CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204326Orig1s000

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY REVIEW/MEMO TO THE FILE

NDA 204326
Submission: SDN 1, serial number 0000, submitted 12/27/12, received on 12/28/12
Drug name: Amphetamine (b) (4) Extended Release orally disintegrating tablet (NT0202)
Sponsor: Neos Therapeutics, Inc.
Indication: Attention Deficit Hyperactivity Disorder (ADHD)
Reviewer: Shiny V. Mathew, Ph.D., Pharmacologist.
HFD-130, Division of Psychiatry Products

Background: The current NDA for Amphetamine (b) (4) Extended Release orally disintegrating tablet is a 505(b)(2) application with ADDERALL XR® (Shire Laboratories, Inc. NDA 21303) as the reference listed drug (RLD). The RLD combines amphetamine salts in an extended release capsule formulation that includes an immediate release component and a delayed component. Similarly, this formulation incorporates a ratio of an immediate release (b) (4) (b) (4) in the same d, l-amphetamine ratio as the RLD, thereby creating an extended release ODT. This product contains a ratio of 3:1 mixture of d- and l- amphetamine in six dosage strengths containing 3.13, 6.27, 9.40, 12.5, 15.7 and 18.8 mg to be equivalent to ADDERALL XR® 5, 10, 15, 20, 25 and 30 mg of mixed amphetamine salts, respectively.

The current submission:
Clinical studies have been submitted to demonstrate bioequivalence to RLD ADDERALL® at 5, 10, 15, 20, 25 and 30 mg.

For nonclinical studies to support the current application, the Sponsor is relying on the Agency's previous findings of safety (and efficacy) for ADDERALL XR®. Additionally, the Sponsor has submitted an *in vivo* pharmacokinetic study in domestic swine to compare the PK of ADDERALL XR®, Mixed Amphetamine Salts Immediate Release (IR), and NT0202 CR ODT when administered as a single oral dose, with and without 20% ethanol. The primary objective of this study was to evaluate the potential for dose-dumping of amphetamine from the ODT formulation in the presence of alcohol compared to ADDERALL XR and mixed amphetamine salts IR. In the presence of 20% ethanol, there was an increase of two-fold in maximum and total D-amphetamine and L-amphetamine exposure.

Summary: Our previous findings of safety (and efficacy) for ADDERALL XR® are considered adequate to support the clinical doses of amphetamine in NT0202, the product currently under review.

No impurities, degradants, or novel excipients in NT0202 (amphetamine extended release tablets) that would require additional toxicological characterization have been identified at this time.

Conclusion: There are no Pharmacology/Toxicology issues that would prevent the approval of this NDA.

Signatures:

Shiny V. Mathew, Ph.D., Pharmacologist *{see appended electronic signature page}*
Linda H. Fossom, Ph.D., Supervisory Pharmacologist *{see appended electronic signature page}*

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/s/

SHINY V MATHEW
08/22/2013

LINDA H FOSSOM
08/22/2013

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 204326 **Applicant: Neos Therapeutics** **Stamp Date: December 28, 2012**

Drug Name: [redacted], Amphetamine [redacted] Extended Release orally disintegrating tablet **NDA/BLA Type: 505(b)(2)**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		This NDA is being submitted as a 505(b)(2) application. The Sponsor is relying on Agency's previous findings of safety and efficacy for the RLD Adderall XR®, an extended release formulation of mixed amphetamine salts from Shire Laboratories (NDA 21-303). Both the RLD and the formulation for this NDA are for oral administration; therefore, no pivotal nonclinical studies have been conducted in support of the submission.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		No non-clinical studies were required or requested under the IND. The only study submitted under the nonclinical section is a (GLP) single-dose oral PK study in swine comparing this drug to Adderall XR (the RLD), with and without 20% ethanol.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			N/A
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?			N/A

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?			N/A
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			N/A
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		This 505(b)(2) application will be relying on content from RLD (Adderall®, Shire Laboratories, Inc.) for the current labeling text.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		There are no currently known issues regarding new excipients, impurities and/or degradants present that may need to be qualified. No filing issues have been identified by the Chemistry reviewer.
11	Has the applicant addressed any abuse potential issues in the submission?			N/A
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ___yes___

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None at this time

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

Shiny Mathew, Ph.D.	{see appended electronic signature page}
Reviewing Pharmacologist	Date
Linda Fossom, Ph.D.	{see appended electronic signature page}
Team Leader/Supervisor	Date

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/s/

SHINY V MATHEW
02/26/2013

LINDA H FOSSOM
02/26/2013