CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	October 2, 2015
Reviewer(s):	Cathy A. Miller, MPH, B.SN Risk Management Analyst Division of Risk Management
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Drug Name(s):	Aristada (aripiprazole lauroxil) extended-release injection
Therapeutic Class:	Atypical Antipsychotic
Dosage and Route:	441 mg/1.6 mL; 662 mg/2.4 mL; 882 mg/3.2mL intramuscular injection
Application Type/Number:	NDA 207533
Submission Number:	ORIG-1 Submission Seq. No. 0000 dated August 22, 2014
Applicant/Sponsor:	Alkermes
OSE RCM #:	2014-1849

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1 INTRODUCTION

The purpose of this review by the Division of Risk Management (DRISK) is to evaluate the need for a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) aripiprazole lauroxil (N-lauroyloxymethyl aripiprazole) (Aristada™) originally submitted by Alkermes on August 22, 2014. The proposed indication for aripiprazole lauroxil is for the treatment of schizophrenia.

Alkermes did not submit a REMS with their application; however, the Sponsor did propose a Medication Guide (MG) that would be maintained outside of a REMS as a component of labeling.

1.1 PRODUCT BACKGROUND

Aripiprazole is an atypical antipsychotic originally approved by the FDA on November 15, 2002 as an oral tablet, Abilify (NDA 021436). Aripiprazole lauroxil has been submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act using Abilify oral aripiprazole tablet as the listed drug (LD). In September 2011, at the end of phase 2 (EOP2) meeting, the applicant discussed the possibility of relying in part on the Agency's previous findings of safety and efficacy for Abilify (aripiprazole) tablets.[1] Subsequently, on August 22, 2014, the applicant submitted an application for aripiprazole lauroxil that relies in part on the Agency's findings of safety and effectiveness for Abilify (aripiprazole) tablets.

Aripiprazole lauroxil consists of aripiprazole covalently bonded to a lauroyloxymethyl ester through a carbon-nitrogen bond. It is an ester of N-hydroxymethyl aripiprazole. . Aripirazole lauroxil is a prodrug of aripiprazole and considered a new molecular entity (NME) by the FDA.[2] The disposition of aripiprazole following aripiprazole lauroxil administration is qualitatively similar to that following oral administration. The mechanism of action of aripiprazole is unknown. However, the efficacy may be mediated through a combination of partial agonist activity D_2 and 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors.

The applicant proposes to supply aripiprazole lauroxil in pre-filled syringes for administration by a healthcare professional in a healthcare facility (physician's office, inpatient hospital, psychiatric inpatient facility) in three strengths including 441 mg/1.6 mL; 662 mg/2.4 mL; 882 mg/3.2mL for intramuscular (IM) injection to the gluteal (all dose levels) or deltoid muscle (441 mg dose only) every four (441 mg, 662 mg, 882 mg) or six weeks (882 mg only). For patients who have never taken aripiprazole before, the dosing regimen includes treatment with oral aripiprazole or other antipsychotics for 21 consecutive days with the first injection of aripiprazole lauroxil. Additional dosing regimen directives are provided when switching from other antipsychotics, when dose(s) are missed and for patients who are poor metabolizers of CYP2D6 or with concomitant use of CYP3A and CYP2D6 Inhibitors, or CYP3A4 Inducers.[3]

[1] Alkermes Original Submission for Aripiprazole lauroxil 505(b)(2) Reference Listed Drug Table appended to cover letter dated August 22, 2014 (Seq. No. 0000).

[2] Division of Psychiatry Products Advice/Information Request Letter for aripiprazole lauroxil (NDA 207533) dated April 3, 2013.

[3] Alkermes Original Submission Draft Package Insert Labeling for ARISTADA (aripiprazole lauroxil) NDA 207433 dated August 22, 2014.

1.2 DISEASE BACKGROUND

Schizophrenia is a severely debilitating mental illness that affects approximately 1% of the world's population. The illness, typically emerging between the late teens and mid-thirties, is characterized by the presence of positive symptoms (e.g., hallucinations and delusions) as well as negative symptoms (e.g., social withdrawal and lack of emotion, energy, and motivation).

The first antipsychotics developed for the treatment of schizophrenia were dopamine D2 receptor antagonists. These agents were effective against positive symptoms (e.g., hallucinations and delusions), but showed low efficacy for negative symptoms (e.g., social withdrawal and lack of emotion, energy, and motivation) and were also associated with a high incidence of hyperprolactinemia and extrapyramidal symptoms (EPS) (including tardive dyskinesia), and other adverse drug reactions including sedation, seizure, agranulocytosis, and neuroleptic malignant syndrome (NMS). Second-generation antipsychotics, commonly referred to as "atypical antipsychotics," are antagonists of both D2 and serotonin 5-HT2 receptors and represent a significant advancement in the treatment of psychotic disorders because they are efficacious and at the same time exhibit a reduced tendency to promote EPS relative to typical antipsychotics, especially tardive dyskinesia. Moreover, treatment with atypical antipsychotics has been shown to be associated with improved safety and tolerability compared to first-generation antipsychotics.

The tolerability of second-generation antipsychotics remains an important cause of medication discontinuation due to adverse drug reactions of somnolence, sedation, akathisia, hyperprolactinemia, and weight gain. Some agents have excess rates of weight gain (e.g., olanzapine and quetiapine), while others have high rates of hyperprolactinemia and associated sexual dysfunction or sedation.

Long-acting injectables (LAI) provide an important option for treating schizophrenia and evidence suggests that LAIs offer an option for treatment that appears to improve adherence, resulting in better outcomes for patients suffering from the disease.[4] Additionally, since LAIs are administered by the health care provider, the risk of deliberate or inadvertent overdoses is minimized. There is a need for an LAI treatment option that could provide greater flexibility in dosing and dose intervals to better suit specific patient needs as well as additional convenience and ease of use with reduced risk for medication errors.

Several LAI formulations currently exist for atypical antipsychotics including Risperdal Consta, Invega Sustenna, Abilify Maintena, and Zyprexa Relprevv. Additionally, older generation depot formulations are available and use typical antipsychotic agents including chlorpromazine, properidol, fluphenazine, haloperidol, loxapine, perphenazine, pimozide, prochlorperazine, thiothixene, thioridazine and trifluoperazine. Of these available options, only Zyprexa Relprevv is available through a restrictive REMS program with elements to assure safe use.

1.3 REGULATORY HISTORY

The following is a summary of the regulatory history relevant for NDA 207533:

[4] Kane, JM et. al. (2009) Clinical guideline recommendations for antipsychotic long-acting injections. Br J Psychiatry Suppl 52:S63-S67.

On August 22, 2014, Alkermes submitted their original submission 505(b)(2) application (NDA 207533) for Aristada (aripiprazole lauroxil) for the proposed indication of treatment of schizophrenia.

On September 9, 2014, Otsuka Pharmaceuticals, the Sponsor for the LD Abilify (NDA 021436), filed a Citizen's Petition (FDA-2014-P-1354) to the Agency asserting Alkermes had not submitted sufficient data for FDA to accept the application for review. On February 3, 2015, FDA denied the Petition without comment on whether FDA would take the actions that Otsuka requested.

On November 3, 2014, Division of Psychiatry Products (DPP) issued a Filing Communication/No Filing Issues Identified letter to Alkermes for NDA 207533. The user fee goal date was subsequently designated as August 22, 2015.[5]

On January 20, 2015, DPP held the mid-cycle meeting for Aristada, reporting findings to-date based on discipline reviews for the NDA. At that time, safety findings for the application were found to align with those reported by the Sponsor in their submission and there were no new findings that needed considerations for risk management strategies. On February 18, 2015, DPP sent a Mid-Cycle Communication reflecting these findings, along with information requests for various disciplines.[6]

On July 13, 2015, Otsuka Pharmaceuticals, the Sponsor for the LD Abilify (NDA 021436), filed a Citizen's Petition (FDA-2015-P-2482) to the Agency asserting that Alkermes had not submitted sufficient data for FDA to approve the application and that the exclusivity for Abilify Maintena bars approval of Alkermes' NDA.

2 MATERIALS REVIEWED

The following is a list of materials used to inform this review:

- Alkermes Original Submission for Aristada (aripiprazole lauroxil) dated August 22, 2014 (Seq. No. 0000):
    - Section 1.14.1 Draft Labeling for Aristada
    - Section 2.7.3 Summary of Clinical Efficacy
    - Section 2.7.4 Summary of Clinical Safety
- Alkermes General Correspondence submission (regarding the Otsuka Citizen Petition) for Aristada (aripiprazole lauroxil) dated October 15, 2014 (Seq. No. 0003)
- Kempf, L., Division of Psychiatry Products Clinical Reviewer (Safety and Efficacy) of Aristada (aripiprazole lauroxil), Division of Psychiatry Products draft review dated October 2, 2015
- Division of Psychiatry Products. Mid-cycle Communication for Aristada (aripiprazole lauroxil) NDA 207533 dated February 18, 2015

[5] Division of Psychiatry Products Filing Communication/No Filing Review Issues Identified for Aristada (aripiprazole lauroxil) NDA 207533 dated November 3, 2014.

[6] Division of Psychiatry Products (DPP) Mid-Cycle Communication for Aristada (aripiprazole lauroxil) NDA 207533 dated February 18, 2015.

3 CLINICAL DEVELOPMENT PROGRAM[7]

ALK9072-003 was a global, multicenter, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy of treatment with once monthly IM aripiprazole lauroxil (441 mg and 882 mg) as compared to placebo over a period of 12 weeks in subjects with schizophrenia experiencing an acute exacerbation episode. Subjects were randomized in a 1:1:1 ratio to 1 of the three treatment groups: aripiprazole lauroxil 882 mg, aripiprazole lauroxil 441 mg, or placebo (Intralipid®). Three doses of IM study drug were administered on Days 1, 29, and 57. In addition to IM study drug, subjects received oral aripiprazole tablets daily for the first three weeks after randomization. Oral aripiprazole tablets were administered in a double-blind fashion. Subjects randomized to an aripiprazole lauroxil treatment group received oral aripiprazole (15 mg daily), and subjects randomized to the placebo group received matching oral placebo.

3.1 OVERVIEW OF EFFICACY

Efficacy for aripiprazole lauroxil was assessed using the Positive and Negative Syndrome Scale (PANSS), a multi-item inventory of psychopathology used to evaluate the effects of drug treatment in schizophrenia, and was chosen as the primary efficacy parameter. The primary efficacy endpoint was the change from baseline to Day 85 in PANSS total score. The Clinical Global Impression – Severity (CGI-S) scale, a 7-point scale ranging from 1 (very much improved) to 7 (very much worse), which measures the change from baseline in the overall severity of illness in the individual patients relative to his/her baseline was used for the secondary efficacy assessment. The secondary endpoints assessed the change from baseline in the overall severity of illness in a patient relative to his/her baseline using the CGI-I scale.

A total of 623 subjects were randomized and 622 received at least one injection of IM study drug. A total of 596 subjects [aripiprazole lauroxil 441 mg (n=196), aripiprazole lauroxil 882 mg (n=204), or placebo (n=196)] were used for all efficacy analyses.

In pivotal study ALK9072-003, there was statistically significant ($p< 0.05$) improvement over placebo for each Aristada dose group for the primary and secondary endpoints, across all three regions where the study was conducted, and across all study time points, starting with Day 8 through Day 85, the end of the 12-week treatment period.

3.2 OVERVIEW OF SAFETY

The safety assessment was based on aripiprazole lauroxil dose ranges of 221 mg to 882 mg IM injection evaluated in the one Phase 3 pivotal study ALK9072-003, and four Phase 1 studies (ALK9072-001, ALK9072-002, ALK9072-101, and ALK9072-102). Long-term safety was assessed using the data from two ongoing 52-week open-label extension studies (ALK9072-003EXT and ALK9072-003EXT2) using the cut-off date of April 30, 2014.

As of the cutoff date, the integrated summary of safety (ISS) for aripiprazole lauroxil included a total of 880 subjects who had received at least one IM injection. Of these, 622 subjects had received at least three IM injections, 276 had received at least six IM injections, and 66 had received at least 12 IM injections. Because of differences in study designs, dosages, and patient populations across all studies, the studies presented in the ISS were organized into two groups:

[7] Alkermes Original Submission of Aristada (aripiprazole lauroxil) NDA 207533 dated August 22, 2014 (Seq. No. 0000)

- Group 1: Subjects from the controlled study (ALK9072-003); treatment groups are placebo, aripiprazole lauroxil 441 mg, aripiprazole lauroxil 882 mg
- Group 2: Subjects from the long-term extension study, ALK9072-003EXT as of April 30, 2014 plus data for aripiprazole lauroxil rollover subjects from Study ALK9072-003. The treatment groups are aripiprazole lauroxil 441 mg (rollover subjects: placebo-441 mg and 441 mg-441 mg) and aripiprazole lauroxil 882 (rollover subjects: placebo-882 mg and 882 mg-882 mg; de novo subjects: 882 mg).

Deaths

Two deaths were reported as of the cut-off date of April 30, 2014. The first subject (Subject 128-006) was the victim of a homicide and the second subject was a 39 year old white male (Subject 710-700) receiving IM aripiprazole lauroxil 882 mg (de novo) and oral aripiprazole 15mg who committed suicide. Following psychiatric review, the investigator recorded this as a serious adverse event (SAE) of schizophrenia (worsening) of moderate intensity and possibly related to study drug by the investigator.

Treatment Emergent Adverse Events (TEAEs)

TEAEs were reported in 526 subjects overall (59.8%) and the event was considered related to study drug in 347 subjects (39.4%). Based on the Sponsor's submission, TEAEs with incidence of ≥2% that were reported more frequently in both aripiprazole lauroxil groups than in the placebo groups include akathisia, injection site pain, weight increase, nausea, blood creatinine phosphokinase increase, sedation and toothache. Akathisia was the only TEAE with incidence of ≥5% in each aripiprazole lauroxil group and at least twice the rate of placebo (11.6%, 11.5% and 4.3% of subjects in the aripiprazole lauroxil 441 mg, 882 mg and placebo groups respectively). Two subjects discontinued with a TEAE of akathisia and the vast majority of the events of akathisia had an onset before the second administration of the drug.

Serious Adverse Events (SAEs)

During the treatment period for Group 1, SAEs were reported by four subjects (1.9%) in the placebo group, three subjects (1.4%) in the aripiprazole lauroxil 441 mg group, and four subjects (1.9%) in the aripiprazole lauroxil 882 mg group. One of the SAEs (akathisia in the 882mg group) was determined by the investigator to probably be related to study drug. There were similar rates of SAEs in all arms of the study and akathisia, the only SAE determined to probably be related to study drug, is expected for atypical antipsychotics.

During the treatment period for Group 2, SAEs were reported in ten subjects. Three of the SAEs were determined by the investigator to possibly be related to the study drug (depressed mood, schizophrenia, completed suicide) and one SAE was determined to probably be related (aggression). All of the SAEs possibly related to the study drug were expected AEs for atypical antipsychotics.

The DPP clinical reviewer stated, in summary, "There were no new safety findings for this 505(b)(2) application. The trials did not reveal any surprising injection site reactions due to aripiprazole lauroxil and *N*-hydroxymethyl aripiprazole."[8]

[8] L Kempf, Clinical Review of aripiprazole lauroxil (NDA 207553), DARRTS October 2, 2015.

4 DISCUSSION

The clinical development program for Aristada demonstrated efficacy for the treatment of schizophrenia. The AEs seen in the clinical program for Aristada were expected findings and were comparable to the AEs seen in the Abilify (aripiprazole) line of products, including Abilify oral tablets[9], oral solution, and injection, along with Abilify Maintena (aripiprazole) extended-release injection. The safety profile of Aristada was also similar to other approved atypical antipsychotics based on their approved labeling.

The proposed labeling includes the same boxed warning, for increased mortality in elderly patients with dementia-related psychosis due to cerebrovascular accidents (CVAs), as all other atypical antipsychotics. It also includes a MG for patients that addresses this same risk and the risk of neuroleptic malignant syndrome, which is also associated with all approved atypical antipsychotics. If approved, Aristada is expected to be prescribed by similar prescribers and to be prescribed to similar patients as other LAI atypical antipsychotics. Therefore, this LAI atypical antipsychotic does not have any unique risks that would need to be specially communicated to either prescribers or patients beyond the proposed professional labeling.

There are 4 other LAI atypical antipsychotics approved in the US for the treatment of schizophrenia: Risperdal Consta (risperdal), Invega Sustenna (paliperidone palmitate), Abilify Maintena (aripiprazole), and Zyprexa Relprevv (olanzapine pamoate). Zyprexa Relprevv has a REMS to mitigate, post-injection delirium sedation syndrome (PDSS). None of the other approved LAI antipsychotics or Aristada have been associated with PDSS. Therefore, PDSS is unique to Zyprexa Relprevv. No other atypical antipsychotics, oral or LAIs, have a REMS.

A REMS is not necessary to ensure that Aristada benefits outweigh the risks. Professional labeling, including a MG, is sufficient to address the risks identified in the clinical development program with Aristada.

5 CONCLUSION AND RECOMMENDATIONS

In conclusion, risk mitigation measures beyond labeling, including a Medication Guide, are not warranted for Aristada (aripiprazole lauroxil). Based on the currently available data, the benefit-risk profile for Aristada is acceptable for the treatment schizophrenia. Therefore, based on the currently available data, DRISK does not recommend a REMS as necessary to ensure the benefits of Aristada outweigh the risks at this time.

Should DPP have any concerns or questions, feel that a REMS may be warranted for this product, or if new safety information becomes available, please send a consult to DRISK.

[9] Otsuka Pharmaceutical Co., Abilify © Prescribing Information, 2014.

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/s/

KIMBERLY LEHRFELD
10/02/2015

REEMA J MEHTA
10/02/2015
I concur.