

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

208147Orig1s000

Trade Name: Dyanavel XR extended-release oral suspension,
2.5 mg amphetamine base per ml.

Generic Name: Amphetamine

Sponsor: Tris Pharma

Approval Date: October 19, 2015

Indication: For the use of Dyanavel XR (amphetamine) extended-release oral suspension, 2.5 mg amphetamine base per ml for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

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RESEARCH**

APPLICATION NUMBER:

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APPROVAL LETTER



NDA 208147

NDA APPROVAL

Tris Pharma
Attention: Yulia Pincus, Ph.D.
Senior Manager, Regulatory Affairs
2033 Route 130
Monmouth Junction, NJ 08852

Dear Dr. Pincus:

Please refer to your New Drug Application (NDA) dated December 18, 2014, and received December 19, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Dyanavel XR (amphetamine) extended-release oral suspension, 2.5 mg amphetamine base per ml.

We acknowledge receipt of your amendments dated:

January 9, 2015	April 14, 2015	July 9, 2015	August 28, 2015
February 13, 2015	April 23, 2015	July 13, 2015	September 2, 2015
March 2, 2015	May 8, 2015	August 13, 2015	September 28, 2015
March 16, 2015	May 11, 2015	August 14, 2015	October 5, 2015
March 23, 2015	June 5, 2015	August 21, 2015	October 13, 2015
March 31, 2015	June 12, 2015	August 26, 2015	October 15, 2015

This new drug application provides for the use of Dyanavel XR (amphetamine) extended-release oral suspension, 2.5 mg amphetamine base per ml for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

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 text.

WAIVER OF HIGHLIGHTS SECTION

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 <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert, and Medication Guide). 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*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 208147.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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 study requirements for ages 0 to 3 years because necessary studies are impossible or highly impracticable. This is because the diagnostic criteria and assessment measures for determining efficacy for the treatment of ADHD in children less than 4 years old are not well defined, and pharmaceutical treatment in this age group is uncommon.

We are deferring submission of your pediatric study for ages 4 to 5 years for this application because pediatric studies should be delayed until additional safety or effectiveness data have been collected. At the current time, FDA has limited experience with the study of

ADHD in younger children (4 to less than 6 years old), so we will defer studies in this younger age group for drugs seeking a claim in ADHD.

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.

2970-1 A single-dose, open-label, randomized pharmacokinetic study of Dyanavel XR (amphetamine extended release) oral suspension in male and female children (4 to less than 6 years of age) with ADHD in fed condition.

Final Protocol Submission: September 2016
Study Completion: January 2018
Final Report Submission: July 2018

2970-2 A randomized, double-blind, placebo-controlled, flexible-dose titration study of Dyanavel XR (amphetamine extended-release) oral suspension in children ages 4 to 5 years diagnosed with ADHD.

Final Protocol Submission: September 2016
Study Completion: August 2019
Final Report Submission: February 2020

2970-3 A one year Pediatric Open-Label Safety Study of patients age 4 to 5 years (at the time of entry into PMR 2970-1 or PMR 2970-2, or at the time of enrollment if directly enrolled into PMR 2970-3) diagnosed with ADHD treated with Dyanavel XR (amphetamine extended release) oral suspension.

Final Protocol Submission: September 2016
Study Completion: January 2020
Report Submission: July 2020

Submit the protocols to your IND 116985, 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.

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.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

- 2970-4 Develop a dissolution method with enough discriminating ability using a single pH media with appropriate ionic strength. Clarify the effects of pH and ionic strength on the dissolution during the development of the dissolution method. Using the developed method test at least five commercial batches and evaluate the stability for the registration/primary batches through at least 12 months of storage under the long-term conditions. These data should be used for the setting of the final dissolution acceptance criteria. You have the option of evaluating an alternative discriminatory dissolution method (b) (4) (b) (4) in case a common dissolution method cannot be successfully developed for drug product (b) (4)

The timetable you submitted on October 5, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: October 2016

Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **“Postmarketing Commitment Protocol,” “Postmarketing Commitment Final Report,” or “Postmarketing Commitment Correspondence.”**

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft

Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

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

If you have any questions, contact CDR Renmeet Grewal, Pharm.D., RAC, Team Leader/ Senior Regulatory Project Manager, at either Renmeet.Grewal@fda.hhs.gov or 301-796-1080.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosures:

Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MITCHELL V Mathis
10/19/2015