NDA 210526

NDA APPROVAL

Tris Pharma, Inc.
Attention: Norma J. Cappetti
Senior VP of Regulatory Affairs
2031 Route 130, Suite D
Monmouth Junction, N 08852

Dear Ms. Cappetti:

Please refer to your new drug application (NDA) dated and received September 25, 2017, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Dyanavel XR (amphetamine) extended-release tablets 5 mg, 10 mg, 15 mg, and 20 mg.

We acknowledge receipt of your amendment dated May 4, 2021, which constituted a complete response to our January 21, 2021, action letter.

This NDA provides for the use of Dyanavel XR (amphetamine) extended-release tablets for the treatment of attention deficit hyperactivity disorder (ADHD) in patients 6 years and older.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Prescribing Information, Instructions for Use, and Medication Guide) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling submitted on May 4, 2021, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 210526**." Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Dyanavel XR (amphetamine) extended-release tablets shall be 36 months from the date of manufacture when stored at 20°C to 25°C (68°F to 77°F).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric studies requirement for ages 0 to less than 4 years because necessary studies are impossible or highly impracticable. Although children under the age of 4 years can exhibit ADHD-like behaviors, diagnosis and treatment recommendations for that age group have not been codified in recognized guidelines such as the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Most of the currently accepted measures for diagnosis and efficacy of treatment of ADHD in older age groups have not been validated for children less than 4 years of age.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

We are deferring submission of your pediatric studies for ages 4 to less than 6 years for this application until additional safety and effectiveness data are collected.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

4179-1 A single-dose pharmacokinetic study of Dyanavel XR (amphetamine) extended-release oral tablet in children aged 4 to 5 years with ADHD.

Final Protocol Submission:	09/2022
Study Completion:	12/2023
Final Report Submission:	06/2024

4179-2 A randomized, double-blind, placebo-controlled, flexible-dose study of Dyanavel XR (amphetamine extended-release) oral tablet in children aged 4 to 5 years diagnosed with ADHD.

Final Protocol Submission:	09/2022
Study Completion:	11/2024
Final Report Submission:	08/2025

4179-3 A one year Pediatric Open-Label Safety Study of patients aged 4 to 5 years diagnosed with ADHD treated with Dyanavel XR (amphetamine extended release) oral tablet.

Final Protocol Submission:	09/2022
Study Completion:	11/2024
Final Report Submission:	08/2025

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit the protocol(s) to your IND 129044, with a cross-reference letter to this NDA. Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

This product is appropriately labeled for use in ages 6 to 17 years for this indication. Therefore, no additional studies are needed in this pediatric group.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[4]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

Postmarketing Safety Reports

We request that periodic safety reports for amphetamine ER tablets contain additional information regarding serious intestinal adverse events reported with this product. This request is based on reports of intestinal necrosis and other serious gastrointestinal adverse events, some fatal, associated with the use of products that contain sodium polystyrene sulfonate (SPS) and sorbitol. Because amphetamine ER tablets contain SPS and mannitol, and mannitol is very similar to sorbitol in terms of molecular weight and physiologic properties, we consider it possible that such reactions might occur with amphetamine ER tablets. We request the following additional information:

A summary, assessment, and listing of cases of serious intestinal adverse events in your global safety system from the time of approval through the end of the reporting period for the report. These events should be retrieved, at a minimum, using the following Standardised MedDRA Queries (SMQs):

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

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

The summary should stratify cases by:

- Total number of cases of serious intestinal adverse events by time period and cumulatively since approval
- Patient outcome:
  - Fatal
    - Cause of death
  - Non-fatal
    - Medical interventions required (e.g., surgery, blood transfusion)
- Age (mean, range)
- Sex
- Indication for amphetamine ER tablet treatment
- Dose of amphetamine ER tablet
- Current and past medical history
- Past surgical history
- Concomitant medications
- Timing of onset of serious intestinal adverse event relative to amphetamine ER tablet initiation (mean, range)
- Action taken regarding amphetamine ER tablet treatment (continued or discontinued)
- Dechallenge, rechallenge with amphetamine ER tablet

In addition, please provide the above data in .xlsx format. This should include the manufacturer control number for each case.

If you have any questions, please contact CAPT Kofi Ansah, Senior Regulatory Health Project Manager, at Kofi.Ansah@fda.hhs.gov or call (301)796-4158.

Sincerely,

{See appended electronic signature page}

Tiffany R. Farchione, MD
Director
Division of Psychiatry
Office of Neuroscience
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
    - Prescribing Information
    - Medication Guide
    - Instructions for Use
- Carton and Container Labeling

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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