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APPLICATION NUMBER:

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NON-CLINICAL REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 209905
Supporting document/s:	Supporting Document Number 1, eCTD Sequence Number 0000
Applicant's letter date:	March 30, 2018
CDER stamp date:	March 30, 2018
Product:	Amphetamine sulfate IR-ODT
	Immediate release – orally disintegrating tablets
Indication:	Attention Deficit Hyperactivity Disorder (ADHD)
Applicant:	Arbor Pharmaceuticals, LLC
Review Division:	Division of Psychiatry Products
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Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
AERS	Adverse Event Reporting System
ANDA	Abbreviated New Drug Application
CNS	Central Nervous System
DARRTS	Document Archiving Reporting and Regulatory Tracking System
DESI	Drug Efficacy Study Implementation
IID	Inactive Ingredient Database
IR-ODT	Immediate Release- Oral Disintegrating Tablet
MAS	Mixed Amphetamine Salts
MDD	Maximum Daily Dose
MRHD	Maximum Recommended Human Dose
ODT	Oral Disintegrating Tablet
RLD	Reference Listed Drug
RPM	Regulatory Project Manager
RS	Reference Standard

1 Executive Summary

1.1 Introduction

NDA 209905 is an initial 505(b)(2) application filed by Arbor Pharmaceuticals, LLC, towards seeking approval for their new immediate release orally disintegrating tablet formulation of amphetamine sulfate as Amphetamine IR-ODT (under the tradename Evekeo ODT™). The applicant states that the new formulation is a line extension to their approved product Evekeo® (ANDA 200166) currently marketed as 5 and 10 mg tablets, and that the current proposed drug product is designed to facilitate treatment of patients who have difficulty swallowing conventional tablets. The proposed strengths are 5, 10, 15, 20, (b) (4) mg tablets, and the indication is for treatment in children (6 – (b) (4) years old) diagnosed with Attention Deficit Hyperactivity Disorder (ADHD).

Data in support of the current application is limited to published literature and clinical bioequivalence bridging studies to Evekeo® (used as the reference standard). Evekeo® (ANDA 200166) is also owned by the applicant and the cross-referenced listed drug for safety and efficacy is NDA 83901Amphetamine sulfate tablets (owned by Lannett Co Inc). Lannett's drug product was approved as a part of FDA's Drug Efficacy Study Implementation (DESI) program that is now listed in the Orange Book under ANDA 83901).

From a nonclinical perspective, Evekeo ODT™ appears to be reasonably safe for approval.

(b) (4)

1.2 Brief Discussion of Nonclinical Findings

No nonclinical studies have been submitted with this application.

Safety information for nonclinical studies is based on findings from published literature, clinical bioequivalence bridging studies to Evekeo® (ANDA 200166 that is owned by the applicant) and the RLD [Lannett's Amphetamine Sulfate tablets under NDA 83901(discontinued), and presently listed in the Orange Book under ANDA 83901].

There are no safety concerns with the active ingredient based on history of clinical use.

There are no new novel excipients. All listed excipients are lower than that used in other FDA-approved products and lower than the maximum potency per unit dose for the same oral route of administration as listed in FDA's IID (as updated on July 11, 2018 per reviewer evaluation). See Table 1 below (see Quality review for more details).

No specific impurities have been identified (see Quality review).

Labeling changes in the nonclinical sections (Sections 8, 12 and 13) are detailed in Section 1.3.3 below. Section 8.1 retains reproductive toxicology information as in

Evekeo® ANDA 200166, (b) (4)

From a nonclinical perspective, Evekeo ODT™ appears to be reasonably safe for approval.

1.3 Recommendations

1.3.1 Approvability

Given the long history of clinical use of the active ingredient, the lack of novel excipients, the use of excipients in reasonable amounts (compared to FDA's IID and/or use in other FDA approved drug products), and impurity levels within reasonable limits, (b) (4) appears to be reasonably safe for approval from a nonclinical perspective.

1.3.3 Labeling

Given that the labels for the RLD (A)NDA 83901 and the RS (ANDA 200166) is meagre (limited to *d*-amphetamine while applicant's drug product includes both *d*- and *l*-amphetamines), and that the nonclinical information in the applicant's proposed label (file labeled "Annotated Draft Labeling Text – PDF" dated 03/30/2018 under Module 1.14.1.2) is limited, an information request was communicated to the applicant requesting clarification on the source and reliance on findings of nonclinical safety to complete information under the nonclinical sections of the label (see Filing Communication in DARRTS dated June 6, 2018). The applicant responded (see DARRTS dated July 16, 2018, eCTD 0009) with a revised label (file labeled "Annotated Draft Labeling Text – Word" dated 07/16/2018 under Module 1.14.1.2) that include revisions to Sections 8 and 13 (nonclinical).

The applicant-submitted revisions include:

a) (b) (4)

b) addition of a sentence on safety margins in the subsection on "Carcinogenesis".
c) citation references for nonclinical information were included in the respective nonclinical sections.

The reproductive toxicology study data under Section 8.1 is similar to Evekeo® (ANDA 200166), (A)NDA 83901, and Dexedrine (NDA 017078) labels. The mechanism of action and pharmacodynamics information has been updated in Section 12.1-12.2 to be consistent with recently approved labels for amphetamine drug products. The carcinogenicity/mutagenicity data has been updated based on published literature in Section 13.1.

Reproductive toxicology data (Section 8.1) is limited to *d*-amphetamine alone (b) (4)

(b) (4)

For consistency with the label for Evekeo (ANDA 200166), it was concluded to retain the existing language for reproductive toxicology data in this applicant's NDA.

For Sections 12.1 and 12.2, the information on mechanism of action and pharmacodynamics has been revised to be consistent with newer labels.
For Section 13.1 (sections on Carcinogenesis and Mutagenesis), the applicant's proposed label includes information on carcinogenesis and mutagenesis based on published literature (Technical Reports from the National Toxicology Program, Tariq et al.,1987, and Zeiger et al.,1987). Safety margins were revised based on confirmation from the sponsor (see e-mail from sponsor to RPM dated Dec 6, 2018 5:29 pm) that the proposed Maximum Daily Dose (MDD) in children for this drug product is 40 mg/day. (b) (4)

Below, Sections 8, 12.1, 12.2, and 13 have been excerpted from the applicant's revised submission with additional nonclinical information (file labeled "Draft Labeling Text – Word" dated 07/16/2018 under Module 1.14.1.3). Proposed changes are in blue below. It should be noted that the following label changes documented in this review are work-in-progress, and may not reflect the finalized label (pending at this time) accurately.

**********Start of Label Excerpt **********

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to (b) (4)

Risk summary

(b) (4) available data from published (b) (4) and postmarketing reports on use of amphetamine in pregnant women (b) (4) a drug-associated risk (b) (4) major birth defects and miscarriage. Adverse pregnancy outcomes, including premature delivery and low birth weight, have been seen in infants born to mothers (b) (4) *[see Clinical Considerations (8.1)]*.

Dextroamphetamine sulfate has been shown to have embryotoxic and teratogenic effects when administered to A/Jax mice and C57BL mice in doses approximately 41 times the maximum human dose. Embryotoxic effects were not seen in New Zealand white rabbits given the drug in doses 7 times the human dose nor in rats given 12.5 times the maximum human dose.

In the U.S. general population, the estimated background risk of major birth defects and (b) (4) in clinically recognized pregnancies is 2% to 4% and (b) (4), respectively.

Clinical Considerations
(b) (4)

Infants born to mothers taking amphetamines (b) (4) for symptoms of withdrawal such as feeding difficulties, irritability, agitation, and excessive drowsiness.

(b) (4)

8.2 Lactation

Risk Summary
Based on limited case reports in published literature, amphetamine (*d*- or *d1*) is present in human milk at relative infant doses of 2% to 13.8% of the maternal weight-adjusted dosage (b) (4) a milk/plasma ratio ranging between 1.9 and 7.5. There are no reports of adverse effects on the breastfed infant. Long-term neurodevelopmental effects on infants from amphetamine exposure are unknown. It is possible that large dosages of (b) (4) might interfere with milk production, especially in women whose lactation is not well established. Because of the potential for serious adverse reactions in nursing infants, (b) (4)

(b) (4) advise patients that breast feeding is not recommended during maternal treatment with EVEKEO ODT.

8.4 Pediatric Use

(b) (4) Safety and efficacy in pediatric patients below the age of 6 years have not been established.

(b) (4)

Long-Term Growth Suppression

Growth should be monitored during treatment with stimulants, including EVEKEO ODT. Pediatric patients aged 6 to 17 years who are not growing or gaining weight as expected may need to have their treatment interrupted [*see Warnings and Precautions (5.5)*].

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Amphetamines are non-catecholamine sympathomimetic amines with central nervous system (CNS) stimulant activity. The mode of therapeutic action in ADHD is not known. (b) (4)

12.2 Pharmacodynamics

Amphetamines block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No evidence of carcinogenicity was found in studies in which d-, l-amphetamine (enantiomer ratio of 1:1) was administered to mice and rats in the diet for 2 years at doses of up to 30 mg/kg/day in male mice, 19 mg/kg/day in female mice, and 5 mg/kg/day in male and female rats. (b) (4) (b) (4) These doses are approximately (b) (4) 2, (b) (4) 1, and 0.5 times, respectively, the maximum recommended human dose of 40 mg/day (b) (4) given to children, on a mg/m^2 basis.

Mutagenesis

d, l-Amphetamine (1:1 enantiomer ratio) has been reported to produce a positive response in the mouse bone marrow micronucleus test, an equivocal response in the Ames test, and negative responses in the *in vitro* sister chromatid exchange and chromosomal aberration assays.

13.2 Animal Toxicology and/or Pharmacology

Acute administration of high doses of amphetamine (d- or d,l-) has been shown to produce long-lasting neurotoxic effects, including irreversible nerve fiber damage, in rodents. The significance of these findings to humans is unknown.

**********End of Label Excerpt**********

2 Drug Information

2.1 Drug

CAS Registry Number:
60-13-0

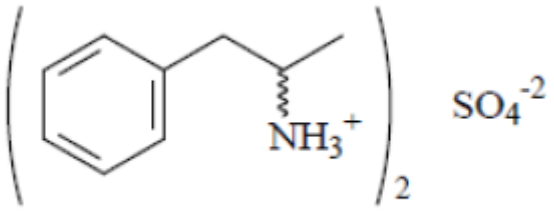
Chemical Name:
Phenyl-2-(R,S)-aminopropane sulfate

Generic Name:
Amphetamine sulfate

Code Names:
Compound 197, Product Code 2003310

Molecular Formula/Molecular Weight:
$C_{18}H_{28}N_2SO_4$ / 368.5 g/mol

Structure:



Stereochemistry:
Amphetamine sulfate is optically inactive

Pharmacologic Class
Central Nervous System (CNS) Stimulant

2.2 Relevant INDs, NDAs, and DMFs

DMFs: (b) (4) (CMC), (b) (4)

IND 124019
Product Name: Amphetamine Sulfate (AR17)
Applicant: Arbor Pharmaceuticals, LLC.
Indication: ADHD
Status: Active since 8/7/2015

(A)NDA 83901
Product Name: Adderall® XR
Applicant: Lannett C., Inc.
Indication: Obesity
Status: Approved on 8/31/1984 (DESI Status)

ANDA 200166
Product Name: Evekeo® ODT
Applicant: Arbor Pharmaceuticals, LLC
Indication: ADHD
Status: Approved on 8/9/2012

2.3 Drug Formulation

The applicant states that the Amphetamine Sulfate Immediate Release (IR) Orally Disintegrating Tablets (ODT) 5 mg, 10 mg, 15mg, 20 mg, (b) (4) are a (b) (4) orally disintegrating dosage form for the delivery of amphetamine sulfate.

The table below includes the drug composition at various strengths excerpted from DMF (b) (4) There are no new novel excipients and all ingredients are within limits of other FDA approved products for the same route of administration (compared to FDA's Inactive Ingredient database - as updated on July 11, 2018 per reviewer evaluation).

Tables 1: Drug Product Composition (Reviewer-generated table from *DMF* (b) (4))

		5 mg IR	10 mg IR	15 mg IR	20 mg IR
Ingredients	**% per tablet**	**mg per tablet**	**mg per tablet**	**mg per tablet**	**mg per tablet**
Amphetamine Sulfate	(b) (4)				
Mannitol					
Silicified Microcrystalline Cellulose NF					
Crospovidone NF					
Citric Acid, Anhydrous USP					
Malic Acid NF					

Sucralose NF	(b) (4)
Magnesium Stearate NF	
(b) (4)	
Total	

2.4 Comments on Novel Excipients

There are no new novel excipients.

All listed excipients are lower than that used in other FDA-approved products and/or lower than the maximum potency per unit dose for the same oral route of administration as listed in FDA's IID (as updated on July 11, 2018 per reviewer evaluation).

No specific impurities have been identified (see Quality review).

2.5 Comments on Impurities/Degradants of Concern

No nonclinical studies on impurities were conducted, and no specific impurities were identified to be of concern from the Quality evaluation.

For a complete review, refer to the Quality review for this NDA.

2.6 Proposed Clinical Population and Dosing Regimen

Children diagnosed with ADHD aged 6-(b) (4) years.

2.7 Regulatory Background

Data in support of the current application is limited to published literature and clinical bioequivalence bridging studies to Evekeo® (used as the reference standard). Evekeo® (ANDA 200166) is also owned by the applicant and was approved on August 9, 2012. The cross-referenced listed drug for safety and efficacy is NDA 83901 Amphetamine sulfate tablets (owned by Lannett Co Inc). Lannett's Amphetamine Sulfate tablets (5 and 10 mg) was approved on August 31, 1984; and discontinued (not for reasons of safety or effectiveness) on April 4, 1994. Lannett's drug product was approved as a part of FDA's Drug Efficacy Study Implementation (DESI) program that is now listed in the Orange Book under ANDA 83901.

3 Studies Submitted

No nonclinical studies have been submitted.

4 Pharmacology

4.1 Primary Pharmacology

Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The exact mode of therapeutic action in ADHD is not known.

11 Integrated Summary and Safety Evaluation

NDA 209905 is an initial 505(b)(2) application filed by Arbor Pharmaceuticals, LLC, towards seeking approval for their new immediate release orally disintegrating tablet formulation of amphetamine sulfate as Amphetamine IR-ODT (under the tradename Evekeo ODT™). The applicant states that the new formulation is a line extension to their approved product Evekeo® (ANDA 200166) currently marketed as 5 and 10 mg tablets, and that the current proposed drug product is designed to facilitate treatment of patients who have difficulty swallowing conventional tablets. The proposed strengths are 5, 10, 15, 20, (b) (4) mg tablets, and the indication is for treatment in children (6 – (b) (4) years old) diagnosed with Attention Deficit Hyperactivity Disorder (ADHD).

No nonclinical studies have been submitted with this application.

Safety information for nonclinical studies is based on findings from published literature, clinical bioequivalence bridging studies to Evekeo® (ANDA 200166 that is owned by the applicant) and the RLD [Lannett's Amphetamine Sulfate tablets under NDA 83901(discontinued), and presently listed in the Orange Book under ANDA 83901].

There are no safety concerns with the active ingredient based on history of clinical use.

There are no new novel excipients. All listed excipients are lower than that used in other FDA-approved products and lower than the maximum potency per unit dose for the same oral route of administration as listed in FDA's IID (as updated on July 11, 2018 per reviewer evaluation). See Table 1 above (see Quality review for more details).

No specific impurities have been identified (see Quality review).

Labeling changes in the nonclinical sections (Sections 8, 12, and 13) include retaining of old information in Section 8.1 to be consistent with the RLD (Evekeo's ANDA 200166) and the RS (A)NDA 83901 since the sponsor did not provide reliance for reproductive toxicology studies. Sections 12 and 13 were updated for consistency with newer labels and re-calculation of safety margins based on the proposed MDD of 40 mg/day.

From a nonclinical perspective, Evekeo ODT™ appears to be reasonably safe for approval.

12 References

Nora JJ, Trasler DG, and Fraser FC. Malformations in mice induced by dexamphetamine sulphate. Lancet, 1965; Nov 13:2(7420):1021-2

Nora JJ, Sommerville RJ and Fraser FC. Homologies for congenital heart diseases: murine models, influenced by dextroamphetamine. Teratology, 1968;1:413-416.

Tariq M, Parmar NS, Qureshi S, El-Feraly FS, and Al-Meshal IA. Clastogenic evaluation of cathinone and amphetamine in somatic cells of mice. Mutation Research, 1987;190:153-157.

Toxicology and Carcinogenesis Studies of dl-amphetamine sulfate in F344/N Rats and B6C3F1 Mice (feed studies). National Institutes of Health, *National Toxicology Program, Technical Report No. 387*, June 1991.
Zeiger E, Anderson B, Haworth S, Lawlor T, Mortelmans K, Speck W. Salmonella mutagenicity tests: III. Results from the testing of 255 chemicals. Environmental Mutagenesis, 1987; 9: 1-110.

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