CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210526Orig1s000

OTHER REVIEW(S)

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: October 18, 2021

To: Tiffany Farchione, M.D., Director
Division of Psychiatry

Through: Dominic Chiapperino, Ph.D., Director
Joshua Lloyd, M.D., Medical Officer Team Leader
Controlled Substance Staff

From: Shalini Bansil, M.D., Medical Officer
Controlled Substance Staff

Subject: **NDA 210526** Amphetamine Extended-Release Tablets (Tradename Dyanavel XR) 5 mg, 10 mg, 15 mg and 20 mg
Indication: Attention Deficit Hyperactivity Disorder (ADHD) in children 6 -17 years of age
NDA Resubmission – Response to the January 21, 2021 Complete Response Letter
PDUFA goal date: 11/4/21

Sponsor: Tris Pharma, Inc.

Materials Reviewed:

- NDA Resubmission, Supporting Document 28, received May 4, 2021
- CSS consult review of Original NDA submission; DARRTS; S Bansil June 20, 2018

Background

This review is in response to a consult request from the Division of Psychiatry (DP) dated June 15, 2021, regarding NDA 210526 for Amphetamine Extended-Release Tablets (Tradename Dyanavel XR) indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children 6 -17 years of age. The Controlled Substance Staff (CSS) had previously reviewed this NDA and recommended edits to Section 9 (Drug Abuse and Dependence) of the labeling (CSS consult review DARRTS; S Bansil June 20, 2018). DP took Complete Response actions in July 2018 and January 2021 due to concerns with manufacturing facilities. This is a Class 2

resubmission, and DP requests CSS "input in reviewing applicable aspects of this NDA resubmission in order to inform the proposed labeling."

The Applicant provided complete responses to the deficiencies outlined in the Complete Response Letter (CRL) of January 2021. The following deficiencies identified in the CRL were addressed in this submission: 1. Facility Inspections 2. Prescribing Information 3. Medication Guide 4. Proprietary Name 5. Safety Update 6. Other, including compendial changes and updated Section 1.3.5.1 and Section 1.3.5.2 for Patent Information and Patent Certification and Exclusivity, respectively.

Regarding labeling, the Agency advised the Applicant that comments on the proposed labeling would be reserved until the application is otherwise adequate.

A full integrated summary of safety (ISS) was submitted, which included safety updates up to July 13, 2020. For this component of the submission, the Applicant performed a literature search using the PubMed literature search engine and spanned the period from July 14, 2020, to March 23, 2021. The search yielded no new publications within the specified time frame. There were no safety updates from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

During the time after initial submission of this NDA, the Applicant completed a clinical efficacy and safety study that assessed the effect of Dyanavel XR tablet in adult patients with ADHD. However, this trial is not part of the review of this submission.

The Applicant is amending the application to add NDA 011522 for Adderall tablets as a listed drug in addition to NDA 208147 for Dyanavel XR (amphetamine) extended-release oral suspension as the listed drugs upon which they are relying for their 505(b)(2) NDA.

Conclusions:

- The Controlled Substance Staff (CSS) had previously reviewed this NDA in 2018 and recommended edits to Section 9 (Drug Abuse and Dependence) of the labeling.
- DP took Complete Response actions in July 2018 and January 2021 due to concerns with manufacturing facilities. In the current resubmission, the Applicant has provided a complete response to the deficiencies outlined in the Complete Response Letter (CRL) of January 2021.
- Regarding labeling, the Agency had advised the Applicant that comments on the proposed labeling would be reserved until the application is otherwise adequate.
- No new studies were reviewed for this submission.
- DP requests CSS input in reviewing applicable aspects of this NDA resubmission in order to inform the proposed labeling.

Recommendations:

- Labeling negotiations are ongoing with the Applicant at this time.

- The Applicant's proposed labeling is mostly consistent with labeling of other ADHD stimulant drug products in the class; however, we recommend incorporating the definitions for abuse, tolerance, and dependence to better align with guidance for industry, *Drug Abuse and Dependence Section of Labeling for Human Prescription Drug and Biological Products — Content and Format*, available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-abuse-and-dependence-section-labeling-human-prescription-drug-and-biological-products-content.
- The CSS recommendations have been incorporated into the working draft labeling (located on the DP SharePoint site for this NDA).

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/s/

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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: October 5, 2021

To: Gregory Dubitsky, MD**,** Clinical Reviewer
Division of Psychiatry (DP)

Kofi Ansah, PharmD, Regulatory Project Manager, DP

Kimberly Updegraff, PharmD, Associate Director for Labeling, DP

From: Lynn Panholzer, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

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

Subject: OPDP Labeling Comments for DYANAVEL XR (amphetamine) extended-release tablets, for oral use, CII

NDA 210526

In response to DP's consult request dated August 26, 2021, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and container labels for the May 4, 2021 resubmission of the NDA for DYANAVEL XR (amphetamine) extended-release tablets, for oral use, CII.

Labeling: OPDP's comments on the proposed PI are based on the draft labeling received by electronic mail from DP on September 24, 2021, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review of the draft Medication Guide was completed, and comments on the proposed Medication Guide were sent under separate cover on October 4, 2021.

Container Labels: OPDP has reviewed the attached proposed container labels submitted by the Applicant to the electronic document room on May 4, 2021, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Lynn Panholzer at (301) 796-0616 or lynn.panholzer@fda.hhs.gov.

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/s/

LYNN M PANHOLZER
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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:	October 4, 2021
To:	Kofi Ansah, PharmD Regulatory Project Manager **Division of Psychiatry (DP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Lynn Panholzer, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	DYANAVEL XR (amphetamine)
Dosage Form and Route:	Extended-release tablets, for oral use, CII
Application Type/Number:	NDA 210526
Applicant:	Tris Pharma, Inc.

1 INTRODUCTION

On May 04, 2021, Tris Pharma, Inc., submitted for the Agency's review a Class 2 Resubmission for 505(b)(2) New Drug Application (NDA) 210526 for DYANAVEL XR (amphetamine) extended-release tablets indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older. The purpose of this resubmission is to address the deficiencies identified in the Complete Response (CR) letter issued by the Agency on January 21, 2021. The reference listed drug (RLD) for this Application is NDA 208147, DYANAVEL XR (amphetamine) extended-release oral suspension, CII.

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 (DP) on August 26, 2021 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for DYANAVEL XR (amphetamine) extended-release tablets.

2 MATERIAL REVIEWED

- Draft DYANAVEL XR (amphetamine) MG received on May 04, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 27, 2021.
- Draft DYANAVEL XR (amphetamine) Prescribing Information (PI) received on May 04, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 27, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6^{th} to 8^{th} grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8^{th} grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

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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/s/

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BARBARA A FULLER
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LASHAWN M GRIFFITHS
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MEMORANDUM

REVIEW OF REVISED LABELS

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

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:	September 2, 2021
Requesting Office or Division:	Division of Psychiatry (DP)
Application Type and Number:	NDA 210526
Product Name and Strength:	Dyanavel XR (amphetamine) extended-release tablets, 5 mg, 10 mg, 15 mg, and 20 mg
Applicant/Sponsor Name:	Tris Pharma, Inc.
OSE RCM #:	2020-1970
DMEPA 1 Safety Evaluator:	Loretta Holmes, BSN, PharmD
DMEPA 1 Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels received on May 4, 2021 for Dyanavel XR. The Division of Psychiatry (DP) requested that we review the revised container labels for Dyanavel XR (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to a comment in the Complete Response Letter (CRL), dated January 21, 2021, regarding the Medication Guide (MG) statement on the container labels.[a]

2 CONCLUSION

The Applicant revised the MG statement according to the following comment in the CRL:
Add the following bolded statement or appropriate alternative to the carton and container labels per 21 CFR 208.24(d): "ATTENTION PHARMACIST: Each patient is required to receive the accompanying Medication Guide."

We find the revision to the container labels acceptable. Therefore, we have no additional recommendations at this time.

[a] Seung, S. Complete Response for Dyanavel XR. Silver Spring (MD): FDA, CDER, OND, DP (US); 2021 Jan 21. NDA 210526.

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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 Surveillance and Epidemiology

Enhanced Pharmacovigilance Plan Memorandum

Date:	October 21, 2020
Reviewer/Team Leader:	Vicky Chan, PharmD, BCPS Division of Pharmacovigilance I
Division Director:	Cindy Kortepeter, PharmD Division of Pharmacovigilance I
Product Name:	Dyanavel XR (Amphetamine) Extended Release Oral Tablets
Subject:	Enhanced pharmacovigilance plan for serious gastrointestinal adverse events
Application Type/Number:	NDA 210526
Applicant/Sponsor:	Emory Partners, LLC
OSE RCM #:	2020-2004

Special thanks to Dr. Jonn Bailey for his assistance with this memorandum.

1 INTRODUCTION

This memorandum provides the Division of Pharmacovigilance's (DPV) recommendation for an enhanced pharmacovigilance (ePV) plan for serious gastrointestinal adverse events reported with the use of Dyanavel XR (amphetamine) extended release (ER) oral tablets, New Drug Application (NDA) number 210526.

2 REGULATORY HISTORY

NDA 210526 is intended to support approval of Dyanavel XR (amphetamine) ER oral tablets for the treatment of Attention-Deficit Hyperactivity Disorder. This is a 505(b)(2) NDA that references NDA 208147 (Dyanavel XR oral suspension). The Division of Psychiatry (DP) took a Complete Response action for NDA 210526 on July 25, 2018 due to concerns with manufacturing facilities.[1] Emory Partners, LLC, the Applicant, submitted a Class 2 resubmission for NDA 210526 on July 22, 2020.[2]

Dyanavel XR (amphetamine) ER oral tablets contain sodium polystyrene sulfonate (SPS) and mannitol as excipients. Cases of intestinal necrosis & other serious gastrointestinal adverse events, some fatal, have been reported with the use of products containing SPS and sorbitol. Mannitol and sorbitol are similar in terms of molecular weight and physiologic properties. Thus, the Division of Psychiatry (DP) is concerned that this product also may have a risk of serious intestinal adverse events. However, it is noted that the amounts of SPS and mannitol in this product are considerably less than in products associated with serious intestinal events. The DP review team met on June 14, 2018, to discuss this issue and agreed that an ePV for serious bowel events in the postmarketing phase of this product was an appropriate plan to address this potential risk as opposed to other measures, such as a labeled warning or Risk Evaluation and Mitigation Strategy. DP requests DPV's assistance in establishing an ePV plan to detect cases of serious intestinal adverse events associated with this product post-approval.

3 APPLICANT'S PROPOSED LABELING

The Applicant's proposed combined labeling for Dyanavel XR (amphetamine) ER oral suspension and oral tablets include the following language regarding gastrointestinal adverse events (underlined for emphasis). Serious intestinal adverse events are not included in the labeling.[3]

> **5.7 Serotonin Syndrome**
> Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or <u>gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea)</u>.
>
> **6.1 Clinical Trials Experience**
> <u>Gastrointestinal: Dryness of the mouth, unpleasant taste, diarrhea, constipation, other gastrointestinal disturbances</u>. Anorexia and weight loss may occur as undesirable effects.

Table 1. Common adverse reactions occurring in ≥2% of Subjects on DYANAVEL XR and greater than Placebo during the double blind phase.

Preferred Term	DYANAVEL XR (N=52)	Placebo (N=48)
Respiratory, thoracic and mediastinal disorders		
Epistaxis	3.8%	0%
Rhinitis allergic	3.8%	0%
Gastrointestinal disorders		
Abdominal pain upper	3.8%	2.1%

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of other amphetamine products. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal: unpleasant taste, constipation, other gastrointestinal disturbances.

4 DPV'S PROPOSED EPV PLAN

An ePV consists of additional activities by the applicant to monitor the safety of their medical product beyond routine pharmacovigilance alone. An ePV may involve the following: special reporting requirements for applicants beyond those specified in the Code of Federal Regulation (CFR), such as expedited reporting of labeled adverse events; use of standardized questionnaires for Adverse Events of Special Interest (AESI) for better data collection; and detailed periodic summaries on AESI.

Serious intestinal adverse events, the AESI, are not labeled events based on the draft labeling proposed by the Applicant. As required under 21 CFR 314.80, the Applicant is to report serious unlabeled adverse event reports to the FDA within 15 days (i.e., expedited reporting). As such, the Applicant is expected to report serious intestinal adverse events to the FDA in an expedited manner.

DPV recommends in future periodic reports to include:
A summary, assessment, and listing of cases of serious intestinal adverse events in the Applicant's global safety system from the time of approval through the end of the time period retrieved by, at minimum, using the following Standardised Medical Dictionary for Regulatory Activities (MedDRA) Queries (SMQ):

- Gastrointestinal perforation, ulceration, haemorrhage or obstruction
- Ischaemic colitis (Broad scope)

The summary includes cases stratified by:

- *Total number of cases of serious intestinal adverse events by time period and cumulative since approval*
- *Patient outcome:*

    - *Fatal*
        - *Cause of death*
    - *Non-fatal: admitted to the hospital; required medical intervention but not hospitalized (i.e., visit to the emergency room)*
        - *Medical interventions required (i.e., surgery, blood transfusion)*
- *Age (Mean, Range)*
- *Sex*
- *Indication for Dyanavel XR extended release oral tablet*
- *Dose of Dyanavel XR extended release oral tablet*
- *Concurrent and past medical history*
- *Past surgical history*
- *Concomitant medications*
- *Onset of serious intestinal adverse event after Dyanavel XR extended release oral tablet initiation (Mean, Range)*
- *Action taken with Dyanavel XR extended release oral tablet (i.e., continued or discontinued treatment)*
- *Dechallenge, Rechallenge with Dyanavel XR extended release oral tablet*

In addition to the summary and assessment in each periodic report, provide above data, including the respective manufacturer control number for each case, in .xlsx format.

5 REFERENCES

1. NDA 210526/TRIS/DYANAVEL XR (amphetamine) ER Tablets/ADHD – Complete Response Letter July 25, 2018
https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af804aa11b

2. Dyanavel XR (amphetamine) ER Tablets Resubmission NDA210526 (210526 - 0019 - (21) - 2020-07-22 - ORIG-1 /Multiple Categories/Subcategories) - Cover Letter (Resubmission Response to July 25, 2018 CRL) - Seq 0019 / 22Jul2020

3. Dyanavel XR (amphetamine) ER Tablets Draft Prescribing Information NDA210526 (210526 - 0023 - (24) - 2020-09-29 - ORIG-1 /Multiple Categories/Subcategories) - Dyanavel XR PI (LBXXXX/ Rev. 0X/ XX-XXXX) Clean - pdf

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/s/

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LABELS AND LABELING 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:	July 3, 2018
Requesting Office or Division:	Division of Psychiatry Products (DPP)
Application Type and Number:	NDA 210526
Product Name and Strength:	Dyanavel XR[a] (amphetamine) extended-release tablets 5 mg, 10 mg, 15 mg, and 20 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Tris Pharma, Inc.
FDA Received Date:	September 25, 2017
OSE RCM #:	2017-2240
DMEPA Safety Evaluator:	Loretta Holmes, BSN, PharmD
DMEPA Team Leader:	Lolita White, PharmD

[a] The proposed proprietary name Dyanavel XR was found conditionally acceptable in OSE RCM # 2018-20331524 on April 13, 2018.

1 REASON FOR REVIEW

The Division of Psychiatry Products (DPP) consulted the Division of Medication Error Prevention and Analysis (DMEPA) to evaluate the container labels, Medication Guide labeling and prescribing information (PI) labeling for NDA 210526 Dyanavel XR (amphetamine) extended-release tablets to determine if they are acceptable from a medication error perspective.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material 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)
Human Factors Study	C (N/A)
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other	F (N/A)
Labels and Labeling	G

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 REGULATORY HISTORY

NDA 208147 for Dyanavel XR extended-release oral suspension was approved on October 19, 2015. With NDA 210526, Tris Pharma, proposes an extended-release oral tablet formulation.

4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed container label, prescribing information (PI), and Medication Guide (MG) to determine if there are any areas of concern or needed improvement from a medication safety perspective. We identified the following:

Container Labels

1. The proprietary name and established names do not appear to have commensurate prominence. Lack of commensurate prominence may lead to poor visibility of the information.

2. Placeholders are used for portions of the NDC number. The entire number is needed in order that we may assess it from a medication error perspective.

3. There is inadequate differentiation between the product strengths. Inadequate differentiation may lead to wrong strength product selection errors.

4. The expiration date format is not indicated. The proposed format is needed in order that we may assess it from a medication error perspective.

5. A linear barcode does not appear to be present on the labels. Lack of a linear barcode may lead to product identification problems.

6. Non-product identifying information such as the "Rx only" and net quantity statements on the principal display panel (PDP) are too prominent due to their bold font and detract attention from more important information on the PDP.

Medication Guide (MG)

The Patient Labeling Team completed a review of the proposed Medication Guide and we have no additional recommendations.

We provide recommendations regarding the container labels in Section 5.1 in order to help minimize the potential for medication errors to occur with the use of the product.

5 CONCLUSION & RECOMMENDATIONS

We identified areas of needed improvement in strength differentiation and the presentation or placement of certain information on the container labels. We provide recommendations in Section 5.1 below. We advise these recommendations are implemented prior to approval of this product.

5.1 RECOMMENDATIONS FOR TRIS PHARMA, INC.

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

A. Container Labels

1. The proprietary name and established name do not appear to have commensurate prominence. Lack of commensurate prominence may lead to poor visibility of the information. Ensure the established name at least ½ the size of the proprietary name in accordance with 21 CFR 201.10(g)(2).

2. Placeholders are used for portions of the NDC number. The entire number is needed in order that we may assess it from a medication error perspective. Remove the placeholders and specify the entire NDC number.

3. There is inadequate differentiation between the product strengths because the font colors used in the proprietary name overlap with the colors utilized to differentiate the 5 mg and 10 mg strengths. We are concerned that the overlap in colors decrease the differentiation of the strengths. Consider revising the scheme of the 5 mg strength ([(b) (4)]-like color) and the 10 mg strength ([(b) (4)]-like color) so that these strengths appear in their own unique color and the color does not overlap

with any other colors utilized in the proprietary name. In addition, ensure the newly selected colors do not overlap with the colors utilized to highlight the 15 mg or 20 mg strengths.

4. The expiration date format is not indicated. Please specify your proposed format for the expiration date. We recommend using one of the following (or similar) formats:

    - DDMMMYYYY (e.g., 31JAN2013)
    - MMMYYYY (e.g., JAN2013)
    - YYYY-MMM-DD (e.g., 2013-JAN-31)
    - YYYY-MM-DD (e.g., 2013-01-31)

5. A linear barcode does not appear to be present on the labels. Lack of a linear barcode may lead to product identification problems, particularly in a hospital setting. If not present, add a linear barcode to the labels and specify its location.

6. Non-product identifying information such as the "Rx only" and net quantity statements on the principal display panel (PDP) are too prominent due to their bold font and detract attention from more important information on the PDP. Unbold these fonts or use a font that is not bold for the "Rx only" and net quantity statements.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Dyanavel XR received on September 25, 2017 from Tris Pharma, Inc.

Table 2. Relevant Product Information for Dyanavel XR	
Initial Approval Date	N/A
Active Ingredient	amphetamine
Indication	Treatment of Attention Deficit Hyperactivity Disorder (ADHD)
Route of Administration	Oral
Dosage Form	Extended-release tablets
Strengths	5 mg (functionally scored), 10 mg, 15 mg, and 20 mg
Dose and Frequency	2.5 mg to 20 mg orally once daily in the morning
How Supplied	30-count bottles
Storage	Store at 20° to 25°C (68° to 77°F); excursions permitted from 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]
Container Closure	Child-resistant closure

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

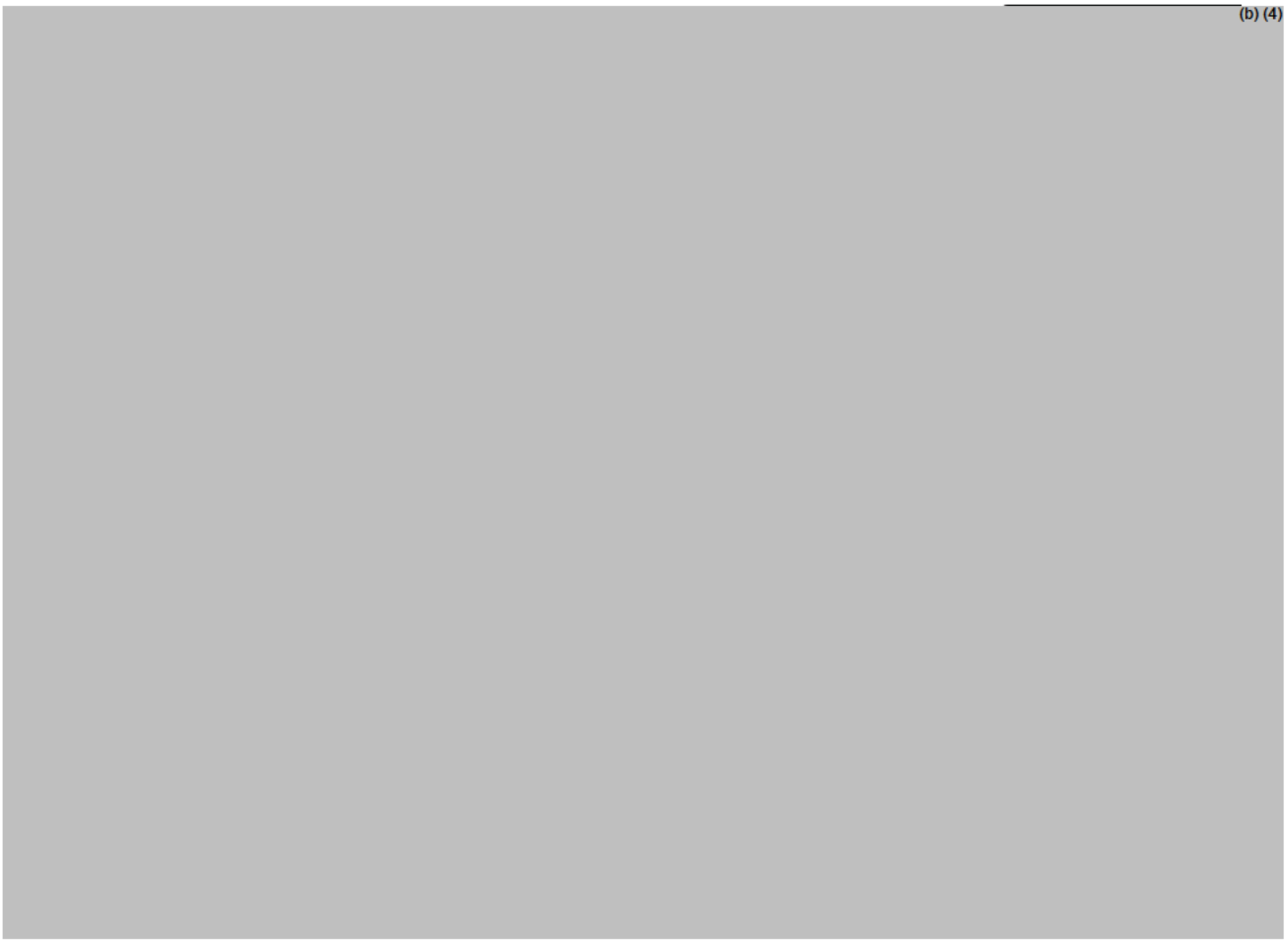
Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Dyanavel XR labels and labeling submitted by Tris Pharma, Inc.

- Container label received on September 25, 2017
- Medication Guide received on September 25, 2017 (image not shown)
- Prescribing Information received on September 25, 2017 (image not shown)

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

Container Labels

(b) (4)



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

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07/03/2018

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:	June 28, 2018
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, CDE Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	DYANAVEL XR (amphetamine)
Dosage Form and Route:	Extended-release oral suspension and tablets
Application Type/Number:	NDA 210526
Applicant:	Tris Pharma, Inc.

1 INTRODUCTION

On September 25, 2017, Tris Pharma, Inc., submitted for the Agency's review an original New Drug Application (NDA) for DYANAVEL XR (amphetamine) extended-release tablets for the proposed indication of use for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in pediatric patients 6 to 17 years of age. This submission is a 505(b)(2) application, relying on the Agency's previous findings of safety and efficacy for the reference listed drug (RLD) DYANAVEL XR (amphetamine) extended-release oral suspension.

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 November 1, 2017 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for DYANAVEL XR (amphetamine).

2 MATERIAL REVIEWED

- Draft DYANAVEL XR (amphetamine) MG received on September 25, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 21, 2018.
- Draft DYANAVEL XR (amphetamine) Prescribing Information (PI) received on September 25, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 21, 2018.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

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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/s/

SHAWNA L HUTCHINS
06/28/2018

DOMENIC G DALESSANDRO
06/28/2018

LASHAWN M GRIFFITHS
06/28/2018

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

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

Memorandum

Date: June 28, 2018

To: Gregory M. Dubitsky, M.D., Clinical Reviewer
Division of Psychiatry Products (DPP)

Kofi Ansah, PharmD, Regulatory Project Manager, (DPP)

Kimberly Updegraff, PharmD, Associate Director for Labeling, (DPP)

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

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

Subject: OPDP Labeling Comments for DYANAVEL® XR (amphetamine) extended-release oral tablets, for oral use, CII

NDA: 210526

In response to DPP consult request dated November 1, 2017, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original NDA for Dyanavel® XR (amphetamine) extended-release oral tablets, for oral use, CII.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DPP on June 21, 2018, 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 June 28, 2018.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DPP on June 26, 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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/s/

DOMENIC G DALESSANDRO
06/28/2018

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: June 20, 2018

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

Through: Dominic Chiapperino, Ph.D., Director
Silvia Calderon, Ph.D., Senior Pharmacologist
Martin S. Rusinowitz, M.D., Senior Medical Officer
Controlled Substance Staff

From: Shalini Bansil, M.D., Medical Officer
Controlled Substance Staff

Subject: NDA 210526 for Amphetamine Extended-Release Tablets.
Trade Name: Dyanavel XR extended-release tablets
Dose: 2.5 mg-20 mg once daily in the morning, available as ER oral suspension 2.5 mg/mL (already approved), or proposed ER tablets, 5, 10, 15, and 20 mg; tablets may be chewed or swallowed whole
IND: 129044
Indication(s): Attention Deficit Hyperactivity Disorder (ADHD) in children 6 -17 years of age
Sponsor: Tris Pharma, Inc.
PDUFA Goal Date: July 25, 2018

Materials Reviewed:

- 1.11.4 Justification for Controlled Substance Scheduling
- 1.14 Labeling
- 2.3 Quality Overall Summary
- 2.4 Nonclinical overview
- 2.7.1 Summary of Biopharmaceutic Studies
- 2.7.4 Summary of Clinical safety
- 5.3.1 Reports of Biopharmaceutic Studies
- CSS Consult Hawkins, E; IND 129044 DARRTS, April 4, 2016

Table of Contents

I. Summary

1. Background

This memorandum responds to a consult request by the Division of Psychiatry Products (DPP) dated December 8, 2017, to evaluate abuse-related data submitted by the Sponsor in NDA 210526 (IND129044) for Amphetamine Extended-Release (ER) Tablets, Trade name Dyanavel XR extended-release tablets.

Amphetamine ER Tablets containing 5, 10, 15, and 20 mg amphetamine base per tablet was developed by the Sponsor to provide patients and healthcare practitioners a once daily, solid oral dosage form of an ER amphetamine for the treatment of Attention Deficit/Hyperactivity Disorder (ADHD) in children aged 6 years and older. The Sponsor asserts that Amphetamine ER Tablets can be either chewed or swallowed whole, while maintaining the extended-release profile. The clinical profile offers a rapid onset of clinical effect within one hour of dosing which persists through 13 hours after dosing. Such attributes fit well with the needs of the ADHD population which requires medication to be effective throughout the day and into the evening, but not to prohibit or obstruct sleeping patterns during the night hours. Amphetamine ER Tablets were developed as an alternate dosage form for Dyanavel® XR (amphetamine) ER oral suspension, NDA 208147, from the same Sponsor. The Sponsor submits a 505(b)(2) NDA for the Amphetamine ER Tablets with a bridge to Dyanavel XR oral suspension as the reference listed drug (RLD) and, therefore, relies on the previously approved clinical data pertinent to the safety and efficacy of the product in the intended population.

Amphetamine is a Schedule II substance under the Controlled Substances Act (CSA) and was initially approved in the USA in 1960.

2. Conclusions

1. Amphetamine ER Tablets have a similar abuse related risk profile as the RLD Dyanavel® XR (amphetamine) oral suspension.
2. The Sponsor proposes control of Amphetamine ER Tablets under Schedule II of the CSA, same as other marketed amphetamine formulations.
3. The label, like other stimulants, has a Black Box warning regarding abuse and dependence. Information on Drug Abuse and Dependence is provided in Section 9 of the label, with content similar to the RLD.

3. Recommendations

Section 9 from the Sponsor's submission is presented here, with suggested CSS edits:

9. DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

DYANAVEL XR contains amphetamine, which is a Schedule II controlled substance (b) (4) (b) (4)

9.2 Abuse

DYANAVEL XR, is a CNS stimulant that contains amphetamine which has a high potential for abuse. (b) (4) .

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 observed. **Abusers of CNS stimulants may chew, snort, inject, or use other unapproved routes of administration which can result in overdose and death [see Overdosage (10)].** .

To reduce the abuse of DYANAVEL XR, 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 DYANAVEL XR use.

9.3 Dependence

Tolerance

Tolerance (b) (4) may occur during the chronic therapy of CNS stimulants including DYANAVEL XR.

Dependence

Physical dependence [redacted] by a withdrawal [redacted] abrupt [redacted] dose reduction, or administration of an antagonist) may occur in patients treated with CNS stimulants including DYANAVEL XR. Withdrawal symptoms after abrupt cessation following prolonged high-dosage administration of CNS stimulants include dysphoric mood; fatigue; vivid, unpleasant dreams; insomnia or hypersomnia; increased appetite; and psychomotor retardation or agitation.

II. DISCUSSION

1. Chemistry

1.1 Drug Substance and Drug Product Information

Amphetamine ER Tablets are an extended-release tablet formulation containing 5 mg, 10 mg, 15 mg, and 20 mg of amphetamine base (Amphetamine [redacted], Dextroamphetamine Sulfate, Amphetamine Aspartate [redacted] The fast onset is contributed by [redacted] the product [redacted] a tablet formulation that may be swallowed whole or chewed. [redacted].

2. Nonclinical Pharmacology

The development program assessed the bioequivalence of the drug product with Dyanavel XR oral suspension when tablets are swallowed whole or chewed in healthy adult volunteers.

The Sponsor states that due to the extensive body of data characterizing the pharmacology, toxicology, absorption, distribution, metabolism, and excretion properties of amphetamine, additional nonclinical pharmacology, pharmacokinetic (PK), or toxicology studies with the drug product were not conducted.

3. Clinical Pharmacology

Protocol 2016-4171: This study examined the relative bioavailability between a test product (Amphetamine ER chewable tablet) as a single 20 mg dose either chewed, or swallowed whole, compared to an equivalent dose of a reference ER oral suspension. Furthermore, the effect of food on the relative bioavailability of the test product was investigated, in addition to the impact of chewing the test product versus swallowing it whole on the resulting PK profile.

Overall, the test product showed comparable bioavailability with respect to both *d* and *l*-amphetamine, when administered as a chewable tablet or swallowed whole, compared to an equivalent 20 mg dose of the reference product, Dyanavel XR (amphetamine) Oral Suspension, 2.5 mg/mL under fasted conditions. These results support the absence of a food effect on the test product when administered as a chewable tablet.

The bioavailability of *d*- and *l*-amphetamine was comparable after administration of the test product when administered as a chewable tablet compared to being swallowed whole, under fasted conditions.

Examination of the individual concentrations versus time profiles following single dose administration suggests that the test product meets the goals of once-daily dosing, without any potential of dose dumping upon repeated administration.

3.1 Drug/Product Interactions

There is no *in vivo* study conducted for the effect of alcohol on drug exposure. *In vitro* alcohol-induced dose dumping studies showed that amphetamine release rates from the tablets increased in the presence of 40% alcohol but not with 5%, 10% or 20% alcohol.

4. Clinical Studies

An Open-Label Randomized, Four-Way Crossover, Pilot Study to Evaluate the Relative Bioavailability of a Test Formulation of Amphetamine ER Chewable/ODTs administered as a Chewable, Orally Disintegrating, and Swallowed Whole, and to an Equivalent Dose of the Reference Product Amphetamine ER Oral Suspension under Fasted Conditions in Healthy Adult Subjects. Protocol 2016-4009

This was a single-dose, four-period, four-treatment, four-sequence, crossover study. This study was designed to evaluate the comparative bioavailability of *d*-amphetamine and *l*-amphetamine in healthy male and female subjects under fasted conditions. Sixteen subjects were enrolled in the study and 13 subjects completed the study. Fifteen subjects received the Test Product and 15 subjects received the Reference Product. The following treatments were administered:

Treatment A: Oral ER chewed under fasted conditions, 20 mg
Treatment B: Oral ER ODT under fasted conditions, 20 mg
Treatment C: Oral ER swallowed whole under fasted conditions, 20 mg
Reference Product (Treatment D): Amphetamine ER Oral Suspension, 20 mg, under fasted conditions

Two of 44 subjects (4.5%) in Treatments A, B, and C noted feeling jittery, and 1 of 15 (6.7%) in Treatment D noted feeling jittery.

An Open-Label Randomized, Three-Way Crossover, Pilot Study to Evaluate the Relative Bioavailability of Two Test Formulations of Amphetamine ER Chewable Tablets to an Equivalent Dose of the Reference Product Amphetamine ER Oral Suspension, Manufactured by Tris Pharma under Fasted Conditions in Healthy Adult Subjects. Protocol 2016-4124.

This was a single-dose, three-period, three-treatment, three-sequence, crossover study. Twelve subjects were enrolled and 11 subjects completed the study. The following treatments were administered:

Test Product 1 (Treatment A): Amphetamine ER Chewable Tablets, 20 mg

Test Product 2 (Treatment B): Amphetamine ER Chewable Tablets, 20 mg
Reference Product (Treatment C): Dyanavel XR (amphetamine) ER Oral Suspension 20 mg

One subject reported feeling jittery in the Treatment C group

An Open-label, Randomized, Four-Way, Crossover, Single-Dose Pivotal Study to Evaluate the Bioavailability of a Test Product Formulation of Amphetamine Extended-Release Chewable Tablets under Fasted and Fed Conditions, Swallowed Whole under Fasted Conditions, and to Evaluate the Relative Bioavailability of the Test Product Formulation to an Equivalent Dose of a Commercially Available Reference Product (Dyanavel® XR, 20 mg) under Fasted Conditions in Healthy Adult Subjects Protocol 2016-4171

The primary objectives of this study were to evaluate:

1. The relative bioavailability under fasted conditions between:
- Amphetamine ER Chewable Tablets, 20 mg, either swallowed whole or chewed; and
- Dyanavel XR (amphetamine) ER Oral Suspension, 2.5 mg/mL, after a single-dose in healthy subjects

2. The effect of food on the PK of the test product.

Secondary Objectives:
1. To evaluate the effect on absorption of the chewable tablets, if not chewed but swallowed whole;
2. To ensure that the plasma concentration versus time profile, established for the ER test product, meets the goal of once-a-day dosing, and to demonstrate that there is no dose dumping; and
3. Assessment of safety and tolerability based primarily on the frequency and severity of Adverse Events (AEs), including clinically significant values for laboratory safety tests and vital signs reported as AEs.

This was an open-label, single-dose, randomized, four-period, four-treatment, four sequence, crossover, relative bioavailability and food effect study.

The study population consisted of healthy, non-smoking, male and female volunteers.

In each period, subjects received one of the following 4 treatments:
- Treatment A – Test Product 20 mg (as a chewable tablet): one tablet administered after an overnight fast of at least 10 hours
- Treatment B – Test Product 20 mg (as a chewable tablet): one tablet administered 30 minutes after the start of a high-fat, high-calorie breakfast
- Treatment C – Test Product 20 mg dose (as a whole tablet): one tablet administered after an overnight fast of at least 10 hours
- Treatment D – Reference Product: Dyanavel XR (amphetamine) ER Oral Suspension, 2.5 mg/mL 20 mg administered after an overnight fast of at least 10 hours

The washout between drug administrations for each subject was at least 7 days. Pharmacokinetic analysis was performed on available data from subjects in the PK dataset.

Thirty-six subjects were enrolled in the study and 32 subjects completed the study. Two subjects were dismissed from the study due to testing positive for THC or opiates.

All AEs were classified according to MedDRA (Medical Dictionary for Regulatory Activities) (version 19.1)
'Feeling jittery' was reported by one subject in the Treatment A group. Anxiety was reported by one subject in Treatment C, and restlessness by one subject each for Treatment C and Treatment D.

4.1 Adverse Event Profile Through all Phases of Development

The only studies performed for this product were single-dose bioequivalence studies. These studies did not reveal evidence of abuse-related AEs, such as euphoria, hallucinations, sedation, etc. The reference product did not produce these AEs either. Amphetamines are known to produce abuse-related AEs and are in Schedule II of the CSA; however, these were not apparent in the studies performed by the Sponsor perhaps because they were small, single-dose studies.

4.2 Safety Profile

No safety concerns related to abuse were noted for Amphetamine ER Tablets during the trials conducted for this NDA.

4.3 Evidence of Abuse, Misuse and Diversion in Clinical Trials

There was no evidence of abuse, misuse, or diversion; however, only single-dose studies were conducted which would make these events unlikely to occur.

4.4 Tolerance and Physical Dependence Studies in Humans

There were no studies conducted related to physical dependence in humans. Chronic therapy with stimulants, including amphetamines, may lead to tolerance and dependence and this has been adequately addressed in the product label.

5. Regulatory Issues and Assessment

The Sponsor supports scheduling of Amphetamine Extended-Release Tablets under Schedule II of the CSA like other amphetamines. The drug substances used in the manufacturing of the drug product are Amphetamine Aspartate (b) (4) Amphetamine (b) (4) and Dextroamphetamine Sulfate. Any material, mixture, etc. containing amphetamine and/or its salts are considered Schedule II products. The label, like other stimulants, has a Black Box warning regarding abuse and dependence. Information for Drug Abuse and Dependence is provided in Section 9 of the label, with content similar to the RLD.

Section 9 from the Sponsor's submission is presented here, with suggested CSS edits:

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Physical dependence (b) (4) a withdrawal (b) (4) abrupt (b) (4) dose reduction, or administration of an antagonist) may occur in patients treated with CNS stimulants including DYANAVEL XR. Withdrawal symptoms after abrupt cessation following prolonged high-dosage administration of CNS stimulants include dysphoric mood; fatigue; vivid, unpleasant dreams; insomnia or hypersomnia; increased appetite; and psychomotor retardation or agitation.

6. Other Relevant Information

The Sponsor states that Amphetamine ER Tablets (b) (4) . The delivery technology results in particle sizes (b) (4) in the finished dosage forms (drug product). The average diameter of a red blood cell (RBC) is ~7-10 microns. Injection of particles greater that the diameter of an RBC may result in particles becoming trapped in capillaries or larger blood vessels, leading to ischemia. Therefore, this product is not conducive to injection, eliminating the predilection of abuse by injection. However, drug users suggest filtering drugs using 0.22 µm filters after grinding to make an intravenous (IV) formulation. Although the particle size of this product was determined to be (b) (4) when dispersed in water, it would be lethal (pulmonary embolism) if not filtered or if filtered incorrectly. Additionally, because drug abusers seem to commonly use a filtering process on dissolved tablets when preparing them for IV administration, it seems unlikely that the particles described by the Sponsor will deter abuse.

According to the Sponsor, the resilience of the individual particles makes conversion of the product to an immediate-release product by crushing or grinding difficult. Physical stress is often used to manipulate extended-release products to obtain a preparation that exhibits an immediate-release profile when abused by snorting intranasally. The controlled-release delivery technology of Amphetamine ER Tablets reduces the attractiveness of abuse by snorting since physical stress or manipulation does not appear to compromise the extended-release properties of the product. However, a simple liquid extraction will dissolve most of the active substance in water where it can be filtered and injected or snorted.

In summary, CSS believes the product has no abuse deterrent properties. The Sponsor has not made abuse deterrent claims in the label.

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/s/

SHALINI M BANSIL
06/20/2018

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SILVIA N CALDERON
06/20/2018

DOMINIC CHIAPPERINO
06/20/2018

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: 2/20/2018

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 210526

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	Pharma Medica Research, Inc.	400 Fountain Lakes Boulevard, St. Charles, MO, USA.
		(b) (4)

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/s/

SHILA S NKAH
02/20/2018