CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204326Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	*{See Appended Electronic Signature Page}*
From	Tiffany R Farchione, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 204,326
Applicant	Neos Therapeutics, Inc.
Date of Submission	7/27/15
PDUFA Goal Date	1/27/16
Proprietary Name / Non-Proprietary Name	Adzenys XR-ODT/Amphetamine
Dosage form(s) / Strength(s)	Extended-release orally disintegrating tablets/3.1, 6.3, 9.4, 12.5, 15.7, and 18.8 mg
Applicant Proposed Indication(s)/Population(s)	Attention Deficit Hyperactivity Disorder Children and adults
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older

1. Background

Under this 505(b)(2) application, NDA 204,326, Neos Therapeutics, Inc. (hereafter, "the applicant") is seeking approval for an extended-release orally disintegrating tablet formulation of amphetamine (trade name Adzenys XR-ODT) for the treatment of attention deficit hyperactivity disorder (ADHD) in children and adults ages 6 years and older. Although a number of amphetamine formulations are available and marketed for the treatment of ADHD, this will be the first orally disintegrating extended-release tablet. An orally disintegrating tablet may be useful for patients who are unable to swallow pills.

This NDA was originally submitted on December 28, 2012; at the conclusion of that review cycle, the Division of Psychiatry Products (DPP, or the Division) issued a Complete Response (CR). The CR letter listed product quality, facility inspections, biopharmaceutics, and clinical pharmacology deficiencies. Key among these deficiencies were problems with tablet hardness, (b) (4) and disintegration failures (b) (4). The current submission is based on data using a reformulated drug product; therefore, it contains an entirely revised CMC section and data from a new single-dose bioequivalence (BE)/food effect study (NT0202.1005) comparing Adzenys XR-ODT to Adderall XR and assessing the effect of food on the pharmacokinetics (PK) of Adzenys XR-ODT. The applicant did not conduct a clinical efficacy study; this application relies on the findings of efficacy and safety from Adderall XR (NDA 21303, the listed drug) and the aforementioned BE/food effect study.

This product is formulated as an orally disintegrating tablet with the highest strength containing 18.8 mg of amphetamine base; this is equivalent to the amount of amphetamine base in the 30 mg dosage strength of the listed drug which contains mixed amphetamine salts. The strengths, isomer mixture, and release profile are designed to be equivalent to the listed drug.

2. Product Quality

The Integrated Quality Assessment is dated December 21, 2015. The review team for this application included Drug Substance, Drug Product, Process, Microbiology, Facility, and Biopharmaceutics reviewers, as well as a Project/Business Process Manager and Application Technical Lead. The Quality team recommended approval, noting that the issues that resulted in a CR action in the previous review cycle have been resolved by reformulation of the drug product. The drug product expiry period of 24 months was granted. The team did not recommend any post-marketing studies.

The applicant initially proposed (b) (4) (b) (4) (b) (4) Thus, the OPQ team recommended that the dosage strengths be expressed in terms of amphetamine base (b) (4) (b) (4) According to the OPQ review:

> Both products contain amphetamine in the salt form. The (b) (4) in Adderall XR is a mixture of salts (b) (4) (polystyrene sulfonate) is the (b) (4)

(b) (4) in the proposed product. The proposed drug product contains a 3:1 mixture of d- and l- amphetamine in six dosage strengths: 3.1, 6.3, 9.4, 12.5, 15.7, and 18.8 mg of amphetamine base equivalent which contains the same amount of amphetamine (b) (4) base equivalent as Adderall XR - 5, 10, 15, 20, 25, and 30 mg, respectively.

During labeling negotiations, the team recommended that the tablet embossing be revised. The applicant proposed embossing on each tablet (b) (4) (b) (4) (b) (4) The applicant proposed an alternative whereby the notation on the tablet (b) (4) (e.g., 3.1 mg tablet embossed with "A1," 6.3 mg with "A2," etc.); this plan was deemed acceptable and the change will be reflected on both the tablets and in Section 3 of the full prescribing information.

All facilities inspections have been completed and the detailed reviews are included in the Integrated Quality Assessment. In his review, Donald C. Obenhuber, Ph.D., concluded that there are no significant outstanding manufacturing risks that prevent approval of this application.

3. Nonclinical Pharmacology/Toxicology

No pharmacology/toxicology review was conducted during this review cycle. No new non-clinical information was submitted with this application. Shiny Mathew, Ph.D., completed a review during the first review cycle (dated 8/22/13). At that time, she concluded that the Agency's previous findings of safety and efficacy for Adderall XR are considered adequate to support the clinical doses of amphetamine in this product. No impurities, degradants, or novel excipients in amphetamine extended release tablets that would require additional toxicological characterization were identified.

4. Clinical Pharmacology

The current application is based on Study NT0202.1005, a single-dose BE/food effect study comparing Adzenys XR-ODT to Adderall XR. This was a single-dose, open-label, randomized, three-period, three-treatment, crossover study with a 7-day washout period between each treatment period. Forty-two healthy adult subjects aged 18 to 72 years old received single doses of Adzenys XR-ODT 18.8 mg under fasted conditions, Adzenys XR-ODT 18.8 mg under fed conditions, and Adderall XR 30 mg under fasted conditions. Each treatment was administered in only one treatment period such that each subject received all treatments over the course of three treatment periods.

In his review dated December 29, 2015, Praveen V. Balimane, Ph.D., noted that the 90% confidence intervals for the log-transformed exposure parameters C_{max}, AUC_{last}, AUC_{inf}, and $AUC_{5\text{-}last}$ were within the 80% to 125% range for both *d*- and *l*-amphetamine. He concluded that Adzenys XR-ODT demonstrated a similar pharmacokinetic profile and exposure compared to Adderall XR and that it is anticipated to have similar efficacy and safety profiles to Adderall XR.

He further concluded that Adzenys XR-ODT has no clinically meaningful food effect and thus can be administered with or without food. Although the presence of food decreased the rate of absorption of Adzenys XR-ODT (decrease in C_{max} of *d*- and *l*-amphetamine by approximately 18% and delay in median T_{max} of approximately 2 hours [*d*-amphetamine] to 2.25 hours [*l*-amphetamine]), this effect of food on PK is very similar to the food effect observed for Adderall XR.

Himanshu Gupta, Ph.D., and Sam H. Haidar, R.Ph., Ph.D., from the Division of Generic Drug Bioequivalence Evaluation (DGDBE) in the Office of Study Integrity and Surveillance (OSIS) conducted the inspection at (b) (4) (b) (4). In their review dated (b) (4), they note that no deficiencies were observed and no Form FDA-483 was issued.

5. Clinical Microbiology

Not applicable.

6. Clinical/Statistical-Efficacy

The applicant did not conduct a clinical efficacy study; this application relies on the findings of efficacy and safety from Adderall XR (NDA 21303, the listed drug) and the BE/food effect study described above.

The Division of New Drug Bioequivalence Evaluation (DNDBE) in OSIS declined to inspect the clinical site at WCTDDS, Clinical Research Services in San Antonio, TX. In her review dated January 25, 2016, Shila Nkah, Consumer Safety Officer, noted that this facility was recently inspected and that inspection outcome at that time was classified as No Action Indicated (NAI).

7. Safety

Given the extensive safety experience to date with amphetamine, the relatively brief duration of the bioequivalence study, and the subject population (healthy adult volunteers), the conducted study is not capable of producing meaningful new safety data that could be extrapolated to the clinical use of Adzenys. There were no deaths, non-fatal serious adverse events, and no adverse events that led to premature discontinuation from the study in any of the studies submitted to support either the original application or this resubmission with the reformulated product. No new, unlabeled safety signals were identified. The most commonly reported AEs in Study NT0202.1005 were nausea (n=3 following Adzenys XR-ODT; n=2 following Adderall XR) and dry mouth (n=2 following Adzenys XR-ODT; n=3 following Adderall XR).

8. Advisory Committee Meeting

This is a 505(b)(2) application. It relies on the findings of safety and efficacy of Adderall XR and there were no questions for an Advisory Committee.

9. Pediatrics

This application relies on the findings of safety and efficacy of Adderall XR, a product approved for the treatment of ADHD in patients ages 6 years and older; the applicant is seeking the same indication and age range for Adzenys XR-ODT. The applicant requested a waiver for studies in patients younger than (b) (4) years; however, because the Division has begun requiring studies in children ages 4 to < 6 years old for all newly approved products indicated for the treatment of ADHD, a waiver for studies in children ages 0 to < 4 years old and a deferral for studies in children ages 4 to < 6 years old were granted.

10. Other Relevant Regulatory Issues

Shire and Neos have entered into a licensing agreement that will allow Neos to market this product immediately on approval even though Shire holds patents for Adderall XR that expire as late as April 21, 2019.

The Center for Drug Evaluation and Research (CDER) Exclusivity Board reviewed this application to determine whether the 3-Year exclusivity for Dyanavel XR (amphetamine extended-release oral suspension, NDA 208,147) blocks the approval of Adzenys XR-ODT. Noting that FDA interprets the scope of exclusivity to be related to the scope of the underlying new clinical investigations that were essential to the approval, the Board concluded that Dyanavel XR's exclusivity should not block approval of Adzenys XR-ODT.

11. Labeling

The applicant references the approved labeling for Adderall XR capsules, using other recently approved amphetamine products as references for format only. A detailed review of our labeling recommendations is presented in Kavneet Kohli-Chhabra, M.D.'s clinical review. Overarching issues that affect multiple sections of the label are described below.

- (b) (4) The applicant initially proposed labeling listing (b) (4) (b) (4) (b) (4) Dosage strengths for amphetamine XR-ODT will be expressed in terms of amphetamine base throughout the label.

- (b) (4) (b) (4) The final negotiated label contains a reference to Adderall XR in section 2.5 Switching from Other Amphetamine Products. The section includes a table describing how to switch directly from Adderall XR to this product. It then lists both the non-proprietary name and the commonly used name, after which the abbreviation "MAS ER" is introduced. Thereafter,

in any section where it is necessary to refer to Adderall XR, the phrase “mixed salts of a single-entity amphetamine product extended-release capsules” will be used for the first reference, then “MAS ER” will be used for any additional references in the section.

12. Postmarketing Requirements

The following post-marketing studies in pediatric patients ages 4 to < 6 years of age will be required under the Pediatric Research Equity Act (PREA):

- A pharmacokinetic study of amphetamine XR-ODT
- A randomized, double-blind, placebo-controlled efficacy and safety study
- A one year open-label safety study

13. Recommendation/Benefit-Risk Assessment

In Study NT0202.1005, bioequivalence was demonstrated between Adzenys XR-ODT and the listed drug, Adderall XR. No new safety signals were identified in the development program that would alter the overall benefit-risk assessment for Adzenys XR-ODT as compared to the approved product. This application is approvable and should be approved by the PDUFA date.

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/s/

TIFFANY R FARCHIONE
01/27/2016

MITCHELL V Mathis
01/27/2016
Application approvable.

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/s/

MITCHELL V Mathis
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