CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209905Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED 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:	January 29, 2019
Requesting Office or Division:	Division of Psychiatry Products (DPP)
Application Type and Number:	NDA 209905
Product Name and Strength:	Evekeo ODT (amphetamine sulfate) Orally Disintegrating Tablets 5 mg, 10 mg, 15 mg, 20 mg
Applicant/Sponsor Name:	Arbor Pharmaceuticals, LLC
FDA Received Date:	January 29, 2019
OSE RCM #:	2018-1016-3
DMEPA Safety Evaluator:	Loretta Holmes, BSN, PharmD
DMEPA Acting Team Leader:	Teresa McMillan, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Psychiatry Products (DPP) requested that we review the revised carton labeling for Evekeo ODT (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 labels and labeling review memorandum.[a]

2 CONCLUSION

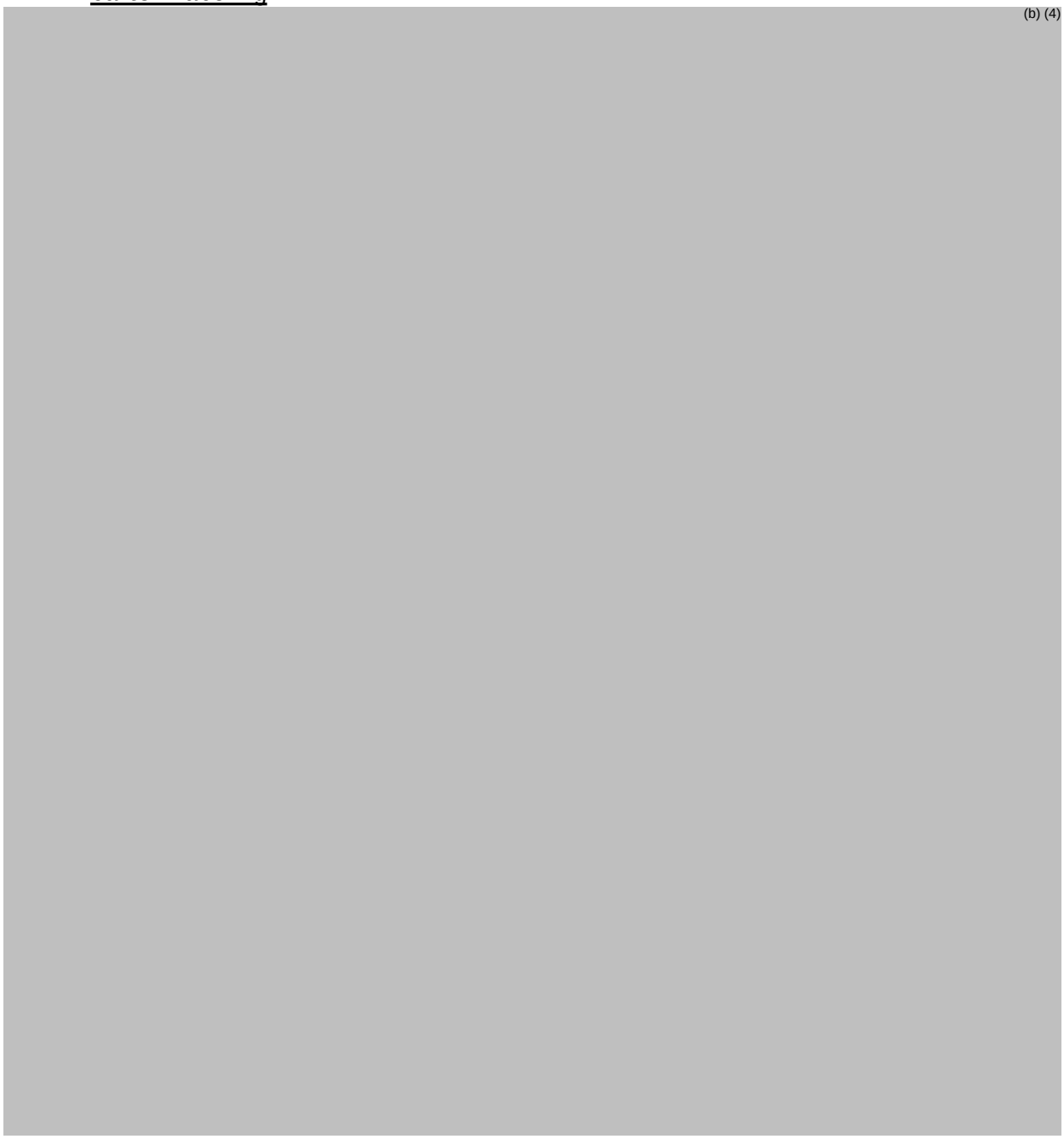
The revised carton labeling for Evekeo ODT are acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Holmes L. Labels and Labeling Review Memo for Evekeo ODT (NDA 209905). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Jan 28. RCM No.: 2018-1016-2.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON JANUARY 29, 2019 (not to scale)

Carton Labeling

(b) (4)



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LORETTA HOLMES
01/29/2019 03:39:23 PM

TERESA S MCMILLAN
01/29/2019 03:46:41 PM

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:	January 28, 2019
Requesting Office or Division:	Division of Psychiatry Products (DPP)
Application Type and Number:	NDA 209905
Product Name and Strength:	Evekeo ODT (amphetamine sulfate) Orally Disintegrating Tablets 5 mg, 10 mg, 15 mg, 20 mg
Applicant/Sponsor Name:	Arbor Pharmaceuticals, LLC
FDA Received Date:	January 28, 2019
OSE RCM #:	2018-1016-2
DMEPA Safety Evaluator:	Loretta Holmes, BSN, PharmD
DMEPA Acting Team Leader:	Teresa McMillan, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Psychiatry Products (DPP) requested that we review the revised blistercard labels, plastic sleeve labeling and carton labeling for Evekeo ODT (Appendix A) to determine if they are acceptable from a medication error perspective.

2 CONCLUSION

The revised carton labeling are unacceptable from a medication error perspective. We noted there are areas where information needs to be clarified or updated for consistency with other components of the labeling.

3 RECOMMENDATIONS FOR ARBOR PHARMACEUTICALS

We recommend the following be implemented prior to approval of this NDA:

A. Carton Labeling (all cartons)

The instructions for use on the carton labeling do not correspond with those in the Medication Guide (MG). For consistency, revise the instructions on the carton labeling so that they correspond with the instructions for use in the MG.

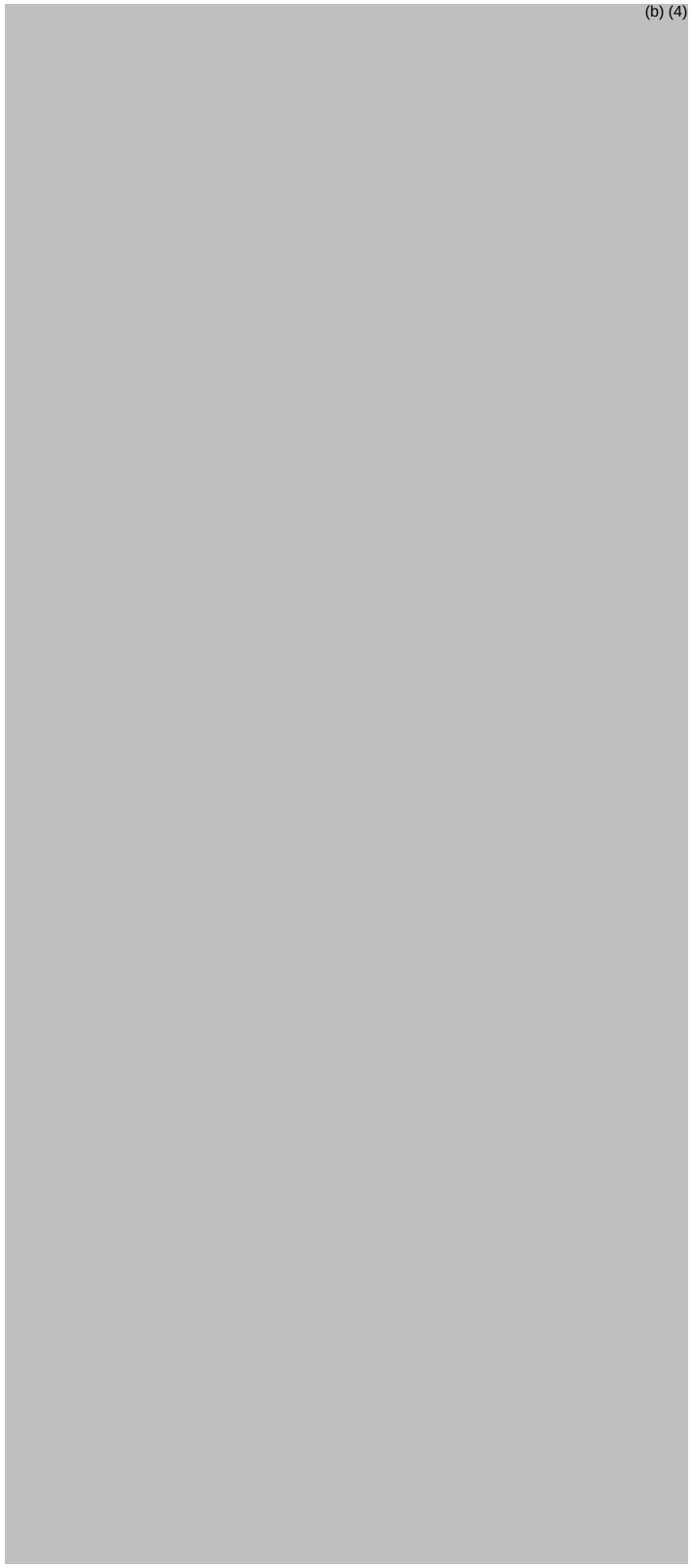
B. Carton Labeling (20 mg strength)

As currently presented, the net quantity statement on the carton labeling is confusing because the total number of tablets contained in the carton may be confused as (b) (4) tablets. For clarity and consistency with Section 16 of the Prescribing Information, revise the statement "Contains 30 tablets (b) (4)" to "Contains 30 tablets (Two 15-count plastic sleeves)".

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON JANUARY 28, 2019 (not to scale)

Blistercard Labels

(b) (4)



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LORETTA HOLMES
01/28/2019 05:29:14 PM

TERESA S MCMILLAN
01/28/2019 05:30:51 PM

M E M O R A N D U M

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: January 25, 2018

To: Mitchell Mathis, M.D., Director
Division of Psychiatry Products

Through: Dominic Chiapperino, Ph.D., Director
Controlled Substance Staff

From: Alicja Lerner, M.D., Ph.D. Medical Officer
Controlled Substance Staff

Subject: **NDA 209905**
Name: EVEKEO, Amphetamine Sulfate Immediate Release Orally Disintegrating Tablets (IR ODT) containing racemic amphetamine sulfate
Proposed Dosages: 5, 10, 15, 20, (b) (4) mg tablets
Indication: Attention Deficit Disorder with Hyperactivity (ADHD) in children 6 years and older.
Sponsor: Arbor Pharmaceuticals, LLC

Materials Reviewed:

NDA submission received March 30, 2018, and subsequent amendements

I. BACKGROUND

This memorandum responds to a consult request by the Division of Psychiatry Products (DPP) to provide feedback on abuse-related issues regarding Amphetamine Sulfate Immediate Release Orally Disintegrating Tablets (Evekeo ODT), NDA 209905.

This NDA is submitted as a 505(b)(2) application. Evekeo IR oral tablets, 5 and 10 mg, were approved under ANDA 200166 on August 9, 2012. The Sponsor provides a bridging study for Evekeo IR ODT to Evekeo IR oral tablets. Evekeo IR 10 mg tablet is the reference standard (RS) in the orange book.

The Sponsor's proposed label includes a section 9 Drug Abuse and Dependence that is generally consistent with other similar amphetamine formulations, although these labels are outdated. DPP and CSS have agreed that CSS will in future provide recommendations for stimulant class labeling language

as a future separate action for this class of products because of the growing abuse of stimulants. In this review, CSS addresses section 9 labeling for Evekeo IR ODT in the event the NDA receives approval.

This review also addresses abuse potential, dependence, and withdrawal based specifically on the data submitted in NDA 209905 for Evekeo ODT.

The Sponsor's amphetamine sulfate immediate release 5 and 10 mg tablets (Evekeo tablets) were approved by FDA on August 9, 2012 (ANDA 200166). Evekeo (amphetamine sulfate) immediate release ODT contains racemic amphetamine sulfate. This formulation was developed for patients who cannot swallow a tablet. Evekeo IR ODT will be indicated for the treatment of Attention Deficit Disorder with Hyperactivity in children 6 years to17 years of age.

NDA 209905 includes three clinical studies, which are:

- Comparative Bioavailability Study # AR17.001 in Healthy Adults Volunteers.
- Food-Effect Bioavailability Study # AR17.002 in Healthy Adult Volunteers under Fed and Fasted Conditions.
- Efficacy study # AR11.001 in children with ADHD.

II. CONCLUSIONS

1. Amphetamine, its salts, optical isomers and salts of its optical isomers are controlled under the Controlled Substances Act (CSA) in Schedule II.

2. In the clinical studies conducted by the Sponsor, no abuse, overdose, or diversion of the study drug was observed.

3. In the clinical study # AR11.001, the adverse event data show a somewhat higher frequency of neuropsychiatric adverse events of stimulant-type, such as insomnia, irritability, fatigue, mood swings, suicidality and appetite decrease which are likely related to the fairly high dose of the study drug the children received (up to 30-40 mg a day).

4. Because amphetamine products are used for treatment of a fairly large population of children with ADHD it would be valuable to pediatric patients and prescribers if withdrawal and rebound in the pediatric population is better studied and described in the label (see Recommendations). However, study # AR11.001 was not designed to include assessments of withdrawal and ADHD rebound.

5. As described above, the Division and CSS agreed to develop, separate from this NDA action, updated labeling language in section 9 Drug Abuse and Dependence as new amphetamine class labeling in the ADHD indication. The presently proposed label by the Sponsor closely resembles the label for Evekeo IR tablets and is mostly acceptable for now, with minor revision (see Recommendations section below).

III. RECOMMENDATIONS

1. We note that amphetamine product labeling for the ADHD indication could be improved with respect to information about withdrawal and rebound in the pediatric population using these products. We recommend that the Division consider for new drug development programs, or in any currently planned pediatric studies, opportunities to collect additional data assessing withdrawal and rebound so that labeling for amphetamine products for ADHD can better inform prescribers, parents, and teachers of treated children. This can be accomplished at the conclusion of any appropriately designed future study of an amphetamine formulation in ADHD children. A dependence and withdrawal evaluation should include relevant withdrawal scales such as depression, anxiety, sleep, and Columbia Suicide Severity Rating Scale, administered for 2-3 weeks after drug discontinuation. An ADHD scale should also be included to evaluate ADHD rebound.

   CSS can provide assistance with the development of the protocol for the withdrawal study.

2. The proposed labeling in section 9 Drug Abuse and Dependence for Evekeo ODT is similar to other amphetamine products, and is acceptable for now, with minor revisions as shown below (added text in bold/underlined font, and deleted text in strikethrough font):

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

EVEKEO ODT contains amphetamine, a Schedule II controlled substance.

9.2 Abuse

EVEKEO ODT is a CNS stimulant that contains amphetamine which has a high potential for abuse. Abuse is characterized by impaired control over drug use, compulsive use, continued use despite harm, and craving.

Signs and symptoms of amphetamine abuse may include increased heart rate, respiratory rate, blood pressure, and/or sweating, dilated pupils, hyperactivity, restlessness, insomnia, decreased appetite, loss of coordination, tremors, flushed skin, vomiting, and/or abdominal pain. Anxiety, psychosis, hostility, aggression, suicidal or homicidal ideation have also been seen. Abusers of amphetamine may use unapproved routes of administration which can result in overdose and death [see Overdosage (10)].

To reduce the abuse of CNS stimulants, including EVEKEO ODT, assess the risk of abuse prior to prescribing. After prescribing, keep careful prescription records, educate patients and their families about abuse and on proper storage and disposal of CNS stimulants. Monitor for signs of abuse while on therapy, and re-evaluate the need for EVEKEO ODT use.

9.3 Dependence

Tolerance

Tolerance (a state of adaptation in which exposure to a specific dose of a drug results in a reduction of the drug's desired and/or undesired effects over time, in such a way that a higher dose of the drug is required to produce the same effect that was once obtained at a lower dose) may occur during the chronic therapy of CNS stimulants including EVEKEO ODT.

Dependence

Physical dependence (a state of adaptation manifested by a withdrawal syndrome produced by abrupt cessation, rapid dose reduction, or administration of an antagonist) may occur in patients treated with CNS stimulants including EVEKEO ODT. Withdrawal symptoms after abrupt cessation **following prolonged high dosage administration** of CNS stimulants include **dysphoric mood;** (b) (4) fatigue**; vivid, unpleasant dreams; insomnia or hypersomnia; increased appetite; psychomotor retardation or agitation** (b) (4)

IV. DISCUSSION

Overview of the Clinical Development Program

The Evekeo ODT clinical development program consists of two bioavailability studies and one clinical trial of efficacy and safety.

The two clinical bioavailability studies performed were:

Comparative Bioavailability Study AR17.001: *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 adults volunteers.*

Abbreviated Design:

- Single dose study
- Population: healthy male and female volunteers , 18-45 years, N=42
- Doses: 20 mg Evekeo ODT

Results

- Abuse related adverse events - none

Food-Effect Bioavailability Study AR17.002: *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.*

Abbreviated Design:

- Single dose study- two-period-two-way crossover, fast and fed
- Dose: 20 mg Amphetamine Sulfate ODT-IR
- Population: Healthy volunteers males and females, 18-45 yo, N=32

Results

- Abuse related adverse events: anxiety 1 (3.1%), change in sustained attention 1 (3.1%), 2 events, fatigue 1 (3.1%).

Clinical Efficacy

The Sponsor did not perform any clinical efficacy studies with Evekeo ODTs.

The only clinical efficacy study performed was with Arbor's Evekeo immediate release tablets (FDA's reference standard):

Efficacy study AR11.001: *A multicenter, dose-optimized, double-blind, randomized, placebo-controlled, crossover study to evaluate the efficacy of ar11 (amphetamine sulfate) in pediatric patients (ages 6-12) with attention deficit hyperactivity disorder (ADHD) in a laboratory classroom.*

Abbreviated Design

- Double-blind, randomized, placebo-controlled
- Duration: 8-week open-label dose optimization/titration phase, followed by a 2-week double-blind, randomized, crossover phase
- Population: Pediatric patients, ages 6-12, with ADHD, N=97
- Doses: the dosing regimen was twice daily, with the first dose in the morning, and the second dose 4 to 6 hours later to the maximal dose allowed 40 mg/day.

Table 1. Abuse related adverse events in the study # AR11.001 in pediatric population based on table 12, p 23, Mod. 2.7.4. and CSS IR from Dec 3 2018, table 1, p 2.; study report AR11.001, Table 14.3.1.6, page 666.

Adverse Events	Evekeo Open-label phase (N=105) n (%)	Evekeo Double-blind period (N=97) n (%)	Placebo Double-blind period (N=97) n (%)
Subjects with at least one TEAE	69 (65.7)	21 (21.6)	14 (14.4)
Psychiatric Disorders			
Insomnia	11 (10.5)	4 (4.1)	0

Affect lability	6 (5.7)	1 (1.0)	0
Mood swings	3 (2.9)	2 (2.1)	0
Abnormal behavior	1 (0.9)		
Agitation	1 (0.9)		
Emotional disorder	1 (0.9)		
Suicidal ideation	1 (0.9)		
General Disorders			
Irritability	15 (14.3)		
Fatigue	10 (9.5)		
Metabolism Disorders			
Decreased appetite	29 (27.6)	4 (4.1)	0

Reviewer's Comment

These AEs are consistent with stimulant adverse events profile. It is possible that the magnitude of the dose, which was up to 40 mg a day, is responsible for more frequent appearence of stimulant AEs.

Discontinuations due to neuropsychiatric adverse events
During open-label phase, 5 subjects prematurely withdrew from study drug due to AEs. Three patients withdrew due to irritability, and 1 subject withdrew due to affect lability and initial insomnia, which was severe.

Columbia Suicide Severity Rating Scale
During open-label phase, 3 subjects reported at least one occurrence of suicidal ideation and 1 subject reported at least one occurrence of non-suicidal self-injurous behavior. Two of these patients had suicidal ideation at Weeks 1 and 3 respectively, with normal baseline, one event occurred at the baseline.

Diversion-Drug Accountability
The Sponsor states that in both Phase 1 bioavailability studies # AR17.001 and AR17.002 in healthy adults, there were no opportunities for abuse, overuse, or overdose or drug diversion because there were single dose studies with drug administration at the clinic administered by the investigators.

In the pediatric study # AR11.001, diversion was not observed.

Withdrawal and Rebound
The Sponsor states that in study # AR11.001 in children 6-12 years old with ADHD who were treated with amphetamine sulfate conventional tablets (Evekeo) for 9 weeks no withdrawal or rebound was reported upon Evekeo discontinuation. However, this study was not designed to evaluate withdrawal or rebound, and did not include any questionnaires such as depression, anxiety, and sleep. Also, these patients had only one visit, approximately one week after drug discontinuation, so any withdrawal symptoms likely would have been missed.

Regarding rebound, there is some dated literature that indicates that amphetamine produces rebound in ADHD children (Rapaport et al., 1978; Porrino et al., 1983). In response to CSS question to the Sponsor on rebound evaluation (IR Dec 3 2018), the Sponsor notes that " *The AR11.001 trial was not set up to assess for potential rebound during the study."*

IV. REFERENCES

1. Garland EJ. Pharmacotherapy of adolescent attention deficit hyperactivity disorder: challenges, choices and caveats. Pharmacotherapy J Psychopharmacol. 1998;12(4):385-95.

2. Porrino, L. J., Rapoport, J. L., Behar, D., Ismond, D. R. & Bunney, W. E. (1983), A naturalistic assessment of the motor activity of hyperactive boys . II. Stimulant drug effects. Arch. Gen. Psychkury, 40:688-693

3. Rapoport J L, Buchsbaun M S, Zahn T P, Weingartner H, Ludlow C, Mikkelsen E J (1978) Dextroamphetamine: cognitive and behavioral effects in normal prepubertal boys. Science 199: 560-563

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

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

Memorandum

Date: January 14, 2019

To: John C. Umhau, M.D.
Division of Psychiatry Products (DPP)

Keith J. Kiedrow, PharmD, Regulatory Project Manager, DPP

Kimberly Updegraff, PharmD, Associate Director for Labeling, DPP

From: Domenic D'Alessandro, PharmD, MBA, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, RN, MPH, Team Leader, OPDP

Subject: OPDP Labeling Comments for EVEKEO ODT (amphetamine sulfate) orally disintegrating tablets, CII

NDA: 209905

In response to DPP consult request dated June 21, 2018, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original NDA submission for EVEKEO ODT (amphetamine sulfate) orally disintegrating tablets, CII.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DPP (Keith Kiedrow) on January 2, 2019, and are provided below.

Medication Guide: A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under separate cover on January 10, 2019.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on December 19, 2018, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Domenic D'Alessandro at (301) 796-3316 or domenic.dalessandro@fda.hhs.gov.

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MEMORANDUM

REVIEW OF REVISED LABEL 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:	January 14, 2019
Requesting Office or Division:	Division of Psychiatry Products (DPP)
Application Type and Number:	NDA 209905
Product Name and Strength:	Evekeo ODT (amphetamine sulfate) Orally Disintegrating Tablets 5 mg, 10 mg, 15 mg, 20 mg, (b) (4)
Applicant/Sponsor Name:	Arbor Pharmaceuticals, LLC
FDA Received Date:	December 19, 2018
OSE RCM #:	2018-1016-1
DMEPA Safety Evaluator:	Loretta Holmes, BSN, PharmD
Acting DMEPA Team Leader:	Teresa McMillan, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Psychiatry Products (DPP) requested that we review the revised blistercard labels, (b) (4) labeling and carton labeling for Evekeo ODT (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 labels and labeling review.[a]

2 CONCLUSION

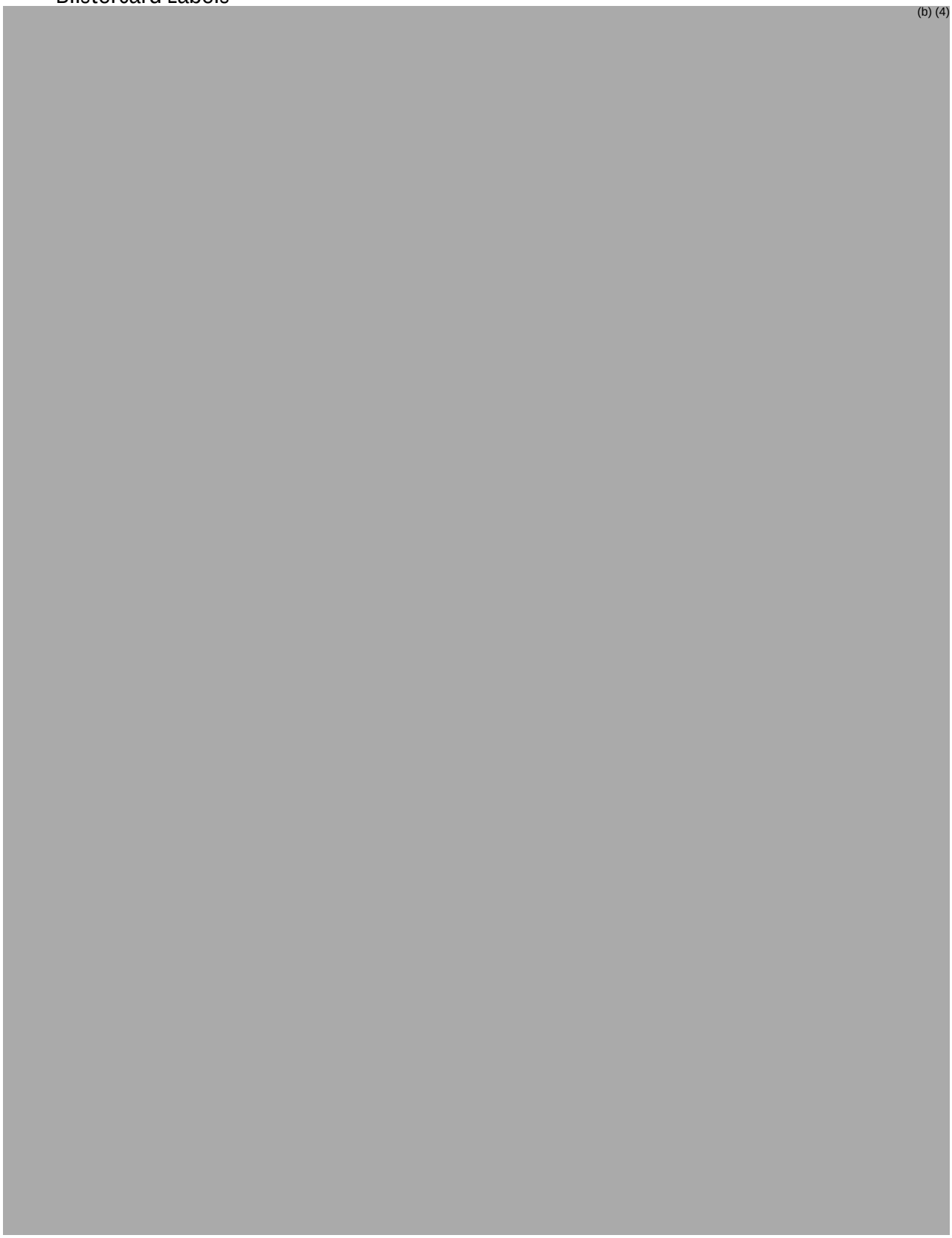
Arbor Pharmaceuticals has implemented our recommendations. The revised blistercard labels, (b) (4) labeling and carton labeling for Evekeo ODT are acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Holmes L. Labels Labeling and Packaging Review for Evekeo ODT (NDA 209905). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Nov 07. RCM No.: 2018-1016.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON DECEMBER 19, 2018

Blistercard Labels

(b) (4)



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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:	January 10, 2019
To:	Mitchell Mathis, MD Director **Division of Psychiatry Products (DPP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	Domenic D'Alessandro, PharmD, MBA, BCPS, CDE Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	EVEKEO ODT (amphetamine sulfate)
Dosage Form and Route:	Orally disintegrating tablets, for oral use
Application Type/Number:	NDA 209905
Applicant:	Arbor Pharmaceutical, Inc.

1 INTRODUCTION

On March 30, 2018, Arbor Pharmaceutical, LLC., submitted for the Agency's review an original New Drug Application (NDA) for EVEKEO ODT (amphetamine sulfate) orally disintegrating tablets, CII, for oral use, for the proposed indication of the treatement of Attention Deficit Hyperactivity Disorder (ADHD).

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 June 21, 2018 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for EVEKEO ODT (amphetamine sulfate) orally disintegrating tablets, CII, for oral use.

2 MATERIAL REVIEWED

- Draft EVEKEO ODT (amphetamine sulfate) MG received on March 30, 2018 and received by DMPP on January 7, 2019.
- Draft EVEKEO ODT (amphetamine sulfate) MG received on March 30, 2018 and received by OPDP on January 2, 2019.
- Draft EVEKEO ODT (amphetamine sulfate) Prescribing Information (PI) received on March 30, 2018, revised by the Review Division throughout the review cycle, and received by DMPP on January 7, 2019.
- Draft EVEKEO ODT (amphetamine sulfate) Prescribing Information (PI) received on March 30, 2018, revised by the Review Division throughout the review cycle, and received by OPDP on January 2, 2019.

3 REVIEW METHODS

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- 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 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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LASHAWN M GRIFFITHS
01/10/2019 01:01:23 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs, ODE-IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

Date of Consult Request:	September 6, 2018
From:	Division of Pediatric and Maternal Health (DPMH) Kerri-Ann Jennings, Regulatory Project Manager (RPM)
To:	Division of Psychiatry Products (DPP)
NDA Number:	209905
Drug:	Evekeo ODT (amphetamine sulfate)
Applicant:	Arbor Pharmaceuticals
Indication:	Central Nervous System (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children 6 years and older.

The Division of Psychiatry Products (DPP) submitted a consult request to the Division of Pediatric and Maternal Health (DPMH) on September 6, 2018, asking for assistance with the review of labeling language for the pregnancy and lactation sections for the above referenced NDA.

DPMH participated in internal team meetings with DPP from September 25, 2018 through November 8, 2018 and proposed labeling recommendations for the above referenced NDA.

DPMH- Maternal Health, has no further comments at this time, thus, this memorandum will close out the consult request.

DPMH Maternal Health MO Reviewer- Cathy Roca, MD
DPMH Maternal Health Team Leader- Miriam Dinatale, DO
DPMH Division Director- Lynne Yao, MD
DPMH RPM- Kerri-Ann Jennings, MS, BSN, RN

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/s/

KERRI-ANN JENNINGS
12/07/2018

LABELS, LABELING AND PACKAGING 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:	November 7, 2018
Requesting Office or Division:	Division of Psychiatry Products (DPP)
Application Type and Number:	NDA 209905
Product Name and Strength:	Evekeo ODT (amphetamine sulfate) Orally Disintegrating Tablets 5 mg, 10 mg, 15 mg, 20 mg, (b) (4)
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Arbor Pharmaceuticals, LLC
FDA Received Date:	March 30, 2018
OSE RCM #:	2018-1016
DMEPA Safety Evaluator:	Loretta Holmes, BSN, PharmD
DMEPA Team Leader:	Teresa McMillan, PharmD

1 PURPOSE OF REVIEW

As part of the approval process for Evekeo ODT (amphetamine) Orally Disintegrating Tablets, 5 mg, 10 mg, 15 mg, 20 mg, (b) (4) the Division of Psychiatry Products (DPP) requested that we review the proposed packaging, label and labeling for areas that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B (N/A)
ISMP Newsletters	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Other	E (N/A)
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Tables 3 below include the identified medication error issues with the submitted packaging, labels and labeling, DMEPA's rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 3: Identified Issues and Recommendations for Arbor Pharmaceuticals, LLC (entire table to be conveyed to Applicant)

General Comment for All Labels and Labeling			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The (b) (4) color used for the established name is difficult to see due to poor contrast against the white background.	Difficulty with reading the established name may contribute to product selection errors.	Consider using a different color or other means to increase the visibility of the established name.
2.	The graphic located to the left of the proprietary name looks like a (b) (4)	The graphic may be interpreted as representative of a (b) (4) which may cause confusion and/or	Consider using a different graphic or deleting it.

		contribute to errors in product administration.	
[redacted] Labeling			
1.	The proposed expiration date format is not indicated.	The expiration date format is needed in order that we may assess it in order to help mitigate use of expired medication.	Indicate the proposed expiration date format. Consider using the same format as presented on the blister labels.
Packaging			
1.	As proposed, the blister card configurations are confusing. For example, the 5 mg strength blister card appears to contain [redacted] However, the blister card contains 30 tablets. [redacted]	The proposed blister card configuration is confusing and may lead to wrong dose medication errors.	Redesign the label or packaging in order to minimize the risk of wrong dose errors. Ideally, the proprietary and established name, strength, lot number, expiration date, bar code, and manufacturer should appear over each blister cell so that this important information remains available to the end user up to the point at which the last dose is removed. Each blister should include only one dosage unit per blister (e.g., one tablet, one capsule). In certain cases, it may not be possible to design the packaging to accommodate all critical information on each blister cell. In such circumstances, a random display of the information can appear multiple times across the back of the blister or the important information should be displayed in such a manner that it is not destroyed or eliminated when dosage units are removed.

4 CONCLUSION

Our evaluation of the proposed packaging, labels and labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to the Applicant so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Evekeo ODT that Arbor Pharmaceuticals, LLC submitted on March 30, 2018.

Table 4. Relevant Product Information for Evekeo ODT	
Initial Approval Date	N/A
Active Ingredient	amphetamine sulfate
Indication	Treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children 6 years and older
Route of Administration	Oral
Dosage Form	Orally Disintegrating Tablets
Strengths	5 mg, 10 mg, 15 mg, 20 mg, (b) (4)
Dose and Frequency	(b) (4) 5 mg once or twice daily; (b) (4) dosage (b) (4) 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.
How Supplied	5 mg, 10 mg, 15 mg • carton containing one (b) (4) 20 mg, (b) (4) • carton containing two (b) (4)
Storage	Store at 20˚C to 25˚C (68˚F to 77˚F); excursions permitted to 15˚C - 30˚C (59˚F to 86˚F) [see USP Controlled Room Temperature].

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Evekeo ODT labels and labeling submitted by Arbor Pharmaceuticals, LLC on March 30, 2018.

- Blistercard labels received on March 30, 2018
- (b) (4) Labeling
- Carton labeling received on March 30, 2018

F.2 Label and Labeling Images (not to scale)

Blistercard Labels

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

15 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

LORETTA HOLMES
11/07/2018

TERESA S MCMILLAN
11/07/2018

M E M O R A N D U M

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

DATE: 6/21/2018

TO: Division of Psychiatry Products
Office of Drug Evaluation I

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 209905

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the sites listed below. The inspectional outcome from the inspections was classified as No Action Indicated (NAI).

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	Worldwide Clinical Trials Early Phase Services, LLC.	2455 NE Loop 410, Suite 150, San Antonio, TX
Analytical	(b) (4)	

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/s/

SHILA S NKAH
06/21/2018