CLINICAL REVIEW

Application Type	NDA 505(b)2
Application Number	204326
Priority or Standard	Standard
Original Submission Date	12/28/2012
Complete Response Sent Date	09/24/2013
Complete Response Received Date	07/27/2015
PDUFA Goal Date	01/26/2016
Reviewer Name	Kavneet Kohli-Chhabra M.D.
Review Completion Date	January 25, 2015
Division/Office	Division of Psychiatry Product (DPP)
Established Name	Amphetamine extended-release orally disintegrating tablets
Trade Name	Adzenys XR-ODT
Applicant	Neos Therapeutics, Inc.
Formulation	Orally disintegrating tablets
Dosing Strengths	3.1, 6.3 , 9.4, 12.5, 15.7, and 18.8 mg tablets
Proposed Indication	Attention Deficit Hyperactivity Disorder (ADHD)
Intended Populations	Patients 6 years and older
Recommended Regulatory Action	Approval

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1 Introduction and Regulatory Background

Neos Therapeutics, Inc. (the applicant) submitted a 505(b)(2) application for amphetamine extended release orally disintegrating tablets (amphetamine XR-ODT) referencing the listed drug (LD) Adderall XR (mixed salt of a single-entity amphetamine product extended release capsule, Shire Laboratories, Inc., NDA 21303). Adderall XR was initially approved on October 11, 2001, for children ages 6 to 12 years. The indicated population was expanded to adults on August 11, 2004, and adolescents on July 21, 2005. Thus, the reference product label includes safety and efficacy information for patients ages 6 years and older. 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 reference product is a salt; the product under review is not. Table 1 lists the proposed tablet strengths of amphetamine XR-ODT along with the dose strengths of the reference product which contain equivalent amounts of amphetamine base. The development program of amphetamine XR-ODT was initiated under IND 112,991 in September, 2011. The applicant is seeking an indication for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older. Amphetamine is classified as a Schedule II drug under the Controlled Substance Act.

Table 1: Equivalent Doses of Mixed Salts of a Single-Entity Amphetamine Product Extended-Release Capsules and Amphetamine Extended Release Orally Disintegrating Tablets (Adzenys XR-ODT)

Product	**Dose Strengths**					
Amphetamine extended-release orally disintegrating tablets (Adzenys XR-ODT)	3.1 mg	6.3 mg	9.4 mg	12.5 mg	15.7 mg	18.8 mg
Mixed salts of a single-entity amphetamine product extended-release capsules	5 mg	10 mg	15 mg	20 mg	25 mg	30 mg

This NDA application was initially submitted on December 28, 2012. The Agency issued a Complete Response (CR) action on September 24, 2013, primarily due to Chemistry Manufacturing and Controls (CMC) deficiencies. Numerous deficiencies were cited in the CR letter including problems with tablet hardness, friability 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 clinical study (NT0202.1005) comparing amphetamine XR-ODT to Adderall XR and assessing the effect of food on the pharmacokinetics (PK) of the amphetamine XR-ODT product.

The first cycle clinical review (dated 08/19/2013) was completed by Cara Alfaro, Pharm.D.. In her review, she noted that, among the 112 subjects who participated in a total of four bioequivalence (BE)/PK studies, there were no deaths or serious adverse events (SAEs), and no subjects who discontinued secondary to adverse events (AEs). She concluded that, although there were some AEs in these trials that were not listed in the reference label (e.g., AST increase from 24 to 74 after a single dose of amphetamine XR-ODT in a 22 year-old, resolved), the lack of a placebo group in any of these studies made it difficult to interpret these events. She did not conduct a labeling review due to the planned CR action.

2 Materials Reviewed

Table 2: List of Material Reviewed

Submission Date	Materials
12/28/2012	Data Listings and Clinical Study Reports: Study NT0202.1001 "A single-dose, three-period, three-treatment, three way crossover bioequivalence study of two controlled release tablet formulations of mixed amphetamine polistirex equivalent to 30 mg mixed amphetamine salts and ADDERALL XR 30 mg (mixed amphetamine salts) under fasted conditions" Study NT0202.1002 "The effect of food on the pharmacokinetics of a controlled release oral disintegrating tablet formulation of amphetamine polistirex (equivalent to 30 mg mixed amphetamine salts) in healthy subjects" Study NT0202.1003 "A two-cohort, single-dose, four-period, four-treatment, four-way crossover study of the effect of alcohol on the pharmacokinetics of NT0202, a controlled release orally disintegrating tablet formulation of amphetamine polistirex (equivalent to 30 mg mixed amphetamine salts), in healthy subjects" Study NT0202.1004 "A single-dose, single-period, one-treatment, pharmacokinetic study of a controlled release formulation of mixed amphetamine resins oral disintegrating tablets (equivalent to 30 mg mixed amphetamine salts) under fasted conditions to children (ages 6-12) with attention-deficit hyperactivity disorder" Past clinical review by Cara Alfaro, Pharm.D., and other discipline reviews.

Submitted on and after 07/27/2015	Data Listings and Clinical Study Report: Study NT0202.1005 "A Single-Dose, Three-Period, Three-Treatment, Three-Way Crossover Bioavailability Study of an Investigational Formulation of NT0202 Amphetamine Extended-Release Orally Disintegrating Tablets (XRODT) 30 mg under Fed and Fasted Conditions and Adderall XR Capsule 30 mg under Fasted Conditions." Debarment Certification Financial Disclosure Certification Patent Certification Request for Waiver of Pediatric Studies Draft Labeling (PLR) and Draft carton labelling Proprietary Name Request for Review

3 Other Discipline Reviews

3.1. Product Quality

The 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 recommends 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 team did not recommend any post-marketing studies.

3.2. 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.

3.3. Clinical Pharmacology

The PK studies were reviewed by Praveen V. Balimane, Ph.D., in his review dated December 29, 2015. He concluded that the amphetamine XR-ODT product demonstrated similar pharmacokinetic profile and exposure as compared to Adderall XR and is anticipated to have similar efficacy and safety profiles to Adderall XR, and that the

amphetamine XR-ODT product has no clinically meaningful food effect and thus can be administered with or without food.

3.4. Controlled Substances Staff

In his review dated January 14, 2015, Edward Hawkins, Ph.D., provided labeling recommendations. He also noted that, despite a dissolution study and swine study demonstrating that ethanol increased dissolution of the API at 40% or 20% ethanol, respectively, a clinical study in humans (NT0202.1003) determined that ethanol did not lead to dose dumping.

3.5. Pediatric and Maternal Health

Donna Snyder, M.D., completed the DPMH review on December 9, 2015. She recommended changes to the applicant's proposed labeling in Highlights, Section 5.2, and Section 8.4.

4 Financial Disclosures

On July 27, 2015, Dorothy J. Engelking, Vice President of Regulatory Affairs for the applicant, certified that Neos had not entered into any financial arrangement with the principal or sub-investigators whereby the value of the compensation could have been affected by the outcome of the study. Also, she certified that each investigator required to disclose a proprietary interest in the product or significant equity interest in the applicant did not disclose any such interests. She further certified that none of these investigators was the recipient of significant payments of other sorts.

5 Review of Clinical Studies

Four Phase 1 BE/PK trials were conducted in support of the initial NDA submission:

NT0202.1001 "A single-dose, three-period, three-treatment, three-way crossover bioequivalence study of two controlled release tablet formulations of mixed amphetamine polistirex equivalent to 30 mg mixed amphetamine salts and ADDERALL XR 30 mg (mixed amphetamine salts) under fasted conditions"

NT0202.1002 "The effect of food on the pharmacokinetics of a controlled release oral disintegrating tablet formulation of amphetamine polistirex (equivalent to 30 mg mixed amphetamine salts) in healthy subjects"

NT0202.1003 "A two-cohort, single-dose, four-period, four-treatment, four-way crossover study of the effect of alcohol on the pharmacokinetics of NT0202, a controlled release orally disintegrating tablet formulation of amphetamine polistirex (equivalent to 30 mg mixed amphetamine salts), in healthy subjects"

NT0202.1004 "A single-dose, single-period, one-treatment, pharmacokinetic study of a controlled release formulation of mixed amphetamine resins oral disintegrating tablets (equivalent to 30 mg mixed amphetamine salts) under fasted conditions to children (ages 6-12) with attention-deficit hyperactivity disorder"

Study reports and data sets for the above trials were reviewed by Cara Alfaro, Pharm.D., in the initial review cycle. The applicant has since reformulated this product and submitted additional data from that trial in support of the current application; this review will focus on the new BE/food effect study, NT0202.1005.

Study NT0202.1005

Study Objectives:

1. To compare the rate of absorption and oral bioavailability of amphetamine XR-ODT 18.8 mg and oral Adderall XR 30 mg following an overnight fast of at least 10 hours.

2. To assess the effect of food on the rate of absorption and oral bioavailability of amphetamine XR-ODT 18.8 mg.

Study Design:

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 a single doses of amphetamine XR-ODT 18.8 mg under fasted conditions, amphetamine XR-ODT 18.8 mg under fed conditions, and Adderall XR 30 mg under fasted conditions.

Subjects remained inpatient for 36 hours after study drug administration and returned for outpatient visits at approximately 48 and 60 hours post-dose in each study period. A detailed listing of study assessments can be found in Table 3.

When subjects received amphetamine XR-ODT, they were instructed to place the tablet in their mouths and allow it to disintegrate without chewing or crushing. Adderall XR 30 mg was administered with 4 oz. water to swallow the capsule. All subjects fasted for 4 hours after dose administration.

Healthy male and non-pregnant, non-breastfeeding female subjects ages 18 and were eligible for inclusion in this study. Female subjects were required to either be postmenopausal (at least 2 years prior to dosing) or to agree to use an acceptable form of birth control from screening until 14 days after completion of the study. A Body mass index (BMI) between 18 and 32 kg/m2 (inclusive), weight $\geq$ 50 kg (110 lbs), and heart rate (40-100 bpm) and blood pressure (90-145/50-95 mmHg) within specified parameters were also required for inclusion.

Subjects were excluded if they had any current or past cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, oncologic, or psychiatric disease; suicidal ideation or behavior as assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS, Baseline version); positive urine drug screen or history of substance abuse; or any other condition that, in the opinion of the Investigator, may have jeopardized the safety of the subject or the validity of the study results. Additional exclusion criteria relate to health status, laboratory assessments, and concomitant medications.

Table 3: Schedule of Assessments

PROCEDURE	Screening	Periods 1 through 3			End-of-Study/ Early Termination
		Check-in	Day 1	Day 2	
Informed consent	X				
Medical and medication history	X	X			
ECG	X				X
Vital signs[1]	X		X	X	X
Physical examination	X				X
Biochemistry, hematology, urinalysis	X				X
Serology	X				
FSH test (postmenopausal female subjects)	X				
Pregnancy test (all female subjects)[2]	X	X			
C-SSRS (Baseline version)	X				
Urine cotinine screen	X	X			
Urine drug screen	X	X			
Urine alcohol screen		X			
Drug administration			X		
Blood sample collection for pharmacokinetic analysis[3]			X	X	
Outpatient visit[4]				X	X
AEs		X	X	X	X

1. Blood pressure, pulse rate, respiration rate, and temperature were measured at screening, prior to each administration of NT0202 Amphetamine XR-ODT, and at the end-of-study visit (prior to last pharmacokinetic blood collection, when possible). Blood pressure and pulse rate were measured at approximately 2, 4, 6, 8, 12, 24, 36, and 48 hours after each dose of study drug.
2. All female subjects underwent a serum pregnancy test at screening and a urine pregnancy test at each check-in.
3. Blood samples (1 x 4 mL) were collected at 0 hours (predose) and at 1.0, 2.0, 3.0, 4.0, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 9.0, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0, and 60.0 hours after dosing.
4. Subjects were to remain in the research center until completion of the 36-hour procedures and were to return for outpatient visits at approximately 48 and 60 hours postdose in each study period.

(Source: NT0202.1005 Appendix 16.1.1 Protocol, Table 12.1, page 30)

A total of 42 subjects participated in the study, and 39 subjects completed all three study periods. Among the subjects who did not complete the study, two withdrew consent and one had a positive urine drug screen. There were no significant protocol deviations during the conduct of the study.

The bioequivalence data was reviewed in detail by Praveen Balimane, Ph.D., in his review dated December 29, 2015. He determined that the PK profile and exposures for amphetamine XR-ODT

and Adderall XR were similar and that the amphetamine XR-ODT product has no clinically meaningful food effect.

6 Review of 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. There were no new, unlabeled safety signals identified in the AE reports, physical exam, vital signs, ECGs, or other safety measures. During both the open-label and double-blind Treatment Periods, no subjects reported any occurrences or types of suicidal ideations or behaviors on the C-SSRS.

There were 46 AEs reported by 17 subjects; 16 following amphetamine XR-ODT treatment group under fasted state, 9 following amphetamine XR-ODT treatment under fed state, and 21 following Adderall XR treatment. The most commonly reported AEs following treatment with amphetamine XR-ODT were nausea (n=3; n=2 following Adderall XR) and dry mouth (n=2; n=3 following Adderall XR).

7 Pediatric Plan

The applicant (b) (4) with the original NDA submission; however, because a CR action was taken at the end of the first review cycle, no agreement was reached.

Since that time, 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. As such, we intend to require three studies in children ages 4 to ≤ 6 years of age with ADHD as Post Marketing Requirements:

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

8 Inspections

The Division of Generic Drug Bioequivalence Evaluation (DGDBE) in the Office of Study Integrity and Surveillance (OSIS) was consulted to inspect the analytical site. Himanshu Gupta, Ph.D., and Sam H. Haidar, R.Ph., Ph.D. conducted the inspection at (b) (4) The lead investigator identified at that analytical site is (b) (4). In their review dated December 14, 2015, they note that no deficiencies were observed and no Form FDA-483 was issued.

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. The lead investigator identified for the clinical trial was Cynthia A. Zamora, M.D. 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).

9 Labeling Review

The applicant references the currently approved labeling language from Adderall XR capsules, using other recently approved amphetamine products as references for format only. The Division provided a number of minor editorial comments; more substantive changes are summarized below.

Overarching Issues

The applicant's initial proposed labeling (b) (4) the relevant issues are discussed in detail in the OPQ Integrated Quality Assessment dated December 21, 2015. Dosage strengths for amphetamine XR-ODT will be expressed in terms of amphetamine base throughout the label.

The proposed label included specific references Adderall XR using the proprietary name. The non-proprietary name for Adderall XR is dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate, and amphetamine sulfate extended-release capsules; however, it is commonly referred to as "mixed salts of a single-entity amphetamine product extended-release capsules." 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.

Specific Sections

1 INDICATIONS AND USAGE

- Simplified of the I&U statement. (b) (4), the indication statement will refer to patients 6 years and older.

2 DOSAGE AND ADMINISTRATION

- Eliminated (b) (4) for dosing instructions under section 2.2.
- Added advice for switching from other amphetamine products, specifically stating that this product should not be substituted for other amphetamine products on a milligram-per-milligram basis due to the differences in amphetamine base composition. A Table for equivalent doses of mixed salts of a single-entity amphetamine product extended release capsules and Adzenys XR-ODT is created.

5 WARNINGS AND PRECAUTIONS

- A new Warning and Precaution is added under section 5.2 Potential Overdose Due to Medication Errors. This was created to avoid substitution errors and overdosage that could be caused by substituting Adzenys with other amphetamine products on a milligram-per-milligram basis. This section refers to section 2.5, where a table lists the correct equivalent doses of mixed salts of a single-entity amphetamine product extended release capsules to Adzenys XR-ODT.
- For section 5.3 Serious Cardiovascular Reactions under Warning and Precautions (b) (4). This information applies to all ages and is part of the class language.
- The warning for (b) (4) listed under section 5.4 under Warning and Precautions is eliminated as it is no longer part of the class language for amphetamine products.

6 ADVERSE REACTIONS

- (b) (4) was eliminated from the pediatric (13-17 years old) and adult population tables listing the adverse reactions observed at incidences of 5% or higher. The incidence rates were the same between drug and placebo.
- (b) (4) sudden death and myocardial infarction (b) (4) under Cardiovascular Adverse Reactions Associated with the Use of Amphetamine.

7 DRUG INTERACTIONS

- Updated to table format.

8 USE IN SPECIFIC POPULATIONS
- Conversion of the Adzenys labeling to the Pregnancy and Lactation Labeling Rule (PLLR) format must occur before June 30, 2019. However, applicant voluntarily proposed labeling under Pregnancy section to be consistent with Dyanavel.
- "Safety and effectiveness have been established in pediatric (b) (4) three adequate and well-controlled clinical trials of up to 4 weeks in duration" statement has been updated under section 8.4 Pediatric Use.

11 DESCRIPTION
- Removed table listing amphetamine base content of this product vs. "Mixed Salts of a Single-Entity Amphetamine Product Extended-Release Capsules". The table is now in section 2.5.

12 CLINICAL PHARMACOLOGY
- The section was modified to include clinical studies results conducted with Adzenys XR-ODT.
- Separated PK information into its own subsection in 12.3.
- Food effect and alcohol effect study results are edited for clarity.

14 CLINICAL STUDIES
- Added descriptions of efficacy endpoint measures.
- Added a table for the primary efficacy result.

16 HOW SUPPLIED/STORAGE AND HANDLING
- The embossing will be changed to reflect the labeled strength.

17 PATIENT COUNSELING AND MEDICATION GUIDE
- Updated to reflect changes in the Full Prescribing Information.

10 Conclusions and Recommendations

From a clinical perspective, I recommend approval of Amphetamine XR-ODT (Adzenys XR-ODT) in patients 6 years and older with ADHD. There will be post-marketing requirements to conduct PK, efficacy, and safety studies in patients ages 4 to 5 years old with ADHD.

[See appended electronic signature]
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cc: NDA #204326
HFD-130 (Div. File)
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01/26/2016

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