CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209905Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review
Division Director Summary Review

Date	*see electronic date*
From	Bernard Fischer, MD Tiffany R. Farchione, MD
Subject	Cross-Discipline Team Leader Review Division Director Summary Review
NDA Number	NDA 209905
Applicant	Arbor Pharmaceuticals
Date of Submission	03/30/2018
PDUFA Goal Date	01/30/2019
Proprietary Name	Evekeo ODT
Non-proprietary Name	amphetamine sulfate, orally disintegrating
Dosage Form(s)/Strength(s)	tablets; 5, 10, 15, 20, (b) (4) mg
Proposed Indication	attention-deficit/hyperactivity disorder (ADHD)
Proposed Population	Children 6 years and older
Recommended Regulatory Action	Approval of 5, 10, 15, and 20 mg strengths

1. Introduction

NDA 209905 is an application for approval of amphetamine sulfate orally disintegrating tablets (ODT) for the treatment of attention-deficit/hyperactivity disorder in pediatric patients 6 to 17 years of age. The Applicant is using the 505(b)(2) pathway and referencing their own immediate-release amphetamine sulfate (Evekeo, ANDA 200166). The original listed drug (NDA 083901), manufactured by Lannett, is discontinued. FDA had approved NDA 083901 as part of the Drug Efficacy Study Implementation (DESI) program.

The Applicant submitted two trials to demonstrate the pharmacokinetic profile of their ODT formulation:

- Comparative bioavailability study (AR17.001), entitled, "Comparative Bioavailability Study of Single-Dose Amphetamine Sulfate Oral Disintegrating Immediate Release Tablets (ODT-IR) Swallowed Intact with Water versus Single-Dose ODT-IR Tablets Disintegrated/Dissolved in the Oral Cavity Swallowed without Water versus Amphetamine Sulfate Immediate Release (IR) Reference Tablets (Evekeo) Administered to Fasting, Healthy Adult Volunteers."

- Food-effect bioavailability study (AR17.002), entitled, "A Single-Dose, Two-Period, Two-Way Crossover Bioavailability Study of Amphetamine Sulfate Oral Disintegrating Immediate Release Tablets (ODT-IR) 20 mg Administered to Healthy Adult Volunteers under Fed and Fasted Conditions."

The Applicant also submitted a clinical efficacy study comparing the listed drug, Evekeo, to placebo for inclusion in section 14 (Clinical Studies) of the ODT formulation's labeling: Study AR11.001, entitled, "A Multicenter, Dose-Optimized, Double-Blind, Randomized, Placebo-Controlled, Crossover Study to Evaluate the Efficacy of AR11 in Pediatric Patients (Ages 6-12) with Attention Deficit Hyperactivity Disorder (ADHD) in a Laboratory Classroom." The review team confirmed with the 505(b)(2) Committee that inclusion of this study in the ODT labeling was permitted because the Applicant owned both drugs. They advised that the decision on its inclusion was ultimately a review issue. The review team evaluated the study under this NDA submission and determined that it was appropriate for inclusion in the ODT label. In addition to section 14, it informed section 6 (Adverse Reactions).

2. Summary of Conclusions and Recommendations from the Review Team

2.1 Office of Study Integrity and Surveillance (OSIS)

OSIS declined to inspect sites related to this application and recommended the data should be accepted because they had recently inspected the sites and the outcome was classified as No Action Indicated (NAI).

2.2 CMC

The CMC review was performed by:

- Drug Substance, Drug Product: Andrei Ponta (primary), Wendy Wilson-Lee (secondary)
- Process/Microbiology, Facility: Hang Guo (primary), Derek Smith (secondary)
- Biopharmaceutics: Parnali Chatterjee
- Technical Lead: David Claffey

2.1.1 Product Overview

The drug substance is a 1:1 racemic mixture. The drug product is an immediate-release orally disintegrating tablet. It should be stored at room temperature with the Applicant's proposed expiration period of 24 months. All proposed strengths (5, 10, 15, 20, (b) (4) met the (b) (4) limit for disintegration. The Applicant's request for biowaivers for 5, 10, 15, (b) (4) mg strengths was acceptable.

2.1.2 Product Assessment Overview

The manufacturing process and facilities are adequate. The drug product is packed in blisters with lower strengths (15 mg and lower) packaged in 30-count blisters and higher strengths in 15-count blisters. The packaging technical specifications and container closure system are adequate.

2.1.3 CMC Recommendation

The CMC Team recommends approval.

2.2 Clinical Pharmacology

The primary Clinical Pharmacology reviewer was Kofi Kumi; the secondary reviewer was Team Leader Luning (Ada) Zhuang.

2.2.1 Clinical Pharmacology Findings

- d,l-amphetamine concentrations after administration of Evekeo ODT with or without water are equivalent to those after administration of Evekeo IR conventional tablet.
- Food does not have significant effect on the exposures (Cmax, AUC) of d,l-amphetamine after administration of Evekeo ODT under fed and fasting conditions. Evekeo ODT can be administered with or without food.
- The dosing regimen of Evekeo IR conventional tablet is acceptable to be used for Evekeo ODT.

2.2.2 Clinical Pharmacology Recommendation

The Clinical Pharmacology Team recommends approval.

2.3 Clinical

The primary Clinical reviewer was John Umhau; the secondary reviewer was Team Leader Bernard Fischer. The primary Biometrics reviewer was Ququan Liu; the secondary reviewer was Team Leader Peiling Yang.

2.3.1 Clinical Findings, Studies AR17.001 and AR17.002

There were no deaths or nonfatal serious adverse events (SAEs) in any of the studies submitted to support this application.

The clinical review found no new safety findings in Studies AR17.001 and AR17.002 that would indicate a difference in the risk-benefit profile for the ODT product versus the listed drug. No adverse event (AE) was reported for more than two subjects and AEs were consistent with other medications of this class (e.g., abdominal pain, headache, anxiety).

2.3.2 Clinical Efficacy Findings, Study AR11.001

Study AR11.001 enrolled children with ADHD ages 6 to 12 years. It included an 8-week “dose optimization” phase on amphetamine (AR11) followed by a placebo-controlled, randomized cross-over phase. During the cross-over phase, subjects were randomly assigned to either continue AR11 or to switch to placebo. After 1 week, subjects received only the morning dose of study drug and completed a laboratory classroom evaluation. For the second week of the cross-over phase, subjects who had been receiving placebo were re-started on their optimized AR11 dose; those who had continued on AR11 were now switched to placebo. Again after 1 week, subjects received only the morning dose of study drug and completed a laboratory classroom evaluation. There was no washout period. On-AR11 periods and on-placebo periods were combined for analysis.

Efficacy was measured using the Swanson, Kotkin, Agler, M-Flynn, Pelham Rating Scale (SKAMP) at 0.75, 2, 4, 6, 8, and 10 hours post-dose. The primary efficacy endpoint was the

SKAMP combined score at 2 hours post-dose. Prespecified secondary endpoints included the first timepoint where AR11 separated from placebo and the last time point where AR11 separated from placebo. The Applicant referred to these time points as "onset of clinical effect" and "duration of clinical effect." However, the Division disagrees that statistical separation from placebo equates to clinical effect. Clinical effect is determined by comparing drug to placebo, but also by the clinical meaning of absolute changes relative to baseline.

Per the Biometrics review:

> …a mixed-model, repeated-measures analyses was performed on the ITT population (defined as all randomized subjects who received at least one dose of double-blind study drug and had at least one post-dose assessment of the primary efficacy variable), with study center, period (1 and 2), sequence (AR11/placebo and placebo/AR11), and time point (0.75, 2, 4, 6, 8, and 10 hours post-dose)-by-treatment (AR11 and placebo) interaction as fixed effects and subject's intercept as a random effect. An unstructured covariance matrix was used to model within subject/within-treatment variability. The treatment difference was estimated using least-squares (LS) means from the mixed-effects repeated-measures model. The treatment comparison was conducted as a 2-sided test at the 0.05 level of significance.

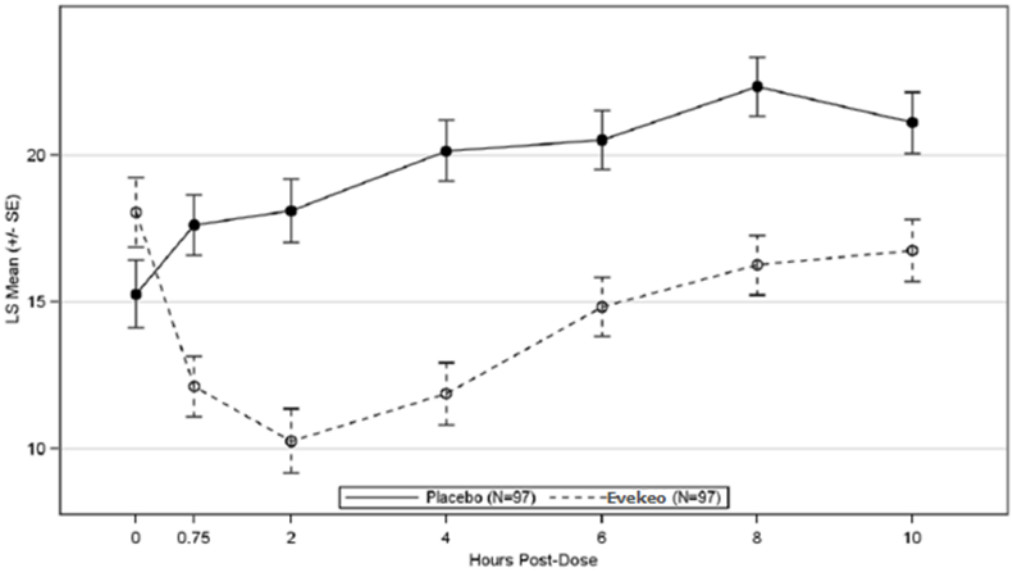
The Applicant demonstrated statistically significant separation from placebo at all time points (see Table 1 and Figure 1). These differences appeared clinically meaningful for time points 0.75, 2, and 4 hours post-dose. At 6 hours post-dose, the AR11 group was equal to the placebo group's baseline. At 8 and 10 hours, the separation from placebo appeared to be due to the placebo group's worsening and the improvement from baseline in the AR11 group was no longer evident.

Table 1. Time Course of Effect on SKAMP Combined Scores.

Time point	AR11 LS Mean (SE) N=97	Placebo LS Mean (SE) N=97	LS Mean (SE) N=97	p-value	95% CI
0.75 hours postdose	12.1 (1.03)	17.6 (1.02)	−5.5 (1.01)	<0.0001	−7.5, −3.5
2 hours postdose	10.3 (1.09)	18.1 (1.09)	−7.9 (1.14)	<0.0001	−10.1, −5.6
4 hours postdose	11.9 (1.05)	20.2 (1.05)	−8.3 (1.06)	<0.0001	−10.4, −6.2
6 hours postdose	14.8 (1.00)	20.5 (1.00)	−5.7 (0.96)	<0.0001	−7.6, −3.8
8 hours postdose	16.3 (1.01)	22.3 (1.00)	−6.1 (0.96)	<0.0001	−8.0, −4.2
10 hours postdose	16.8 (1.05)	21.1 (1.04)	−4.3 (1.05)	<0.0001	−6.4, −2.3

Source: FDA, Biometrics Review.

Figure 1. Least-square Mean SKAMP Combined Score.



Source: Applicant study report.

2.3.2 Clinical Safety Findings, Study AR11.001

The Study's design (an 8-week dose optimization phase) makes interpretation of safety findings difficult. During the dose optimization phase, AEs reported in > 5% of patients included: anorexia (28%), infections (22%), abdominal pain (15%), irritability (14%), headache (13%), nausea (6%), vomiting (6%), affect lability (includes mood swings; 9%), tachycardia (109%), insomnia (10%), fatigue (10%),and dry mouth (6%). Six patients discontinued due to adverse reactions during the dose-optimization phase: irritability (n=3), affect lability (n=1), initial insomnia (n=1), and rash (n=1).

During the double-blind cross-over phase, AEs were as represented in Table 2.

Table 2. AEs Reported in ≥ 2%, and > Placebo, of EVEKEO -Treated Pediatric Patients (6 to 12 Years) During the Double-Blind Cross-Over Weeks; Study AR11.001.

System Organ Class Preferred Term	**AR11** n=97	**Placebo** n=97
Subjects with at least one AE	22%	14%
Gastrointestinal Disorders		
Abdominal pain	3%	0%
Injury, Poisoning, and Procedural Complications		
Injury	3%	2%
Metabolism and Nutrition Disorders		
Decreased appetite	4%	0%
Psychiatric Disorders		
Affect lability[a]	3%	0%
Insomnia	4%	0%

[a]Includes mood swing.
Source: FDA, Clinical Review.

There were no clinically meaningful differences in abnormal laboratory results or vital signs between the two groups.

2.3.3 Clinical Concerns with Tablet Strengths

Dosing and administration for the listed drug state, “Start with 5 mg once or twice daily; daily dosage may be raised in increments of 5 mg at weekly intervals until optimal response is obtained. Only in rare cases will it be necessary to exceed a total of 40 milligrams per day.” The listed drug, Evekeo, is only available in 5 and 10 mg strengths. In clinical practice, IR stimulants are dosed twice-per-day as they are generally only clinically effective for approximately 4 hours. ODT formulations are usually targeted to younger children who have difficulty swallowing tablets.

(b) (4)

(b) (4)

2.3.4 Clinical Recommendation

The Clinical Team recommends approval of the 5, 10, 15, and 20 mg strengths.

2.4 Pharmacology/Toxicology

The primary Pharmacology/Toxicology Reviewer was Deepa Rao; the secondary reviewer was Team Leader Ikram Elayan.

2.3.1 Pharmacology/Toxicology Findings

The Applicant did not submit any nonclinical studies. There are no new or novel excipients; all listed excipients are at acceptable levels per the Agency's Inactive Ingredients Database.

2.3.2 Pharmacology/Toxicology Recommendation

The Pharmacology/Toxicology Team recommends approval.

2.5 Controlled Substance Staff (CSS)

The primary CSS reviewer was Alicja Lerner; her Director is Dominic Chiapperino.

2.4.1 Controlled Substance Staff Findings

- Section 9 (Drug Abuse and Dependence) of the proposed label is consistent with other amphetamine formulations, but is outdated. The Division and CSS will update language for stimulants as a class at a future date.
- Amphetamines are subject to the Controlled Substances Act in Schedule II.
- In the submitted studies, the Applicant did not observe abuse, overdose, or study drug diversion.

2.4.2 Controlled Substance Staff Recommendations

CSS recommends a future class-update to section 9 of stimulant labeling. They also recommend the Division consider future studies on stimulant withdrawal and rebound. Neither recommendation precludes approval of this application.

3. Summary of Labeling Review

The review team and the Applicant negotiated labeling to reach agreement. Below are the summaries for labeling-related reviews.

3.1 Division of Pediatrics and Maternal Health (DPMH)

The DPMH-Maternal Health medical officer, Cathy Roca, participated in internal team meetings with the Division. She determined no changes to labeling from the listed drug were warranted. DPMH Director Lynne Yao and Deputy Director John Alexander provided feedback on the phrasing of the pediatric dosing recommendations in section 2.

3.2 Division of Medication Error Prevention and Analysis (DMEPA)

Loretta Holmes, DMEPA reviewer, and Teresa McMillan, DMEPA Team Leader, reviewed the Applicant's proposed labeling and packaging. After communication with the Applicant to adjust the printing on the blister cards, DMEPA found the labeling and packaging acceptable.

3.3 Office of Prescription Drug Promotion (OPDP)

Domenic D'Alessandro, OPDP reviewer, and Aline Moukhtara, OPDP Team Leader, reviewed the Applicant's proposed labeling and packaging. After communication with the Division and negotiation with the Applicant, OPDP found the labeling and packaging acceptable.

4. Recommendations for Postmarketing Studies

The Division will require the postmarketing development of a 2.5 mg strength ODT tablet for use in children (b) (4) This postmarketing requirement (PMR) includes formulation development, pharmaceutical testing, generation of adequate stability data, and collection of adequate data supporting a biowaiver of this strength.

5. Conclusion and Recommendation

5.1 Recommended Regulatory Action

Approval of tablet strengths of 20 mg or less.

5.2 Risk-Benefit Assessment

The risk-benefit profile of this amphetamine sulfate formulation, in tablet strengths of 20 mg or less, does not differ from that of the approved listed drug.

5.3 Recommendation for Postmarketing Risk Evaluation and Management

The FDA-approved label and routine pharmacovigilance are adequate to manage the risk-benefit profile of this product.

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/s/

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