CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204325Orig1s000

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: August 30, 2017

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SUBJECT: Cross Discipline Team Leader Review
Division Director Summary Review

NDA #: 204325

Proprietary/ Established name: Amphetamine (Adzenys ER®)

Dosage forms: Extended Release Oral Suspension

Strength: 1.25 mg/mL

Sponsor: Neos Therapeutics

Indication: Treatment of Attention Deficit Hyperactivity Disorder (ADHD)

Recommendation: Approval

I. Introduction

NDA 204325 is a 505(b)(2) application for amphetamine (AMP) extended release oral suspension (ER-OS) indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in patients 6 years and above. The AMP ER-OS contains both an immediate release (IR) component and an extended release (ER) component. The formulation is similar to Adzenys ® XR-ODT that was developed by the same applicant and approved on January 27, 2016. The applicant demonstrated that AMP ER-OS exhibited similar exposure and pharmacokinetic profile (met bioequivalence criteria) as compared to the listed drug (LD), Adderall XR ®, in a relative bioavailability trial.

The submission includes the following two major clinical trials:

1. Study NT0201.1008: A single-dose, two-period, two-treatment, two-way crossover relative bioavailability study of AMP ER-OS and Adderall ER capsule under fasted conditions
2. Study NT0201.1007: A single-dose, three-period, three-treatment, three-way crossover bioavailability study of a commercial scale formulation of AMP ER-OS under fed and fasted conditions and a clinical trial formulation of AMP ER-OS under fasted conditions

In addition, the applicant submitted the pharmacokinetic findings in pediatric patients 6-12 years of age (Study NT0201.1004).

II. Summary of Conclusions and Recommendations from the Review Team

1. CMC

The CMC review was performed by Drs. Andrei Ponta, Wendy Wilson-Lee, (Drug Master Files / Drug Substance, and Drug Product), Chunseng Cai, Akm Khairuzzaman, (Process), Elizabeth Bearr, Erika Pfeilerr (Microbiology), Ruo (Rose) Xu (Facility), Mei Ou, Ta-Chen Wu (Biopharmaceutics), Grafton Adams (Regulatory Business Process Manager), Jason Rodriguez (Laboratory), and David Claffey (Application Technical Lead).

The findings are summarized below:

- Product Overview: Data found that common oral delivery devices (spoon, cup, and syringe) reliably delivered typical measured dose. The drug product requires shaking (b) (4) before administration. Data support a 30 day in-use period for the drug product after opening the bottle and a 36 month shelf life for the drug product when stored at controlled room temperature. This product should not be diluted or mixed with food or liquids before administration as it may cause dose dumping, (b) (4) In an in vitro alcohol-induced dose dumping study, a substantial increase in AMP release occurred in the presence of 40% alcohol but not with 5%, 10% and 20% alcohol.
- Product Assessment Overview: The product manufacturing process was found adequate. The biopharmaceutics team found the two-stage (pH 1.2 and 6.8) dissolution method acceptable. (b) (4) are used for microbial control. The microbiological reviewer found that the preservative and microbiological testing of the stability batches assures the microbiological quality of the drug product and that data support a 30 day in-use period. The manufacturing sites were found acceptable by OPF on 28 AUG 2017. Drug substance information

was referenced to DMF (b) (4) Both were reviewed in 2015 and found adequate. The claimed categorical exclusion from an EA per 21CFR 25.31 was found acceptable.

Overall, the CMC team recommends an approval action for this NDA submission.

2. Clinical Pharmacology

Dr. Kofi Kumi is the primary clinical pharmacology reviewer. The clinical pharmacology findings are summarized as follows.

- An adequate link has been established between the AMP ER-OS and the listed product, Adderall XR ®, through a relative bioavailability study.
- The exposures and average pharmacokinetic profiles after administration of AMP ER-OS and Adderall XR were similar (met bioequivalence criteria); therefore, the efficacy and safety profiles following the treatment of AMP ER-OS should be similar to those of the approved Adderall XR.
- The general dosing instructions for AMP ER-OS are similar to those for Adderall XR. The pharmacokinetic profile of AMP ER-OS supports a once daily doing. AMP ER-OS can be administered with or without food.
- Increased gastric pH due to concomitant use of a gastric pH modulator (e.g., a H2-blocker or a proton pump inhibitor) may change the exposure and pharmacokinetic profile of AMP. Concomitant use of the AMP ER-OS with a gastric pH modulator is not recommended.

The clinical pharmacology team recommends approval of the AMP ER-OS.

3. Division of New Drug Bioequivalence Evaluation (DNDBE)

Dr. Shila Nkah from the DNDEB recommends accepting the pharmacokinetic data from the relative bioavailability study without an on-site inspection.

4. Clinical

Drs. Bernard Fischer and Tiffany Farchione performed clinical review of the submitted clinical trials. No new safety findings were identified that would indicate a difference in the risk-benefit considerations for AMP ER-OS to treat ADHD. There were no deaths or non-fatal serious adverse events (AEs) in any of the studies submitted to support this application. No new, unlabeled safety signals were identified. The most commonly reported AEs in the studies were nausea, vomiting, and decreased appetite.

The clinical team recommends approval of the AMP ER-OS.

5. Pharmacology / Toxicology

Drs. Deepa Rao and Ikram Elayan reviewed the pharmacology/toxicology information in the submission. Safety information for nonclinical studies is based on findings from published literature, information for Adzenys XR-ODT, and information from the LD. No safety concerns with the active ingredient were identified. There are no new novel excipients. All listed excipients are lower than that used in other FDA-approved products or lower than the maximum potency per unit dose for the same oral route of administration as listed in FDA's IID. It was noted that intestinal necrosis has been reported in published literature with the concomitant use of two excipients, sorbitol and sodium polystyrene sulfonate. This issue has been addressed in the product label.

The proposed label from the applicant was reviewed and modified to include summary statements and nonclinical findings from reproductive and juvenile animal toxicology studies for the active ingredient – amphetamine. The inclusion of this data was based on studies reviewed under Adderall XR (LD), and/or Adzenys XR-ODT (owned by the applicant).

The pharmacology/toxicology team supports approval of the AMP ER-OS.

6. Controlled Substance Staff

Drs. Shalini Bansil, Martin Rusinowitz, and Silvia Calderon evaluated abuse-related data in the NDA submission. They agreed with the applicant's request to maintain AMP ER-OS in Schedule II of the CSA. They also determined that periodic adverse reports (PADERS) are adequate for reviewing and reporting abuse related adverse events. No labeling changes for abuse related information are recommended.

III. Summary of the Labeling Related Reviews

Comments/suggestions/edits from the team were sent to the applicant multiple times for concurrence. Below are the summaries of the labeling related reviews.

1. Division of Pediatrics and Maternal Health (DPMH)

Drs. Jane Liedtka, Miriam Dinatale, and Lynne Yao from DPMH revised the HPI and Sections 8.1, 8.2 and 17 of Adzenys ER (b) (4) labeling for compliance with the Pregnancy and Lactation Labeling Rule (PLLR) format.

Drs. Yeruk Mulugeta, Hari Sachs, and John Alexander participated the labeling meeting and agreed with the revisions on dosage administration and juvenile toxicity class labeling.

2. Division of Medication Error Prevention and Analysis (DMEPA)

Drs. Loretta Holmes and Lolita White assessed the applicant's proposal of using the proprietary name of Adzenys ER ® from a safety and misbranding perspective. They conclude that the proposed name is acceptable.

In addition, they reviewed the container label and prescribing information for areas of vulnerability that may lead to medication errors. They provided several labeling recommendations to address their concerns.

3. Division of Medical Policy Program (DMPP) and Office of Prescription Drug Promotion (OPDP)

Drs. Susan Bedwood, Christine Bradshaw, Barbara Fuller, and Lashawn Griffiths provided a joint review on the applicant's proposed medication guide (MG). They concluded that the MG is acceptable with their recommended changes.

4. Office of Prescription Drug Promotion (OPDP)

Dr. Christine Bradshaw from OPDP reviewed the substantially completed version of the product labeling, carton/container labeling, and medication guide for the AMP ER-OS. She provided the relevant comments.

IV. Recommendations for Postmarketing Studies

The review team recommends that the applicant obtain efficacy and safety information of AMP ER-OS in pediatric patients 4-5 years of age, because the product will likely be used in this patient population. At a meeting on August 9, 2017, PerC indicated that the division cannot require studies in pediatric patients 4-5 years of age under PREA, because there is a marketed AMP ER-OS (Dyanavel XR). It is noted that the applicant has an ongoing pediatric program for patients 4 to 5 years for the approved Amphetamine Orally Disintegrating Tablet (Adzenys XR-ODT) product under NDA 204326. Both Adzenys XR-ODT and Adzenys ER-OS exhibited similar exposure and pharmacokinetic profiles (met bioequivalence criteria) to the same LD, Adderall XR. Therefore, the clinical pharmacology team concluded that the efficacy and safety findings in patients 4-5 years of age from Adzenys XR-ODT can be extended to Adzenys ER (b) (4) without additional studies. If, for any reason, the applicant withdraws the Adzenys XR-ODT from the market prior to completing the clinical program in pediatric patients 4-5 years of age, the applicant should complete the required pediatric trials with the oral suspension.

V. Conclusion and Recommendation

Recommended Regulatory Action: Approval

Risk Benefit Assessment: The benefits continue to outweigh the risks for this new formulation of AMP.

Recommendation for Postmarketing Risk Evaluation and Management Strategies: Routine risk minimization (i.e., FDA-approved product label) and routine pharmacovigilance will

be adequate to manage the risk-benefit profile of the AMP ER-OS.

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/s/

HAO ZHU
08/30/2017

MITCHELL V Mathis
09/13/2017