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APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Deputy Office Director Decisional Memo

Date	(electronic stamp)
From	Robert Temple, MD
Subject	Deputy Office Director Decisional Memo
NDA/BLA # **Supplement #**	207553
Applicant Name	Alkermes Inc
Date of Submission	August 22, 2014
PDUFA Goal Date	August 22, 2015
Proprietary Name / **Established (USAN) Name**	Aristada/Aripiprazole lauroxil
Dosage Forms / Strength	extended-release injectable suspension, for intramuscular use
Proposed Indication(s)	Schizophrenia
Action:	

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Lucas Kempf, MD
Statistical Review	Jinglin Zhong, PhD (reviewer) Peiling Yang, PhD (TL) HM James Hung, PhD
Pharmacology Toxicology Review	Amy Avila, PhD (reviewer) Aisar Atrakchi, PhD (TL)
CMC Review	Sherita McLamore-Hines, PhD (reviewer) Wendy Wilson-Lee, PhD (Branch Chief)
Microbiology Review	Vinayak Pawar, PhD (reviewer) Stephen Langille, PhD (TL)
Clinical Pharmacology Review	Praveen Balimane, PhD (reviewer) Hao Zhu, PhD (TL)
OSI	Jenn Sellers, MD, PhD, FAAP Susan D Thompson, MD (TL) Kassa Ayalew, MD, MPH (Branch Chief)
CDTL Review	Lucas Kempf, MD/Mitch Mathis, MD
OSE/DMEPA	Loretta Holmes, BSN, PharmD (reviewer) Rhiannon Leutner (TL)
OSE/DRISK	Cathy Miller, MPH, BSN Kim Lehrfeld, PharmD
Dep Dir for Safety Review	none

OND=Office of New Drugs
OPDP=Office of Prescription Drug Products
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Reference ID: 3829345

I. Background

Aristada contains aripiprazole lauroxil which is an ester of N-hydroxymethyl aripiprazole. N-hydroxymethyl aripiprazole is the active moiety of aripiprazole lauroxil. Although an ester of aripiprazole would not be a new molecular entity (NME) because an ester of a previously approved or previously marketed active moiety is not considered an NME, an ester of N-hydroxymethyl aripiprazole is an NME, as N-hydroxymethyl aripiprazole has never been approved or marketed. Following intramuscular injection, aripiprazole lauroxil is probably converted by enzyme-mediated hydrolysis to N-hydroxymethyl aripiprazole (the NME), which is then hydrolyzed to aripiprazole. NDA 207533 for Aristada was submitted as a 505(b)(2) NDA, relying in part on the Agency's previous finding that Abilify Tablets (oral aripiprazole tablets) is safe and effective. Aripiprazole lauroxil is prepared as an extended release intramuscular injection. It is available in 3 strengths, 441, 662, and 882 mg and is given every 4 or 6 weeks (only the 882 mg dose is given every 6 weeks) as maintenance treatment for schizophrenia initially treated with oral aripiprazole. There are many long-acting injectable formulations of atypical and typical antipsychotics. All have the advantage of avoiding the need for daily oral dosing in a population that would not be expected to be uniformly compliant.

The usefulness, effectiveness, and safety tolerability of injectable atypical antipsychotic drugs is discussed by Drs. Kempf and Mathis and I will not consider these issues in detail. Dr. Kempf also summarizes chemistry issues, noting the sponsor's commitment to performing ongoing stability analyses "to assess the mechanical reliability of the fully assembled device through the expiration of the drug product." These assessments will be reported in annual reports. Pre-clinical information is also summarized by Dr. Kempf. The active moiety determination for purposes of the new chemical entity (or NCE) analysis is set forth in Dr. Schmuff's memorandum and I will not duplicate it here.

II. Effectiveness

Details of the phase 3 clinical trial, ALK 9072-003, supporting the effectiveness of aripiprazole lauroxil can be found in the reviews by Drs. Kempf and Zhong and the trial is further discussed in Dr. Mathis's Division Director Review. As Dr. Mathis notes, it might be argued that pharmacokinetic (PK) aripiprazole blood level data alone could support the effectiveness of the new drug. Aripiprazole has quite steady blood levels after oral administration (half-life is 75 hours). If oral and injected drug yielded similar levels or aripiprazole after a reasonable period, effectiveness would be assured. On the other hand, blood levels after aripiprazole lauroxil rise quite slowly, and oral aripiprazole must be given when it is initiated, so that a study of just how to use it is a reasonable requirement.

Fig 1 from Dr. Kempf's review shows the simulated mean aripiprazole concentrations after 3 different doses of aripiprazole lauroxil and oral doses of 10 mg or 30 mg daily. It takes a full 4-8 weeks before the blood levels after injection reach blood levels produced by 10 mg of oral aripiprazole, clearly showing the need for an oral lead-in period, but also showing that levels are in the therapeutic range.

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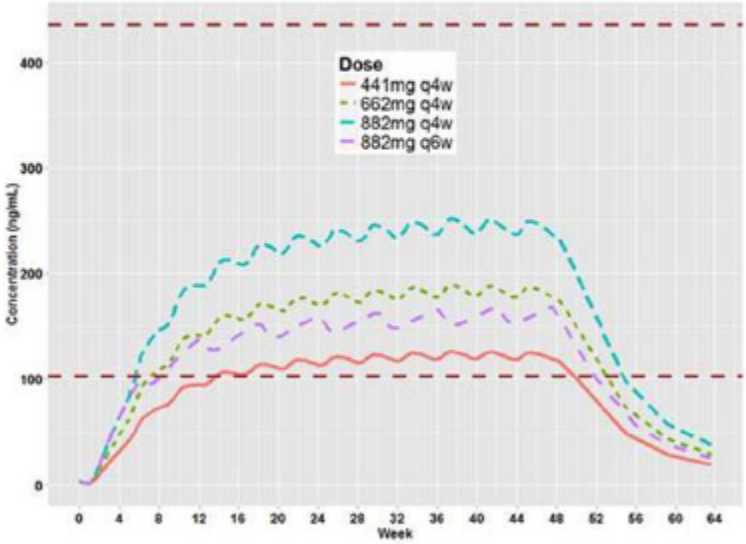
Figure 1: Shows the simulated mean aripiprazole Concentration Time Profiles following 441 mg, 662 mg, and 882 mg Monthly and 882 mg every 6 weeks doses up to Steady State. The Lower Dash Line Represents the Mean Steady State Cmin following 10 mg Daily Oral Doses of Abilify Tablets and the Upper Dash Line Represents the Mean Steady State Cmax following 30 mg Daily Oral Doses of AbilifyTablets.



Study ALK 9072-003 was a global, randomized, double-blind comparison of IM aripiprazole lauroxil at 2 doses, 441 and 882 mg with placebo over 12 weeks in schizophrenic patients experiencing an acute exacerbation. During the first 3 weeks patients randomized to active drug were given oral aripiprazole doses of 15 mg per day, which would give aripiprazole blood levels of about 150 ng/mL (in the figure above 10 mg gives blood levels of about 100 ng/mL).

Patients were age 18-70 with an acute exacerbation or relapse of schizophrenia and had to have, at screening and baseline, a PANSS (Positive and Negative Syndrome Scale) of 70-120, with a score of ≥ 4 on at least 2 of the following 4 items (delusions, conceptual disorganization, hallucinatory behavior, and suspiciousness/persecution), as well as a score of ≥ 4 on Clinical Global Impression (CGI) severity.

A total of 623 patients were randomized, with 360 completing the 12-week study. Analyses using LOCF (last observation carried forward) and MMRM (mixed model for repeated measures) gave similar results.

An obvious concern with the design would be whether the effect of aripiprazole lauroxil injection could be distinguished from the effect of the 3 weeks of oral therapy, which could have an effect that persisted. The statistical reviewer considered this issue and found a clear effect of the test drug using 21 day and 29 day values as baselines, a time after the oral treatment was stopped, showing a clear effect of aripiprazole lauroxil well after the oral drug would have been eliminated (see Zhong's review, pages 21-2).

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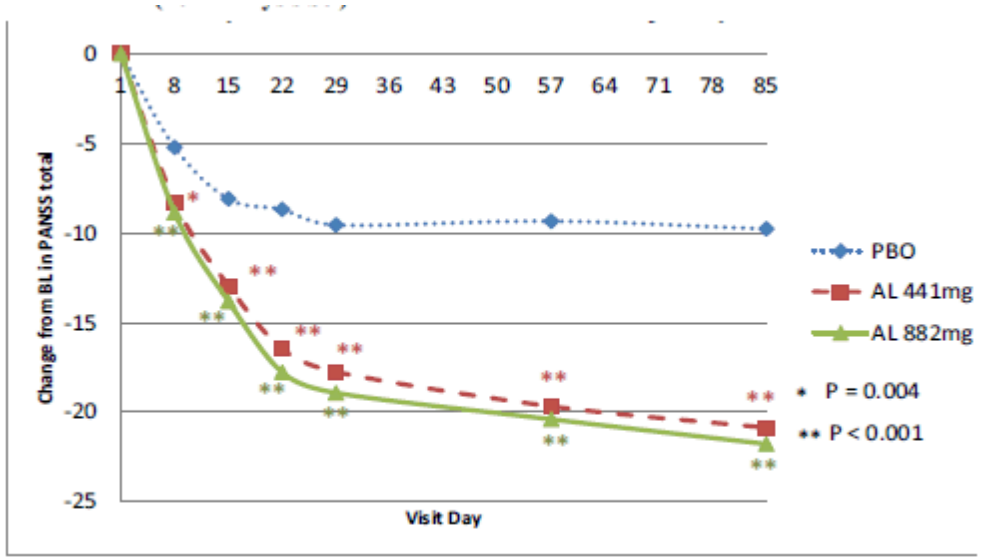
The overall study results are described in the Division Director, Medical Reviewer, Statistical Reviewer, and Pharmacology Reviewer memos. The LOCF analysis of all patients showed the following results (MMRM gave a similar result).

	Placebo n = 196	Aripiprazole 441 mg n = 196	Aripiprazole 882 mg n = 204
Baseline Mean (SD)	93.9 (11.3)	92.6 (10.2)	920 (10.8)
Change, day 85	-9.8 (1.4)	-20.9 (1.4)	-21.8 (1.4)
Diff vs Plbo	___	-11.1 (1.8)	-12.0 (1.8)
P value vs Plbo	___	< 0.001	< 0.001

Results of the trial are also shown in Figure 2 (from the statistical review).

Figure 2: Change from baseline in PANSS total score by visit by ANCOVA LOCF (FAS)



Abbreviations: AL=aripiprazole lauroxil; ANCOVA=analysis of covariance; PBO=placebo; PANSS=Positive and Negative Syndrome Scale; LOCF=last observation carried forward.

There was clearly no advantage in this study of the higher dose, but given the dose range of the marketed oral drug, I do not believe dose should be restricted.

The figure above shows a continued gain vs placebo after 21-26 days (when oral drug was stopped). Dr. Zhong's analysis of data after those days (see tables 18, 19 from the review) shows a clear continued gain over placebo that can be attributed only to the IM drug, clear evidence of its effect.

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Table 18: Change from baseline in PANSS total score using ANCOVA LOCF (Day 22 as Baseline)

	Total (n = 455)		
	Placebo (n=136)	441 mg (n =154)	882 mg (n = 165)
Day 22: Mean (SD)	79.9 (17.3)	74.6 (15.6)	73.3 (15.7)
Day 85: Mean (SD)	79.7 (20.2)	69.7 (18.6)	69.2 (19.0)
Change from Day 22 to Day 85: Mean (SD)	-0.2 (14.7)	-4.8 (11.3)	-4.2 (13.9)
LSmean change from Day 22 to Day 85 Mean(95% CI)	-0.6 (-2.9, 1.6)	-5.9 (-8.1, -3.7)	-5.3 (-7.4, -3.2)
Diff from placebo: LSMean (95% CI) pvalue		-5.3 (-8.3, -2.3) 0.0005	-4.6 (-7.6, -1.7) 0.002

Note: The confidence intervals and p-values are not adjusted by multiple comparisons.
Source: This reviewer.

Table 19: Change from baseline in PANSS total score using ANCOVA LOCF (Day 29 as Baseline)

	Total (n=412)		
	Placebo (n=115)	441 mg (n=144)	882 mg (n=153
Day 29: Mean (SD)	76.5 (17.2)	72.6 (16.9)	71.5 (16.8)
Day 85: Mean (SD)	76.8 (19.1)	68.8 (18.6)	68.2 (18.9)
Change from Day 29 to Day 85: Mean (SD)	0.2 (13.8)	-3.9 (11.6)	-3.2 (12.1)
LSmean change from Day 29 to Day 85 Mean(95% CI)	-0.01 (-2.3, 2.3)	-4.5 (-6.6, -2.4)	-4.0 (-6.0, -2.0
Diff from placebo: LSMean (95% CI) pvalue		-4.5 (-7.4, -1.6) 0.0026	-4.0 (-6.9, -1.1 0.0073

Note: The confidence intervals and p-values are not adjusted by multiple comparisons.
Source: This reviewer.

Demographic Analyses [Mathis review] showed similar results in men and women, somewhat smaller effects in blacks and in North America, but overall, no large differences.

Based on blood level data and study results, in addition to the tested 441 and 882 mg every 4 week dosing, we are approving a 662 mg dose and an 882 mg dose given every 6 weeks.

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III. Conclusion

Aristada (aripiprazole lauroxil) is an effective intramuscular treatment for schizophrenia that should be approved at doses of 441, 662, and 882 mg monthly, and 882 mg given every 6 weeks. The drug should always be initiated as an addition to oral aripiprazole at 10, 15 or 20 mg per day, depending on the planned IM dose (441, 662, or 882 mg). The drug has the usual adverse effects of the atypical antipsychotic class, notably akathisia and dystonia, and would be expected to cause tardive dyskinesia with long use. Aristada has been demonstrated to be safe.

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/s/

ROBERT TEMPLE
10/05/2015