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| <p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p> | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <p><u>CMC Labeling Review</u></p> <p>Comments:</p> | <input type="checkbox"/> Review issues for 74-day letter |
| <p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? If so, were the late submission components all submitted within 30 days? | <input type="checkbox"/> N/A <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO |

| | |
|---|--|
| <ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? | N/A |
| <ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| <ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| <ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Ellis F. Unger, M.D.

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 1/20/2015

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

| | |
|-------------------------------------|---|
| <input type="checkbox"/> | The application is unsuitable for filing. Explain why: |
| <input checked="" type="checkbox"/> | <p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p> |

| ACTIONS ITEMS | |
|--------------------------|--|
| <input type="checkbox"/> | Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug). |
| <input type="checkbox"/> | If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER). |
| <input type="checkbox"/> | If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review. |
| <input type="checkbox"/> | BLA/BLA supplements: If filed, send 60-day filing letter |
| <input type="checkbox"/> | If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier) |
| <input type="checkbox"/> | Send review issues/no review issues by day 74 |
| <input type="checkbox"/> | Conduct a PLR format labeling review and include labeling issues in the 74-day letter |
| <input type="checkbox"/> | Update the PDUFA V DARRTS page (for NME NDAs in the Program) |
| <input type="checkbox"/> | BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f] |
| <input type="checkbox"/> | Other |

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

/s/

SHARONJIT K SAGOO
10/21/2014