# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 208510Orig1s000

# CROSS DISCIPLINE TEAM LEADER 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:** January 9, 2017

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**SUBJECT:** Cross Discipline Team Leader Review

**NDA #**: 208510

**Proprietary/ Established name:** Lisdexamphetamine Dimesylate (Vyvanse ®)

**Dosage forms:** Immediate Release Chewable Tablet

**Strength:** 10, 20, 30, 40, 50, and 60 mg

**Sponsor:** Shire

**Indication:** Treatment of Attention Deficit Hyperactivity Disorder (ADHD) and Moderate to Severe Binge Eating Disorder (BED)

**Recommendation:** Approval

## I. Introduction

In this 505 b (1) submission, the applicant is seeking approval to market lisdexamphetamine chewable tablet for the treatment of ADHD in patients 6 years and above, and moderate to severe BED in adults. The chewable tablet was developed to provide an alternative option for patients who have difficulty swallowing a capsule, or who have difficulty opening a capsule. The applicant references its own marketed product, lisdexamphetamine capsule (Vyvanse ® capsule), as the listed product, and intends to demonstrate that the chewable tablet is bioequivalent to the capsule.

The submission includes the following studies:

- Study SHP489-126: A phase I, crossover study to assess relative bioavailability between the lisdexamphetamine chewable tablet and the capsule (listed drug) under fasting condition.
- Study SHP489-127: A phase I, crossover study to assess food effect of the lisdexamphetamine chewable tablet.
- Study SPD489-125: A pilot pharmacokinetic study to evaluate prototype formulations.

In the review cycle, the team has discussed the following issues.

The program contains no information regarding alternative ways of administration besides chewing. Based on the feature of the product, the team concludes that all statements regarding administration instructions in the prescribing information and medication guide should indicate that the drug product **must be** chewed prior to swallowing.

It is noted that the strengths developed for the chewable tablet do not exactly match the available strengths for the listed drug, Vyvanse ® capsule. The capsule has an additional strength of 70 mg to match the maximum dose of 70 mg. There is a concern that the lack of 70 mg strength of the chewable tablet may require a combination of lower strengths of the chewable tablets to reach the maximum dose of 70 mg in patients. Therefore, there is a risk of both under dosing and overdosing as patients may mix up tablets when combing. However, the team recognizes that the agency does not have a basis to compel the applicant to develop and commercialize a 70 mg strength chewable tablet. In addition, it is unclear at the current stage if the potential safety risk rises to a level sufficient to enable the agency with further action.

## II. Summary of Conclusions and Recommendations from Review Team

### 1. CMC

The CMC review was performed by Drs. Mariappan Chelliah (Drug Substance and Drug Product), Arwa ElHagrasy (Process and Microbiology), Zhong Li (Facility), Gerlie Gieser (Biopharmaceutics), Grafton Adams (Regulatory Business and Process Manager), Wendy Wilson-Lee (Application Technical Lead), and Mariappan Chelliah (Environmental Analysis). The findings are summarized below:

- Drug Substance: The applicant has cross-referenced NDA 021977 (lisdexamfetamine dimesylate Capsules) for all the drug substance related CMC information. This CMC review relies on the adequacy of the CMC information that was reviewed under NDA 021977.
- Drug Product: The chewable tablets possess the necessary attributes to ensure that the product meets the quality target product profile of being easy to chew, palatable, and appropriately sized while exhibiting fast disintegration. Based on the tablet diameters and the lack of reports of adverse events related to choking and obstruction

in clinical studies, the proposed tablet sizes and shapes are considered to be low risk with respect to patient safety. All the dose strengths of the chewable tablets have unique size, shape, and debossing, which assures the visual differentiation among different dose strengths of the tablets. The proposed specification for the drug product is adequate to ensure that the critical quality attributes of a chewable tablet formulation are well controlled. The available stability data supports the proposed shelf life of 24 months when the tablets are stored at 20-25°C (68-77°F); excursion permitted to 15-30°C (59-86°F).

- Biopharmaceutics: The applicant's biowaiver request for the 5 lower strengths (i.e., 10, 20, 30, 40, and 50 mg) is granted based on the proportional similarity and comparable *in vitro* dissolution profiles of these lower strengths to the bio-strength (60 mg). The proposed commercial manufacturing process is adequately bridged to the process that was used to manufacture the clinical and registration batches. The applicant's proposal to use disintegration (in lieu of dissolution) for routine QC testing of the product is acceptable. The dissolution method approved for Vyvanse capsule, with a light modification, is acceptable to support biowaiver requests and post-approval CMC changes of the chewable tablet.
- Process: The manufacturing process for the product is acceptable. The applicant has provided adequate in-process controls for consistent batch to batch product quality.
- Facilities: The manufacturing facilities are found acceptable.

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

**2. Clinical Pharmacology**

Dr. Huixia Zhang is the primary clinical pharmacology reviewer. The clinical pharmacology findings are summarized as follows.

- An adequate link has been established between the chewable tablet and the listed product, Vyvanse ® capsule through a relative bioavailability study.
- The average exposure of the pharmacologically inactive prodrug, lisdexamfetamine (LDX), was not considered similar (i.e., slightly beyond the bioequivalence limits) between the chewable tablet and the listed product. However, the average exposure of the active moiety, d-amphetamine (d-AMP), has been demonstrated to be similar (within bioequivalence limits for Cmax and AUC). In addition, the mean pharmacokinetic profiles of d-AMP between the two products are almost superimposable. Hence, the efficacy and safety profiles of the chewable tablet in general population are expected to be similar to those for the listed product.
- Based on the low variability of d-AMP while switching between the listed product and the chewable tablet, no large difference in clinical response is expected when patients switch between the two products at the same dose.
- The chewable tablet can be administered without regard to food.

The clinical pharmacology team recommends approval of the chewable tablet.

**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. John Umhau and Javier Muniz performed clinical review of the submitted relative bioavailability study (Study SHP489-126) and food effect study (Study SHP489-127). The chewable tablet was found to be generally well tolerated. There were no new safety findings for this chewable tablet. There were no death, no serious or severe treatment-emergent adverse events (TEAEs), and no discontinuations due to TEAEs from the two studies. In general, the safety profiles of the chewable tablet were shown to be consistent with the labeled safety information of the listed product.

The clinical team recommends approval of the chewable tablet.

## III. Labeling

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

**1. Division of Medication Error Prevention and Analysis (DMEPA)**

Drs. Loretta Holmes and Lolita White assessed the applicant's proposal of using the priority name of Vyvanse ® for the chewable tablet, which is the same for the currently marketed capsule formulation (i.e., the listed product). They conclude that this proposal is acceptable.

**2. Division of Medical Policy Program (DMPP)**

Drs. Amanpreet Sarai and Marcia Williams reviewed the proposed medication guide. They conclude the medication guide is acceptable with the recommended modifications.

**3. Office of Prescription Drug Promotion (OPDP)**

Dr. Christine Bradshaw from the OPDP reviewed the substantially completed version of the product labeling, carton/container labeling, and medication guide for the chewable tablet. She found that no further comments are needed at this time.

## IV. Conclusion and Recommendation

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| Recommended Regulatory Action: | Approval |
| Risk Benefit Assessment: | The benefits continue to outweigh the risks for this new formulation of lisdexamphetamine. |
| 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 chewable tablet. |
| Recommendation for other Postmarketing Requirements and Commitments: | Deferred pediatric studies under PREA for the treatment of ADHD in pediatric patients aged 4 to less than 6 years old will be required at this point of time including PK, efficacy, and long term safety studies. The required studies may be considered being fulfilled after the studies in pediatric patients 4 to less than 6 years of age in Vyvanse ® capsule (i.e., the listed product) are completed and accepted by the agency. |

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HAO ZHU
01/09/2017