CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208147Orig1s000

SUMMARY REVIEW

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	(electronic stamp)
From	Mitchell V. Mathis, MD
Subject	Division Director Summary Review
NDA/BLA #	208147
Applicant Name	Tris Pharma, Inc.
Date of Submission	12/19/2014
PDUFA Goal Date	10/19/2015
Proprietary Name / Established (USAN) Name	Dyanavel XR/Amphetamine ER Oral Suspension
Dosage Forms / Strength	2.5 mg/mL
Proposed Indication(s)	Attention Deficit Hyperactivity Disorder (ADHD)
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Tiffany Farchione, MD
Statistical Review	Semhar Ogbagaber, Ph.D. Eiji Ishida, MS Peiling Yang, Ph.D. H.M. James Hung, Ph.D.
Pharmacology Toxicology Review Supervisory	Ikram Elayan, Ph.D. Linda Fossom, Ph.D.
CMC Review/OBP Review	David Claffey, Ph.D. Fang Wu, Ph.D. John Duan, Ph.D.
Clinical Pharmacology Review, Genomics Review, and Pharmacometrics	Kofi Kumi, Ph.D. Li Zhang, Ph.D. Kevin Krudys, Ph.D. Hao Zhu, Ph.D.
OPDP	Susannah O'Donnell, MPH, RAC
OSI/DSI	Jen Sellers, MD

OND=Office of New Drugs
OSI=Office of Scientific Investigation
OPDP=Office of Prescription Drug Promotion
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
CMC=Chemistry, Manufacturing, and Controls

Background and Summary

With this application, the applicant is seeking approval to market Amphetamine ER oral suspension (TRI102) for the treatment of attention deficit hyperactivity disorder (ADHD) in patients ages six to

twelve years old. The applicant submitted a phase 3 dose-optimized, randomized, double-blind, placebo-controlled study in the laboratory classroom setting. This study was conducted in five US sites. This 505(b)(2) application references Adderall immediate release as the reference listed drug (RLD). This was a positive study and no safety issues identified for this formulation that were different from the RLD.

This product is an ion-exchange resin (polystyrene sulfonate) complexed with amphetamine to provide an extended-release profile for once daily treatment of symptoms of ADHD. This product was formulated for patients who have difficulty swallowing pills or capsules.

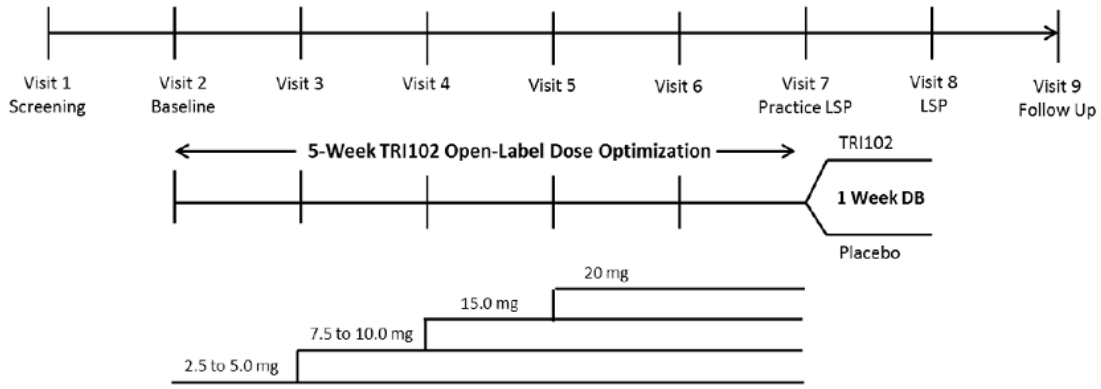
Clinical Summary and Statistics

Efficacy

Drs. Farchione and Ogbagaber and Eiji Ishida reviewed the clinical and statistical data to support this application. The single efficacy study, TRI102 used the SKAMP Combined Score to evaluate efficacy. The pre-specified efficacy endpoints were based on change from pre-dose baseline SKAMP score to evaluation time (four hours after dose was primary) and multiple evaluation times were tested (1, 2, 4, 6, 8, 10, 12, and 13 hours after dose). Two secondary endpoints of interest were measured: time of onset of clinical effect and duration of clinical effect. Using a pre-specified multiple testing procedure that controlled study-wise Type I error, the statistical team concluded that the study met its primary and secondary objectives. Dr. Farchione reviewed the data and agreed with the statistical reviewers, and I agree that the study is well-designed and a positive study.

Study Design

TRI102-ADD-001 was a dose-optimized, randomized, double-blind, placebo-controlled study in pediatric patients with ADHD. The schematic of the study is below.



DB = double-blind; LSP = laboratory school protocol study day
The dosing paradigm is presented as maximum daily dose within the given weekly intervals; not all subjects needed to be titrated to the highest dose of 20 mg/day.
Visit 7 (LSP 1) was an abbreviated practice laboratory school day with a shorter duration than the laboratory school day on Visit 8 (LSP 2).

Source: Dr. Farchione's Review

Results

The primary efficacy endpoint was change from Time 0 in model-adjusted SKAMP Combined scores at four hours post-dose measured during the laboratory school day (Visit 8). Onset of clinical effect and duration of clinical effect were secondary measures determined by change from time 0 in SKAMP Combined scores at 1, 2, 6, 8, 10, 12, and 13 hours post-dose during Visit 8. A total of 108 patients enrolled, 100 were randomized

and 99 patients completed the study. The primary efficacy analysis at 4 hours was clearly positive (p less than 0.0001); secondary endpoints were similarly positive (see the clinical and statistical reviews for details).

Safety was evaluated in the usual fashion and no new meaningful safety signals were identified for this formulation of this well-known active drug.

Office of Clinical Pharmacology (OCP)
Dr. Kumi was the primary reviewer for this application. His findings are summarized below.

- An adequate link has been established between the amphetamine ER oral suspension and amphetamine IR tablet.
- The similarity of PK profiles in adults, adolescents, and children in combination with what is known about the PK of amphetamine IR tablet and common clinical practice support the approval and dosing recommendations made in labeling.
- The pharmacokinetic profiles of amphetamine ER oral suspension in patients of different age ranges are sufficient to support once daily dosing.
- Food does not affect exposure.

OCP has recommended approval.

Chemistry Manufacturing and Controls (CMC)
The CMC team recommended approval from a product quality perspective and recommended a post-marketing commitment to develop more discriminatory single-medium dissolution methods for both the drug product and for the extended-release (b) (4). They confirmed that once-daily dosing was supported by data from the RLD. Dose-dumping was identified at 40 percent alcohol and the labeling reflects this fact.

Office of Scientific Investigation—Facilities Inspections
OSI inspected two sites and no significant regulatory violations were noted and the data were judged to be acceptable and the study was found to have been conducted adequately.

Office of Prescription Drug Promotion (OPDP)
OPDP reviewed the medication guide, the prescribing information, and the carton/container labeling and had several recommendations which were included in the final negotiated labels/container labeling.

Nonclinical Pharmacology/Toxicology
Drs. Elayan and Fossom conducted the nonclinical review. No new non-clinical data submitted with the application and no outstanding chemistry issues regarding impurities or new excipients were identified. The inactive polystyrene sulfonate is present in the formulation at (b) (4) which is considered safe. They concluded that the application was approvable.

Labeling
The team constructed labeling based upon the data from this application using other drugs in the class as models. Comments/suggestions/edits from the team were considered and sent to the applicant multiple times for concurrence. The Office of Prescription Drug Promotion also reviewed the label and the changes that they suggested were incorporated. The applicant has accepted the labeling changes and a final version will be attached to the letter.

Advisory Committee
Not applicable.

Postmarketing Requirements/Commitments
In addition to the post-marketing commitment recommended by the Quality team, there will be post-marketing requirements to conduct PK and efficacy and safety studies in pediatric patients ages 4 to 5 years old.

Conclusions
Sufficient information has been submitted to conclude that amphetamine ER suspension is safe and effective for the treatment of pediatric patients with ADHD. I recommend that this application be approved.

The labeling has been negotiated to current Division standards.

Post-marketing requirements and commitments have been identified and agreed upon.

The applicant has agreed to the negotiated label.

This application will be approved by the PDUFA date.

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