# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 219847Orig1s000

# MULTI-DISCIPLINE REVIEW

**Summary Review**
**Clinical Review**
**Non-Clinical Review**
**Statistical Review**
**Clinical Pharmacology Review**

# NDA/BLA Multi-Disciplinary Review and Evaluation

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|---|---|
| **Application Type** | NDA |
| **Application Number(s)** | 219847 |
| **Priority or Standard** | Standard |
| **Submit Date(s)** | 08/16/2024 |
| **Received Date(s)** | 08/16/2024 |
| **PDUFA Goal Date** | 06/16/2025 |
| **Division/Office** | Division of Psychiatry/Office of Neuroscience |
| **Review Completion Date** | 06/16/2025 |
| **Established/Proper Name** | Lisdexamfetamine dimesylate |
| **(Proposed) Trade Name** | Arynta |
| **Pharmacologic Class** | Central nervous system (CNS) stimulant |
| **Code name** | N/A |
| **Applicant** | Azurity Pharmaceuticals |
| **Doseage form** | Oral solution (10 mg/mL) |
| **Applicant proposed Dosing Regimen** | Attention-deficit/hyperactivity disorder (ADHD)<br>The recommended starting dosage in adults and pediatric patients 6 years and older is 30 mg once daily in the morning. Dosage may be adjusted in increments of 10 mg or 20 mg at approximately weekly intervals up to maximum recommended dosage of 70 mg once daily.<br><br>Binge eating disorder (BED)<br>The recommended starting dosage in adults is 30 mg once daily to be titrated in increments of 20 mg at approximately weekly intervals to achieve the recommended target dose of 50 mg to 70 mg once daily. The maximum recommended dosage is 70 mg once daily |
| **Applicant Proposed Indication(s)/Population(s)** | ADHD in adults and pediatric patients 6 years and older.<br>Moderate to severe BED in adults. |
| **Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication** | 406506008 \|Attention-deficit/hyperactivity disorder (disorder)\|<br>439960005 \|Binge eating disorder (disorder)\| |
| **Recommendation on Regulatory Action** | Approval |
| **Recommended Indication(s)/Population(s)** (if applicable) | ADHD in adults and pediatric patients 6 years and older.<br>Moderate to severe BED in adults. |
| **Recommended Dosing Regimen** | ADHD:<br>The recommended starting dosage in adults and pediatric patients 6 years and older is 30 mg once daily in the morning. |

| | |
|---|---|
| | Dosage may be adjusted in increments of 10 mg or 20 mg at approximately weekly intervals up to maximum recommended dosage of 70 mg once daily.<br><br>BED:<br>The recommended starting dosage in adults is 30 mg once daily to be titrated in increments of 20 mg at approximately weekly intervals to achieve the recommended target dose of 50 mg to 70 mg once daily. The maximum recommended dosage is 70 mg once daily. |

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| **OSE/Division of Epidemiology (DEPI)** | Qiang Yandong |

## Signatures

See archived review memos for each discipline.

# Glossary

| | |
|---|---|
| AC | advisory committee |
| ADHD | attention deficit hyperactivity disorder |
| ADME | absorption, distribution, metabolism, excretion |
| AE | adverse event |
| ANDA | abbreviated new drug application |
| ANOVA | analysis of variance |
| AR | adverse reaction |
| AUC | area under the plasma concentration-time curve |
| BA | bioavailability |
| BED | binge eating disorder |
| BLA | biologics license application |
| BMI | body mass index |
| BP | blood pressure |
| Bpm | beats per minute |
| BPCA | Best Pharmaceuticals for Children Act |
| BRF | Benefit Risk Framework |
| CBER | Center for Biologics Evaluation and Research |
| CDER | Center for Drug Evaluation and Research |
| CDRH | Center for Devices and Radiological Health |
| CDTL | Cross-Discipline Team Leader |
| CFR | Code of Federal Regulations |
| CI | confidence interval |
| $C_{max}$ | peak plasma concentration |
| CMC | chemistry, manufacturing, and controls |
| CNS | central nervous system |
| COA | clinical outcome assessment |
| COSTART | Coding Symbols for Thesaurus of Adverse Reaction Terms |
| CRF | case report form |
| CRO | contract research organization |
| CRT | clinical review template |
| CSR | clinical study report |
| CSS | Controlled Substance Staff |
| CYP | cytochrome P450 |
| DBP | diastolic blood pressure |
| DHOT | Division of Hematology Oncology Toxicology |
| DMC | data monitoring committee |
| DSM-5 | Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition |
| ECG | electrocardiogram |
| eCTD | electronic common technical document |
| ETASU | elements to assure safe use |

| | |
|---|---|
| FDA | Food and Drug Administration |
| FDAAA | Food and Drug Administration Amendments Act of 2007 |
| FDASIA | Food and Drug Administration Safety and Innovation Act |
| GCP | good clinical practice |
| GMR | geometric mean ratio |
| GRMP | good review management practice |
| HR | heart rate |
| ICF | informed consent form |
| ICH | International Conference on Harmonisation |
| IND | Investigational New Drug |
| iPSP | initial pediatric study plan |
| ISE | integrated summary of effectiveness |
| ISS | integrated summary of safety |
| ITT | intent to treat |
| LD | Listed drug |
| LOU | Limitation of Use |
| MAOI | monoamine oxidase inhibitor |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mITT | modified intent to treat |
| NCI-CTCAE | National Cancer Institute-Common Terminology Criteria for Adverse Event |
| NDA | new drug application |
| NME | new molecular entity |
| OCP | Office of Clinical Pharmacology |
| OCS | Office of Computational Science |
| OPQ | Office of Pharmaceutical Quality |
| OSE | Office of Surveillance and Epidemiology |
| OSI | Office of Scientific Investigation |
| OSIS | Office of Study Integrity and Surveillance |
| PBRER | Periodic Benefit-Risk Evaluation Report |
| PD | pharmacodynamics |
| PI | prescribing information |
| PI | principal investigator |
| PIND | pre-investigational new drug application |
| PK | pharmacokinetics |
| PMC | postmarketing commitment |
| PMR | postmarketing requirement |
| PP | per protocol |
| PPI | patient package insert (also known as Patient Information) |
| PREA | Pediatric Research Equity Act |
| PRO | patient reported outcome |
| PSUR | Periodic Safety Update report |
| REMS | risk evaluation and mitigation strategy |
| RR | respiratory rate |

| | |
|---|---|
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SBP | systolic blood pressure |
| SGE | special government employee |
| SOC | standard of care |
| SNRI | serotonin-norepinephrine reuptake inhibitor |
| SSRI | selective serotonin reuptake inhibitor |
| Sub-I | sub-investigator |
| TEAE | treatment emergent adverse event |
| $T_{max}$ | time to reach maximum plasma concentration |
| $T_{1/2}$ | the time required for plasma concentration of a drug to decrease by 50% |
| WRO | Written Response Only |

# 1 Executive Summary

## 1.1. Product Introduction

Azurity Pharmaceuticals has submitted a 505(b)(2) application for lisdexamfetamine dimesylate oral solution (proprietary name, Arynta) for the treatment of attention-deficit/hyperactivity disorder (ADHD) in adults and pediatric patients 6 years and older and moderate-to-severe binge eating disorder (BED) in adults. The Applicant proposes to rely on the Agency's previous findings of safety and effectiveness for the listed drug (LD), lisdexamfetamine dimesylate (Vyvanse) capsules (NDA 021977; initial approval 2007). The Applicant anticipates that this product may be useful for patients with swallowing difficulties. Lisdexamfetamine is a prodrug of dextroamphetamine. Amphetamines are non-catecholamine sympathomimetic amines with central nervous system (CNS) stimulant activity. The exact mode of therapeutic action in ADHD and BED is not known.

The Applicant plans to supply the drug product as a 10 mg/ml, clear and colorless solution packaged as 100-mL bottle with a (b) (4) oral dosing syringe. The proposed dosage and administration instructions are identical to the LD. For ADHD, the recommended starting dosage in adults and pediatric patients 6 years and older is 30 mg once daily in the morning. Dosage may be adjusted in increments of 10 mg or 20 mg at approximately weekly intervals up to maximum recommended dosage of 70 mg once daily. For BED, the recommended starting dosage in adults is 30 mg once daily to be titrated in increments of 20 mg at approximately weekly intervals to achieve the recommended target dose of 50 mg to 70 mg once daily. The maximum recommended dosage is 70 mg once daily.

## 1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of effectiveness for the treatment of ADHD in adults and pediatric patients 6 years and older and moderate-to-severe BED in adults is provided by the Agency's previous findings of effectiveness for the LD and the establishment of an acceptable scientific bridge between the LD and lisdexamfetamine dimesylate oral solution using pharmacokinetic (PK) data. Study (b) (4) 2793, a single-dose, two-way crossover study demonstrated comparable bioavailability between lisdexamfetamine dimesylate oral solution (10 mg/mL) 70 mg and lisdexamfetamine dimesylate capsules 70 mg, establishing an adequate scientific bridge to the LD. Lisdexamfetamine dimesylate oral solution is expected to have the same effectiveness and safety for the treatment of ADHD in adults and pediatric patients 6 years and older and moderate-to-severe BED in adults as the approved lisdexamfetamine dimesylate (Vyvanse) capsules.

## 1.3. Benefit-Risk Assessment

**Benefit-Risk Summary and Assessment**

This NDA relies on the Agency's previous findings of effectiveness and safety for the listed drug (LD), lisdexamfetamine dimesylate capsules (Vyvanse; NDA 021977) and the pharmacokinetic (PK) bridge established between the LD and the proposed product, lisdexamfetamine dimesylate oral solution (Arynta). The effectiveness and safety of lisdexamfetamine oral solution are expected to be similar to the LD. No new safety issues were identified from the Applicant's PK studies. The benefit-risk profile of lisdexamfetamine dimesylate oral solution does not differ from the LD. This assessment supports the marketing approval of lisdexamfetamine dimesylate oral solution for the treatment of ADHD in adults and pediatric patients 6 years and older and moderate-to-severe BED in adults and provides an additional formulation option for treatment based on patients' needs and preferences.

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Analysis of Condition | • ADHD is a chronic, neurodevelopmental condition marked by a persistent pattern of inattention or hyperactivity/impulsivity or by a combination of symptoms from these two domains.<br>• ADHD is the most common neurodevelopmental disorder of childhood.<br>• ADHD has been associated with depression, suicidal behavior, substance abuse, and poor educational and occupational outcomes.<br>• BED is characterized by recurrent episodes of binge eating in the absence of regular compensatory behavior (e.g., vomiting, laxative abuse, or excessive exercise).<br>• Binge eating disorder (BED) is frequently associated with obesity and related medical conditions, depression, and suicide attempts, as well as high economic costs. | ADHD and BED are serious conditions associated with increased morbidity and mortality and high social and economic costs. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Current Treatment Options | • Stimulant and nonstimulant treatment options are available for ADHD. Lisdexamfetamine dimesylate capsules (Vyvanse), the LD, is the only FDA-approved treatment for BED.<br>• The LD is a central nervous system (CNS) stimulant approved for the treatment of ADHD in adults and pediatric patients 6 years and older and for moderate-to-severe BED in adults.<br>• Approved labeling for the LD recommends once-daily dosing for both indications. Lisdexamfetamine dimesylate oral suspension is also intended for once-daily dosing.<br>• Several ADHD medications are available as oral suspension (e.g., methylphenidate hydrochloride, dextroamphetamine sulfate). | Effective treatment of ADHD and BED reduces functional impairment in the short-term, and may result in long-term benefits.<br><br>Patients with ADHD or BED and difficulty swallowing capsules may benefit from additional treatment options. |
| Benefit | • The Applicant submitted two relative bioavailability studies (Study 2793 and Study 2794) to establish a pharmacokinetic (PK) bridge between the lisdexamfetamine dimesylate oral solution formulation and the LD. Study 2794 also evaluated food effect.<br>• The Office of Clinical Pharmacology (OCP) review found that the exposures (peak plasma concentrations (Cmax) and area under the plasma concentration-time curve (AUC)) from equal total doses of lisdexamfetamine dimesylate oral solution were comparable to that of the LD (lisdexamfetamine dimesylate capsules). | The Applicant has provided an adequate pharmacokinetic bridge between lisdexamfetamine dimesylate oral solution and the LD in order to rely on the Agency's findings of effectiveness and safety described in approved labeling. |
| Risk and Risk Management | • The most common adverse reactions (incidence at least 5% and twice the rate of placebo) with the LD in pediatric patients and/or adults with ADHD were anorexia, anxiety, decreased appetite, decreased weight, diarrhea, dizziness, dry mouth, irritability, insomnia, nausea, upper abdominal pain, and vomiting.<br>• The most common adverse reactions (incidence 5% and at a rate at least twice placebo) in adults with BED were dry mouth, | The safety of this product is expected to be similar to that of the LD. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | insomnia, decreased appetite, increased heart rate, constipation, feeling jittery, and anxiety.<br>• Warnings and precautions include the potential for abuse and dependence; serious cardiovascular reactions; blood pressure and heart rate increases; psychiatric adverse reactions; suppression of growth; peripheral vasculopathy, including Raynaud's phenomenon; serotonin syndrome.<br>• Contraindications include:<br>○ Known hypersensitivity to amphetamine products or other ingredients of the drug product. Anaphylactic reactions, Stevens-Johnson syndrome, angioedema, and urticaria have been observed in postmarketing reports.<br>○ Patients taking monoamine oxidase inhibitors (MAOIs), or within 14 days of stopping MAOIs (including MAOIs such as linezolid or intravenous methylene blue), because of an increased risk of hypertensive crisis. | |

## 1.4. Patient Experience Data

**Patient Experience Data Relevant to this Application** (check all that apply)

| | | | | |
|---|---|---|---|---|
| ☐ | **The patient experience data that were submitted as part of the application include:** | | | Section of review where discussed, if applicable |
| | X | Clinical outcome assessment (COA) data, such as | | |
| | | X | Patient reported outcome (PRO) | Organoleptic Evaluation questionnaire (acceptability, bitterness, sweetness, aftertaste, flavor) |
| | | ☐ | Observer reported outcome (ObsRO) | |
| | | ☐ | Clinician reported outcome (ClinRO) | |
| | | ☐ | Performance outcome (PerfO) | |
| | ☐ | Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.) | | |
| | ☐ | Patient-focused drug development or other stakeholder meeting summary reports | | |
| | ☐ | Observational survey studies designed to capture patient experience data | | |
| | ☐ | Natural history studies | | |
| | ☐ | Patient preference studies (e.g., submitted studies or scientific publications) | | |
| | ☐ | Other: (Please specify): | | |
| ☐ | **Patient experience data that were not submitted in the application, but were considered in this review:** | | | |
| | ☐ | Input informed from participation in meetings with patient stakeholders | | |
| | ☐ | Patient-focused drug development or other stakeholder meeting summary reports | | |
| | ☐ | Observational survey studies designed to capture patient experience data | | |
| | ☐ | Other: (Please specify): | | |
| ☐ | **Patient experience data was not submitted as part of this application.** | | | |

# 2 Therapeutic Context

## 2.1. Analysis of Condition

**Attention-Deficit/Hyperactivity Disorder**

ADHD is a chronic, neurodevelopmental condition marked by a persistent pattern of inattention or hyperactivity/impulsivity or by a combination of symptoms from these two domains. ADHD typically presents in childhood with symptoms of difficulty paying attention, hyperactivity, and impulsive behavior. ADHD is the most common neurodevelopmental disorder of childhood. The prevalence in the pediatric population is estimated to be approximately 11%. ADHD may persist into adulthood and has a 4% prevalence in adults. Pediatric patients with this disorder often experience difficulty with school performance, difficulty interacting with peers, and engaging in dangerous activities due to impulsivity. Adults with ADHD may experience impairment in their workplace, social relationships, and with completing tasks. Many individuals with ADHD obtain symptom reduction with appropriate medication treatment resulting in significant decreases in impairment in daily tasks and functioning.

**Binge Eating Disorder**

BED is a serious illness, characterized by recurrent episodes of binge eating in the absence of regular compensatory behavior (e.g., vomiting, laxative abuse, or excessive exercise). Current prevalence based on Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) criteria has been estimated at 1.5% for women and 0.3% for men based on several studies (Erskine 2018). BED is frequently associated with obesity, depression, and suicide attempts, as well as high economic costs (Keski-Rahkonen 2021, Streatfeild 2021).

According to the DSM-5, the criteria for BED are as follows (Criteria A through E must be met to establish the diagnosis).

A. Recurrent episodes of binge eating which are characterized by both eating an amount of food in a discrete period of time that is larger than what most people would eat in a similar timeframe and a sense of lack of control over eating during the episodes.

B. Binge eating episodes are associated with at least three of the following:
   - Eating much more rapidly than normal
   - Eating until feeling uncomfortably full
   - Eating large amounts of food when not feeling physically hungry
   - Eating alone because of embarrassment by how much is eaten
   - Feelings of disgust, depression, or guilt after an episode

C. Marked distress over binge eating.

D. Binge eating occurs, on average, at least once a week for at least 3 months.

E. Binge eating is not associated with the recurrent use of inappropriate compensatory behavior as in bulimia nervosa and does not occur exclusively during the course of bulimia nervosa or anorexia nervosa.

BED severity is based on the number of episodes per week:

- Mild: 1 to 3 episodes per week
- Moderate: 4 to 7 episodes per week
- Severe: 8 to 13 episodes per week
- Extreme: 14 or more episodes per week

## 2.2. Analysis of Current Treatment Options

**Attention-Deficit/Hyperactivity Disorder**

There are numerous drugs approved for the treatment of ADHD that are classified as stimulants (including methylphenidate, d-methylphenidate, amphetamine, dextroamphetamine, methamphetamine, lisdexamfetamine, and dextroamphetamine) and non-stimulants (norepinephrine reuptake inhibitors and alpha-adrenergic agonists). Methylphenidate products are available as immediate-release and extended-release formulations; a once-a-day administration of an extended-release tablet can offer ADHD symptom reduction for an entire day, whereas an immediate release tablet requires dosing at least twice daily. The once-daily dose administration may increase medication adherence and can alleviate the stress associated with pediatric patients requiring dosing during school hours, thus, avoiding interruptions in their school day to have drug administration by the school nurse.

**Binge Eating Disorder**

Psychotherapy is the first-line treatment for BED (Giel 2022). Lisdexamfetamine dimesylate is the only drug approved for BED. Several drugs are used off-label for the treatment of BED, including including antidepressants (e.g, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), bupropion), anticonvulsants (e.g., topiramate), and anti-obesity agents.

# 3 Regulatory Background

## 3.1. U.S. Regulatory Actions and Marketing History

The Agency approved lisdexamfetamine dimesylate capsules (a prodrug of the stimulant d-amphetamine) in 2007 for treatment of ADHD in pediatric patients ages 6 to 12 years (NDA 21977; Vyvanse capsules). Lisdexamfetamine dimesylate was approved for the treatment of ADHD in adults in 2008, for the treatment of ADHD in pediatric patients ages 13 to 17 years in 2010, for the maintenance treatment of ADHD in adults in 2012, for the treatment of moderate-to-severe BED in adults in 2015, and for the maintenance treatment of BED in adults in 2016. In 2017, the Agency approved lisdexamfetamine dimesylate chewable tablets (NDA 208510) for the treatment of ADHD in patients age 6 years and older and for the treatment of moderate-to-severe BED in adults based on pharmacokinetic (PK) studies demonstrating comparable bioavailability to lisdexamfetamine dimesylate capsules and a cross-reference to NDA 21977.

## 3.2. Summary of Presubmission/Submission Regulatory Activity

Prior to submitting the new drug application for lisdexamfetamine dimesylate oral solution for the treatment of ADHD in children, adolescents, and adults and of moderate-to-severe BED in adults, the Applicant received advice from the Agency under pre-investigational new drug application (PIND) 157133. The Applicant conducted both clinical studies in Canada, outside of an IND. The list below is not exhaustive; rather, it is focused on major pre-submission activities, decisions, and advice.

**August 12, 2021: Pre-IND Written Response**
This meeting involved discussion of the 505(b)(2) regulatory pathway for this product and of the adequacy of a single comparative bioavailability study of the oral solution versus the LD at the highest approved dose under fasted conditions. The Agency informed the Applicant that it would be acceptable to demonstrate the comparative bioavailability between lisdexamfetamine dimesylate oral solution and the LD at 70 mg under fasting conditions. However, the Agency also informed the Applicant that food effect should be evaluated for the proposed product to support a future NDA submission. In addition, the Agency clarified that comparative bioavailability should be established based on the active moiety dexamphetamine, not the prodrug lisdexamfetamine and that lisdexamfetamine data should be submitted as supportive evidence.

**March 7, 2022: Initial Pediatric Study Plan submission**
In the initial pediatric study plan (iPSP), the Applicant proposed a plan to request a (b) (4) waiver of studies for pediatric patients (b) (4). The iPSP did not include a plan for pediatric patients (b) (4) for attention deficit hyperactivity disorder (ADHD) or for any pediatric age group for binge eating disorder (BED). The Agency informed the Applicant that the iPSP must address all pediatric age groups and all indications for which the

drug is being developed that are subject to PREA and a justification for any plans to request waivers or deferrals.

The Agency advised that for pediatric patients ages 0 to less than 4 years old with ADHD, the Applicant should plan to request a waiver because studies are impossible or highly impracticable. (b) (4) (b) (4) (b) (4). The Agency also advised that if the Applicant planned to request waivers or deferrals of pediatric studies for the BED indication, the iPSP must include a justification for these plans specific to each pediatric age group.

**August 5, 2022: "Agreed Initial Pediatric Study Plan" submission**
The Applicant submitted an "Agreed Initial Pediatric Study Plan" for ADHD in children, adolescents, and adults and moderate-to-severe BED in adults on August 5, 2022. The Applicant proposed a plan to request a (b) (4) waiver in pediatric patients (b) (4). The Applicant did not propose any plan to address the BED indication in the iPSP. The Agency responded in a Pediatric Study Plan – Initial No Agreement letter on August 31, 2022. The Agency explained that given the plan to rely on the Agency's previous findings of safety and effectiveness for the LD, the Applicant's iPSP should outline a plan to provide a pediatric assessment, not a waiver, for the populations with data in the LD label.

**February 28, 2023: "Initial Pediatric Study Plan" submission**
The Applicant submitted an "Initial Pediatric Study Plan" on February 28, 2023, proposing a plan to request partial waiver of studies for pediatric patients 0 to <4 years of age for ADHD, an assessment for pediatric patients ages 4 to 17 years for ADHD, and a full waiver for pediatric patients 0 to 17 years of age for BED. On July 19, 2023, the Agency responded with a Pediatric Study Plan – Other letter providing comments on the revised iPSP. The Agency commented that the iPSP document included certain unnecessary details and required other content or editorial changes.

**June 9, 2023: Request for Type C, Written Response Only Meeting**
The Applicant submitted a request for a Type C meeting to seek Agency's advice on June 9, 2023. The meeting request included one question: "Does the Agency agree that the 505 (b)(2) NDA regulatory pathway is appropriate to submit dossier with 6M long term & accelerated stability data of Lisdexamfetamine Dimesylate Oral Solution 10 mg/mL?" On June 20, 2023, the Agency denied the meeting request, but provided an answer to the Applicant's questions in the Meeting Request Denied letter. The letter informed the Applicant that the Agency would expect the initial NDA to contain 6-month accelerated and at least 12-month longterm stability data for a minimum of three representative drug product batches of each strength manufactured using the proposed commercial manufacturing process and packaged in the proposed commercial container closure system.

**August 23, 2023: Agreed Initial Pediatric Study Plan submission**
The Applicant submitted a revised Agreed iPSP on August 23, 2023, which incorporated all the changes recommended by the Agency in the July 19, 2023 letter. On October 5, 2023, the Agency sent the Applicant a Pediatric Study Plan - Initial Agreement letter.

**May 3, 2024: Type C Meeting Written Response**
On February 20, 2024, the Applicant requested a meeting to gain the Agency's feedback regarding the acceptability of the protocol for a human factor study, preservative content in formulation, biocompatibility study, and syringe design. On March 7, 2024, the Agency sent a Meeting Granted letter dated for a Type C Written Response Only (WRO) meeting. On May 3, 2024, the Agency sent a final written response. The Agency advised the Sponsor that submission of protocols as part of a meeting package is not the appropriate mechanism to obtain a full Agency review. The Agency advised the Applicant to submit the protocol separately to the IND.

Regarding the preservative content level, the Agency informed the Sponsor that although the proposal to include the test for preservative content in the drug product specification appeared reasonable, the acceptability of the proposed limits for preservative content would be a review issue upon submission of the NDA. Regarding the need for a biocompatibility study, the Agency disagreed with the Applicant, indicating that an extractables and leachables study would be necessary.

The Agency indicated that the proposal to use a (b) (4) oral medication syringe (b) (4) (b) (4) along with a bottle adaptor appeared reasonable. However, suitability of the syringe and the adaptor for dosing of the drug product would ultimately be a review issue upon submission of the NDA. The Agency's Office of Combination Products provided additional comments, informing the Applicant that the product and dosing syringe were considered a combination product under 21 CFR 3.2(e) and outlined information that would need to be submitted in the future specific to combination products. The Agency's Controlled Substance Staff (CSS) provided additional comments regarding data needed to assess abuse potential and overdosage. CSS indicated that the NDA should include a proposal for scheduling of lisdexamfetamine based on the data in the submission (which may be that it appropriately remains as a Schedule II controlled substance or that it may be more appropriately controlled in another schedule).

**August 8, 2024: Administrative Change/Sponsor submission**
The Applicant notified the Agency on August 8, 2024, that ownership of preIND 157133 had been transferred from Adalvo Limited to Azurity Pharmaceuticals, Inc. on July 16, 2024.

# 4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

## 4.1. Office of Study Integrity and Surveillance (OSIS)

An Office of Study Integrity and Surveillance (OSIS) consult request was submitted to conduct an inspection for the clinical sites (BioPharma Services, Inc. and Alpha Laboratories, Inc.) and bioanalytical site ( (b) (4) on October 15, 2024.

OSIS determined that an inspection for the clinical site at the BioPharma Services, Inc. is not needed as a previous inspection of the same site on NON-RESPONSIVE (ANDA NON-RESPONSIVE ) suggests that data from the reviewed studies were reliable. For another clinical site, Alpha Laboratories, Inc., OSIS determined that an inspection is not needed because there were no subjects randomized at the site.

OSIS conducted an inspection for the bioanalytical site (b) (4) (b) (4) for NON-RESPONSIVE . As data from the reviewed studies were reliable, OSIS concluded that an inspection for the bioanalytical site is not needed.

## 4.2. Product Quality

The Office of Product Quality (OPQ) recommends approval for this application based on drug substance, drug product, manufacturing, and microbiology reviews.

**Drug Substance:** The chemistry, manufacturing, and control (CMC) information for the drug substance, lisdexamfetamine dimesylate, is crossreferenced to Type II Drug Master File (DMF) (b) (4) Lisdexamfetamine dimesylate is manufactured by the Holder of the referenced DMF – (b) (4) The DMF was originally submitted on May 18, 2018. Since then, the DMF has been reviewed seven times. The latest review on the most recent quality amendments (SDNs 20, 21, and 23) was completed on November 18, 2024, with the conclusion of Adequate. The Applicant refers to the DMF and provides a brief description of the general properties, specification, impurities, analytical methods and validations, batch analyses and stability for the drug substance. All the information is adequate.

Based upon the information disclosed in the DMF, the controls on the impurities in the lisdexamfetamine dimesylate drug substance are adequate. There are no concerns of potential genotoxic impurities and (b) (4) for the drug substance, including (b) (4) drug substance-related impurities ( (b) (4)

Based upon the stability data in the DMF, the DMF Holder assigned a retest period of (b) (4) months for lisdexamfetamine dimesylate when stored at the USP controlled room temperature (b) (4) in the proposed container closure system. However, the Applicant followed a retest period of (b) (4)

months for the drug substance.

**Drug Product:** The proposed drug product, Lisdexamfetamine Dimesylate Oral Solution 10 mg/mL is supplied as 100 mL of solution in a 100-mL polyethylene terephthalate (PET) bottle and sealed with a 28-mm child-resistant closure. Each sealed bottle is co-packaged with one press-in bottle adapter and one (b) (4) oral dispenser assembly (i.e., dosing syringe) along with the prescribing information leaflet in a mono carton.

All excipients used in the formulation are of compendial grade and are listed in the Inactive Ingredients Database (IID) and are within maximum daily exposure (MDE) values of approved oral formulations. The Applicant has performed adequate product development studies to support the selection of the formulation composition. The Applicant has provided adequate information regarding the proposed container closure system; the submitted (b) (4) extractables and leachables data are adequate to support its use. In addition, the Applicant has provided dose accuracy data for the co-packaged syringe. The proposed drug product release and stability specification are adequate for an oral solution product. The analytical methods for batch release and stability sample analysis are adequately validated and suitable for the intended regulatory purpose. The Applicant has provided adequate justification for not including elemental impurity testing in the specification. Moreover, the Applicant has provided an adequate (b) (4) risk assessment, indicating lack of (b) (4) risk in the proposed drug product.

The Applicant has provided 18 months of long-term and 6 months of accelerated stability data in the current submission. All the stability data met the proposed specification except for the delivered volume test. One of the reasons for the failure of the delivered volume test appears to be (b) (4) throughout the product's shelf-life. The delivered volume test failure issue will be mitigated (b) (4). Based on the available (b) (4) stability data, it is likely that some batches will exceed the proposed specification limit of (b) (4) by the 24-month timepoint. Therefore, a shorter shelf-life of 18 months is granted for this product instead of the proposed (b) (4). The in-use stability data supports the proposed discard period of (b) (4). Overall, the submitted information in this NDA submission, support 18 months of shelf-life when the product is stored at the following proposed storage condition: “Store at 20°C to 25°C (68°F to 770F); excursions permitted to 15°C to 30°C (59°F to 86°F). Keep the container tightly closed. Discard unused drug product (b) (4) after first opening the bottle.”

**Manufacturing:** The manufacturing process, equipment, process controls (process parameters) and inprocess controls are suitable for the drug product. The tests for description, pH, assay of the API, (b) (4), microbial attributes have been evaluated before and after (b) (4). The same quality attributes are proposed for product (b) (4) for commercial manufacture. The bulk solution is filled into 100-mL (b) (4) PET bottles with a child-resistant (CR) cap and tamper evident ring. The in-process controls include (b) (4)

(b) (4). The labeled containers will be co-packaged with a dosing syringe and bottle adapter.

Visual inspection has been conducted and also proposed at all intermediate stages of (b) (4). The general sampling plan and inspection acceptance criteria follow ANSI/ASQ Z1.4. Adequate limits for the (b) (4) duration and yield/reconciliation limits have been proposed, which are supported by the corresponding data on the registration batches.

Adequate certifications for suitability of the manufacturing equipment contact surfaces, (b) (4) components, have been provided. Following Office of Pharmaceutical Manufacturing Assessment (OPMA) Review Guide, the drug product and manufacturing process are determined to be low risk for contamination with potential leachables.

The overall manufacturing process for the registration batches and that proposed for commercial batches has been determined to be adequate for Lisdexamfetamine Dimesylate Oral Solution 10 mg/mL. The manufacturing facilities supporting NDA 219847 are compliant. The application is approvable from the Manufacturing (Process and Facilities) discipline.

**Microbiology:** The drug product is a non-sterile, clear, colorless solution for oral administration. The drug substance is not provided sterile. Therefore, a product quality microbiology review of the drug substance is not reviewed. The applicant has provided sufficient description of the drug product composition and container closure system. The applicant provided antimicrobial effectiveness testing (AET) data that is consistent with USP <51> criteria for an aqueous oral product (category 3). The applicant has adequately described the location and responsibilities of the drug product manufacturers. The applicant provided a sufficient description of the manufacturing process that meets regulatory expectations for a non-sterile product. The applicant has met regulatory expectations for the product release specifications regarding microbiological tests. Exhibit batches meet the microbiological release specification. The applicant has adequately verified the suitability of the test methods for microbial limits and Burkholderia cepacia Complex (BCC) testing. These methods are suitable for use in routine commercial testing. The applicant has described an appropriate stability testing program to support the drug product's microbiological quality throughout its shelf life. The stability data submitted to date support the microbiological quality of the drug product.

Refer to the integrated quality assessment review from the OPQ for additional information.

## 4.3. Clinical Microbiology

There were no clinical microbiology data submitted with this application.

## 4.4. Devices and Companion Diagnostic Issues

There were no data related to devices or companion diagnostics submitted with this application.

# 5 Nonclinical Pharmacology/Toxicology

## 5.1. Executive Summary

This NDA relies on the Agency's previous findings of safety and efficacy of the LD, Vyvanse (lisdexamfetamine didimesylate) capsule. The nonclinical submission for this NDA did not contain any nonclinical studies or data for review. Review of the chemistry and manufacturing information did not identify any issues that required safety evaluation from a nonclinical perspective. There were no proposed labeling changes to the nonclinical sections of the label and these sections are consistent with those of the LD label.

# 6 Clinical Pharmacology

## 6.1. Executive Summary

The Applicant submitted a 505(b)(2) NDA for Lisdexamfetamine Dimesylate Oral Solution 10 mg/mL for the treatment of ADHD in adults and pediatric patients 6 years and older and moderate-to-severe BED in adults. Lisdexamfetamine is a pro-drug and is biotransformed to an active metabolite, dextroamphetamine. The parent drug, lisdexamfetamine, does not bind to the sites responsible for the reuptake of norepinephrine and dopamine in vitro. The proposed oral solution formulation of lisdexamfetamine dimesylate is an alternative dosage form to the currently available capsule and chewable tablet solid oral dosage formulations. This formulation is designed for ease of dosing and administration to patients with swallowing difficulties. This application relies on the Agency's previous findings of safety and efficacy of the LD (Vyvanse, lisdexamfetamine dimesylate capsule (NDA 021977 held by Takeda)).

The clinical pharmacology program in this submission consists of two single-dose, two-way crossover, comparative bioavailability studies (one study under fasted state and another study under fed state) to compare the pharmacokinetics (PK) between the proposed lisdexamfetamine dimesylate oral solution and the LD, and also to evaluate food effects on the proposed product. The Office of Clinical Pharmacology (OCP) finds that the scientific bridge between lisdexamfetamine dimesylate oral solution (10 mg/ml) and the LD is adequate and the proposed drug product can rely on the efficacy and safety of the LD.

OCP recommends the approval of lisdexamfetamine dimesylate oral solution 10 mg/mL for the treatment of ADHD in adults and pediatric patients 6 years and older and moderate-to-severe BED in adults.

## 6.2. Summary of Clinical Pharmacology Assessment

The Applicant submitted two single-dose, two-way crossover, comparative bioavailability studies (one study under fasted state and another study under fed state) to establish a pharmacokinetic (PK) bridge between the proposed drug product, lisdexamfetamine oral solution and the LD, and to evaluate food effects on the proposed drug product.

In a relative bioavailability study under fasted conditions, the geometric mean ratios (GMRs) and 90% confidence intervals (CI) around GMRs of PK parameters of dextroamphetamine are within the regulatory criteria of 80% to 125%. The GMRs (90% CI) of dextroamphetamine $C_{max}$ are 1.01 (0.97 to 1.04) and $AUC_{inf}$ are 0.98 (0.95 to 1.02)). The median $T_{max}$ of dextroamphetamine following administration of lisdexamfetamine oral solution and the LD under fasted condition is approximately 3.5 hours and 3.7 hours, respectively. Similarly, a relative bioavailability study conducted under fed conditions showed similar exposures for dextroamphetamine between lisdexamfetamine dimesylate solution and lisdexamfetamine dimesylate capsule. The GMRs (90% CI) of dextroamphetamine $C_{max}$ are 0.98 (0.96 to 1.01) and

$AUC_{inf}$ are 0.99 (0.97 to 1.02), respectively. The median $T_{max}$ of dextroamphetamine following administration of lisdexamfetamine oral solution and the LD under fed condition is approximately 4.5 hours and 4.9 hours, respectively. As the systemic exposures ($C_{max}$ and $AUC_{inf}$) of dextroamphetamine were similar between the proposed product and LD administered under fasted and fed conditions, the PK bridge between lisdexamfetamine oral solution and lisdexamfetamine capsules is deemed adequate.

A cross-study comparison (fasted study vs fed study) was performed to compare the PK of dextroamphetamine following administration of lisdexamfetamine oral solution under fasted state and fed state. No appreciable differences in dextroamphetamine exposures ($C_{max}$ and $AUC_{inf}$) were observed between fasted state and fed state. The median (range) Tmax of dextroamphetamine was delayed for an hour under fed conditions compared to fasted conditions (approximately 4.4 (3.00 to 6.00) vs 3.4 (2.00 to 6.00)). Given that the PK bridging between the proposed product and LD was adequately established under both fasted state and fed state and the food effect on Tmax of dextroamphetamine (1 hour delay in Tmax under fed state compared to fasted state) was similar between the proposed product and LD, the impact of food on the PK of the proposed product is considered minimal. Therefore, the proposed product, lisdexamfetamine oral solution, can be administered with or without food as similar to the LD.

As noted in Section 4.1, OSIS found that both the clinical and bioanalyticals sites of the pivotal relative bioavailability study are acceptable.

### 6.2.1. Clinical Pharmacokinetics

Pharmacokinetic studies of lisdexamfetamine dimesylate have been conducted in healthy adults (capsule and chewable tablet formulations) and pediatric (6 to 12 years) patients with ADHD (capsule formulation). Following single dose administration of lisdexamfetamine dimesylate, pharmacokinetics of dextroamphetamine was found to be linear between 30 mg and 70 mg in pediatric population (6 to 12 years), and between 50 mg and 250 mg in adults. Dextroamphetamine pharmacokinetic parameters following administration of lisdexamfetamine dimesylate in adults exhibited low inter-subject (<25%) and intra-subject (<8%) variability. There is no accumulation of lisdexamfetamine and dextroamphetamine at steady state in healthy adults.

Absorption

Following single-dose administration of lisdexamfetamine dimesylate oral solution under fasted conditions, Tmax of lisdexamfetamine and dextroamphetamine was reached at approximately 1 hour and 3.5 hours post-dose, respectively.

*Effect of Food*
No clinically significant differences in lisdexamfetamine dimesylate pharmacokinetics were observed following administration of a high-fat meal (1000 calories, 50% fat). Food delayed the median time to reach Cmax (Tmax) of dextroamphetamine from 3.5 hours to 4.5 hours.

Elimination

Plasma concentrations of unconverted lisdexamfetamine are low and transient, generally becoming non-quantifiable by 8 hours after administration. The plasma elimination half-life of lisdexamfetamine typically averaged less than 1 hour in volunteers ages 6 years and older. The plasma elimination half-life of dextroamphetamine was approximately 8.6 to 9.5 hours in pediatric patients 6 to 12 years and 10 to 11.3 hours in healthy adults.

*Metabolism*

Lisdexamfetamine is converted to dextroamphetamine and l-lysine primarily in blood due to the hydrolytic activity of red blood cells after oral administration of lisdexamfetamine dimesylate. *In vitro* data demonstrated that red blood cells have a high capacity for metabolism of lisdexamfetamine; substantial hydrolysis occurred even at low hematocrit levels (33% of normal). Lisdexamfetamine is not metabolized by cytochrome P450 enzymes.

*Excretion*

Following oral administration of a 70-mg dose of radiolabeled lisdexamfetamine dimesylate to 6 healthy subjects, approximately 96% of the oral dose radioactivity was recovered in the urine and only 0.3% recovered in the feces over a period of 120 hours. Of the radioactivity recovered in the urine, 42% of the dose was related to amphetamine, 25% to hippuric acid, and 2% to intact lisdexamfetamine.

### 6.2.2. General Dosing and Therapeutic Individualization

**General Dosing**

Because the exposures following lisdexamfetamine dimesylate oral solution were similar to the LD, the information relevant to dosing and therapeutic individualization of the proposed drug product can rely upon the LD.

## 6.3. Comprehensive Clinical Pharmacology Review

### 6.3.1. Clinical Pharmacology Questions

**Is the PK bridge between the proposed product, lisdexamfetamine dimesylate oral solution (10 mg/mL) and the listed drug, Vyvanse (lisdexamfetamine dimesylate capsule), under fasted conditions, acceptable?**

Yes. The PK bridge between the formulations is acceptable.

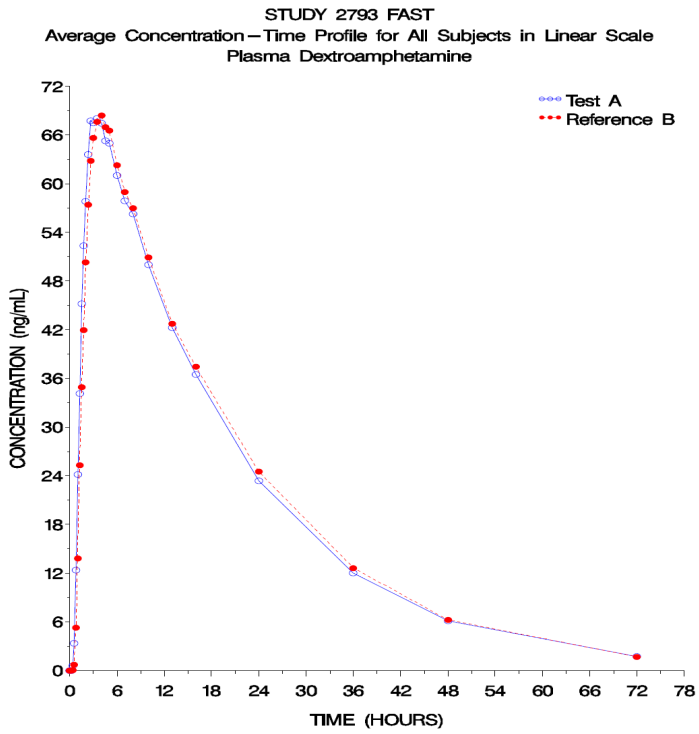
A pivotal, single-dose, randomized, open-label, two-way crossover, comparative bioavailability study was conducted to evaluate the relative bioavailability of lisdexamfetamine dimesylate oral solution 10 mg/ml (test product) and Vyvanse 70 mg (lisdexamfetamine dimesylate capsule; reference product) in healthy volunteers under fasted conditions (Study 2793). The Applicant also conducted another single-dose, relative bioavailability study to compare the pharmacokinetics between the formulations under fed conditions (Study 2794).

Treatment A (Test) is 7 mL of lisdexamfetamine dimesylate oral solution 10 mg/mL (Adalvo Limited (previous sponsor)) and Treatment B (Reference) is one Vyvanse (lisdexamfetamine dimesylate) capsule 70 mg (Takeda Pharmaceuticals USA Inc.).

Lisdexamfetamine is a pro-drug. It is biotransformed to an active metabolite, dextroamphetamine. The parent drug, lisdexamfetamine, does not bind to the sites responsible for the reuptake of norepinephrine and dopamine in vitro. The systemtic exposure (AUCinf) of lisdexamfetamine is approximately 3% compared to that of dextroamphetamine. Therefore, the scientific bridge is primarily established based on the PK comparison of the major active moiety, dextroamphetamine. More details of lisdexamfetamine PK can be found in the Appendix 18.4.

Plasma concentration-time profiles and pharmacokinetic (PK) parameters of dextroamphetamine following administration of test and reference products under fasted conditions (Study 2793) are shown in Figure 1 and Table 1, respectively. Some partial AUCs ($AUC_{0\text{-}1.5}$, $AUC_{1.5\text{-}4}$, $AUC_{0\text{-}4}$, $AUC_{4\text{-}t}$) for dextroamphetamine were investigated as part of the exploratory analysis (refer to Appendix 18.4 for more information).

**Figure 1. Mean Plasma Concentration-Time Profiles of Dextroamphetamine Following Administration of 70 mg Lisdexamfetamine Dimesylate Oral Solution (Test) and 70 mg Lisdexamfetamine Dimesylate Capsule (Reference) Under Fasted Condition in Healthy Adults (Study 2793)**




*Source: Study 2793 report, Figure 14-3, p. 87.*

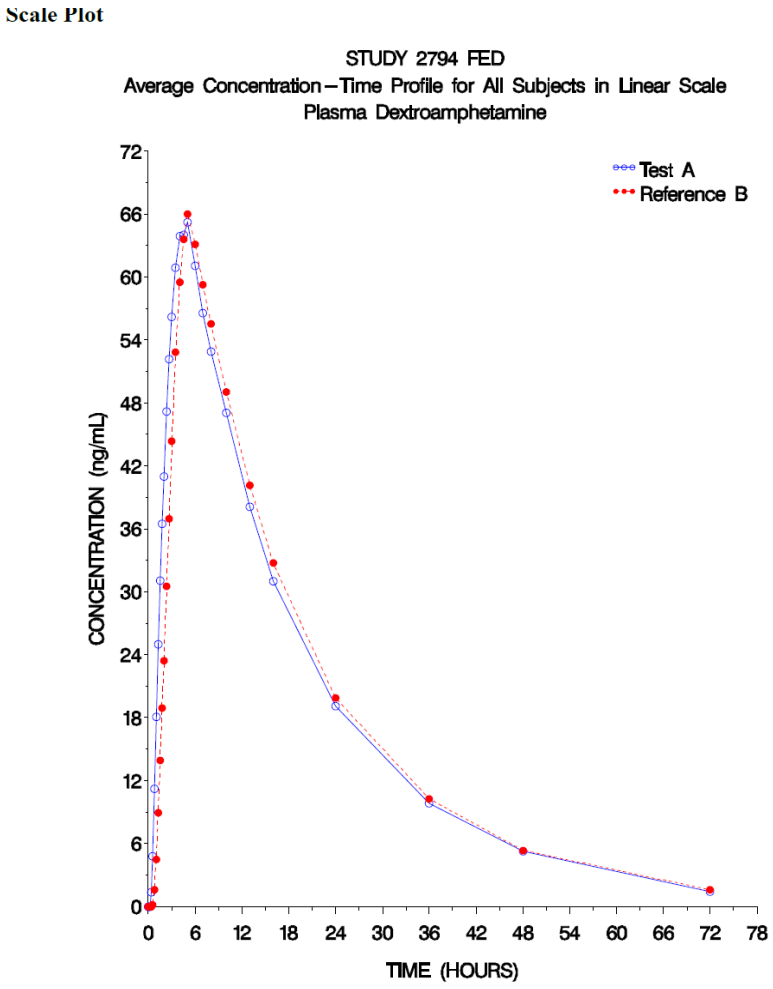
**Table 1. Plasma Pharmacokinetic Parameters of Dextroamphetamine Following Administration of Lisdexamfetamine Oral Solution (Test) and Vyvanse Capsule (Reference) Under Fasted Conditions in Healthy Adults (Study 2793)**

| PK Parameters | Treatment A (Test)[1] | Treatment B (Reference)[1] | T/R Ratio[3] |
|---|---|---|---|
| **$C_{max}$ (ng/mL)** | 72.61 (18.69) | 71.75 (15.84) | 1.01 (0.970. – 1.04) |
| **$T_{max}$[2] (h)** | 3.42 (2.00 – 6.00) | 3.70 (1.75 – 6.00) | - |
| **$AUC_t$ (ng.h/mL)** | 1444.17 (27.60) | 1456.98 (26.05) | 0.98 (0.95 – 1.02) |
| **$AUC_{inf}$ (ng.h/mL)** | 1479.12 (27.61) | 1492.39 (26.04) | 0.98 (0.95 – 1.02) |

[1] Reported as geometric mean (geometric CV%)
[2] Reported as median (range)
[3] Values are displayed as geometric mean ratios (GMR, T/R) and 90% CIs around GMRs.
AUC=area under the curve; $C_{max}$=peak plasma concentration; $T_{max}$=time post dose to reach peak plasma concentration
*Source: Reviewer's analysis and Applicant's study report for Study 2973, Appendix 16.2.6.2.5, p. 158.*

Plasma concentration-time profiles and pharmacokinetic (PK) parameters of dextroamphetamine following administration of test and reference products under fed conditions (Study 2794) are shown in Figure 2 and Table 2, respectively.

**Figure 2. Mean Plasma Concentration-Time Profiles of Dextroamphetamine Following Administration of 70 mg Lisdexamfetamine Dimesylate Oral Solution (Test) and 70 mg Lisdexamfetamine Dimesylate Capsule (Reference) Under Fed Conditions in Healthy Adults (Study 2794)**




*Source: Study 2794 report, Figure 14-3, p. 87.*

**Table 2. Plasma Pharmacokinetic Parameters of Dextroamphetamine Following Administration of Lisdexamfetamine Oral Solution (Test) and Vyvanse Capsule (Reference) Under Fed Conditions in Healthy Adults (Study 2794)**

| PK Parameters (unit) | Treatment A (Test)[1] | Treatment B (Reference)[1] | T/R Ratio[3] |
|---|---|---|---|
| **$C_{max}$ (ng/mL)** | 68.04 (19.69) | 68.92 (19.69) | 0.98 (0.96 – 1.01) |
| **$T_{max}$[2] (h)** | 4.45 (3.00 – 6.00) | 4.88 (2.00 – 7.03) | - |
| **$AUC_t$ (ng.h/mL)** | 1260.10 (26.20) | 1261.65 (25.72) | 0.99 (0.97 – 1.02) |
| **$AUC_{inf}$ (ng.h/mL)** | 1296.12 (26.19) | 1296.66 (25.74) | 0.99 (0.97 – 1.02) |

[1] Reported as geometric mean (geometric CV%)
[2] Reported as median (range)
[3] Values are displayed as geometric mean ratios (GMR, T/R) and 90% CIs around GMRs.
AUC=area under the curve; $C_{max}$=peak plasma concentration; $T_{max}$=time post dose to reach peak plasma concentration
*Source: Reviewer's analysis and Applicant's study report for Study 2974, Appendix 16.2.6.2.5, p. 158.*

The results from the reviewer's analyses are consistent with those from the Applicant. The geometric mean ratios (GMRs; Test/Reference) and 90% confidence intervals around GMRs of PK parameters, $C_{max}$, $AUC_{last}$, and $AUC_{inf}$ of dextroamphetamine are within the regulatory criteria of 80% to 125% under fasted and fed conditions.

The median $T_{max}$ of dextroamphetamine following administration of lisdexamfetamine oral solution and the LD under fasted state is approximately 3.5 hours and 3.7 hours, respectively. The median $T_{max}$ of dextroamphetamine following administration of lisdexamfetamine oral solution and the LD under fed condition is approximately 4.5 hours and 4.9 hours, respectively.

Given that the PK of test and reference products are similar under fasted and fed conditions, the PK bridge between lisdexamfetamine oral solution 10 mg/mL and Vyvanse Capsule is deemed adequate. Therefore, lisdexamfetamine oral solution can rely on the Agency's previous findings of effectiveness and safety of the LD.

**Are there clinically relevant food-drug interactions, and what is the appropriate management strategy?**

No. There are no clinically relevant food-drug interaction.

The cross-study PK comparison (fasted study vs fed study) showed that the exposures ($C_{max}$ and $AUC_{inf}$) of dextroamphetamine are similar following administration of lisdexamfetamine oral solution under fasted and fed conditions (Table 3). The median (range) Tmax of

dextroamphetamine was delayed for an hour under fed conditions compared to fasted conditions (approximately 4.4 (3.00 to 6.00) vs 3.4 (2.00 to 6.00)), which is consistent with the LD's label.

**Table 3. Statistical Comparison of the PK of Dextroamphetamine Under Fed and Fasted Conditions Following the Administration of Lisdexamfetamine Oral Solution**

| PK Parameters | Fed[1] | Fasted[1] | Fed/Fasting Ratio[3] |
|---|---|---|---|
| $C_{max}$(ng/mL) | 68.04 (19.69) | 72.61 (18.69) | 0.96 (0.83 - 1.14) |
| $T_{max}$[2](h) | 4.45 (3.00 – 6.00) | 3.42 (2.00 – 6.00) | - |
| $AUC_t$(ng.h/mL) | 1260.10 (26.20) | 1444.17 (27.60) | 0.87 (0.82 - 1.32) |
| $AUC_{inf}$(ng.h/mL) | 1296.12 (26.19) | 1479.12 (27.61) | 0.89 (0.82 - 1.32) |

[1] Reported as geometric mean (geometric CV%)
[2] Reported as median (range)
[3] Values are displayed as geometric mean ratios (GMR, T/R) and 90% CIs around GMRs.
AUC=area under the curve; $C_{max}$=peak plasma concentration; $T_{max}$=time post dose to reach peak plasma concentration
*Source: Reviewer's analysis*

Given that the PK bridging between the proposed product and LD was adequately established under both fasted state and fed state and the food effect on Tmax of dextroamphetamine (1 hour delay in Tmax under the fed state compared to the fasted state) was similar between the proposed product and LD, the impact of food on the PK of the proposed product is considered minimal. Therefore, the proposed product, lisdexamfetamine oral solution can be administered with or without food similar to the LD.

# 7 Sources of Clinical Data and Review Strategy

## 7.1. Table of Clinical Studies

This 505(b)(2) NDA consists of two studies: (b) (4) 2793 and (b) (4) 2794. See Table 1 for a description of each study.

**Table 4. Listing of Clinical Trials Relevant to this NDA/BLA**

| Trial Identity | Trial Design | Regimen/ schedule/ route | Study Endpoints | Treatment Duration/ Follow Up | No. of patients enrolled | Study Population | No. of Centers and Countries |
|---|---|---|---|---|---|---|---|
| ***Controlled Studies to Support Efficacy and Safety*** | | | | | | | |
| (b) (4) 2793 | Randomized, open-label, two-way crossover | 7 mL of 10mg/mL lisdexamfetamine dimesylate oral solution 10mg/mL versus Vyvanse (lisdexamfetamine dimesylate) capsules 70mg | Comparative bioavailability of dextroamphetamine under fasting conditions | Single dose | 32 | Healthy male and female subjects ages 18 to 55 years | Single center |
| (b) (4) 2794 | Randomized, open-label, two-way crossover | 7 mL of 10mg/mL lisdexamfetamine dimesylate oral solution 10mg/mL versus Vyvanse (lisdexamfetamine dimesylate) capsules 70mg | Comparative bioavailability of dextroamphetamine under fed conditions | Single dose | 32 | Healthy male and female subjects ages 18 to 55 years | Single center |

## 7.2. Review Strategy

As noted previously, the Applicant relies on the Agency's findings of safety and effectiveness from the LD and did not conduct any efficacy studies. The clinical review provides a brief overview of the submitted bioavailability (BA) study trial designs.

This review focuses on the safety information from comparative BA studies (b) (4) 2793 and (b) (4) 2794. The safety review included evaluation of adverse events, vital sign parameters, laboratory assessments, and use of concomitant medications in the BA studies. The major objective of the clinical review was to assess whether there are safety findings associated with this oral solution that are different from the safety profile of the LD.

# 8 Statistical and Clinical and Evaluation

## 8.1. Review of Relevant Individual Trials Used to Support Efficacy

### 8.1.1. (b) (4) 2793

**Trial Design**

(b) (4) 2793 (Study 2793) was conducted with a randomized, single-dose, open-label, two-way, crossover design to assess the comparative bioavailability of dexamphetamine from lisdexamfetamine dimesylate oral solution 10 mg/mL and lisdexamfetamine dimesylate capsules 70 mg (Vyvanse) under fasting conditions. The study was designed to expose all participants to each condition: 7 mL of 10 mg/mL lisdexamfetamine dimesylate oral solution (Treatment A) and 70mg lisdexamfetamine dimesylate (Vyvanse) capsules (Treatment B). Participants were randomly assigned to a treatment sequence. Participants served as their own controls in the study. The lisdexamfetamine dimesylate dose administered in each treatment condition was 70 mg once daily. Participants remained in the study facility from at least 10 hours prior to each drug administration until after the 24-hour blood sample collection in each study period. Participants were asked to come back to the clinical facility for return visits. The treatment phases were separated by a washout interval of at least 7 (± 3 hours) days.

Healthy, male and non-pregnant, non-lactating female non-smokers (for at least 6 months prior to first drug administration) between 18 to 55 years of age (inclusive) were eligible to participate in the study.

Select inclusion criteria:

- Systolic blood pressure (SBP) between 95 and 140 mmHg, inclusive, and diastolic blood pressure (DBP) between 55 and 90 mmHg, inclusive, and heart rate (HR) between 50 and 100 beats per minute (bpm), inclusive

- Body mass index (BMI) between 18.5 and 30.0 kg/m2 (inclusive).

Select exclusion criteria:

- Clinically significant history or presence of any clinically significant gastrointestinal pathology (e.g., chronic diarrhea, inflammatory bowel disease), unresolved gastrointestinal symptoms (e.g., diarrhea, vomiting), or other conditions known to interfere with the absorption, distribution, metabolism or excretion of the drug experienced within 7 days prior to first study drug administration, as determined by the PI/Sub-Investigator.

- Known history or presence of:

  - Alcohol abuse or dependence within 1 year prior to first study drug administration
  - Drug abuse or dependence
  - Family history of sudden death or ventricular arrhythmia
  - Hypersensitivity or idiosyncratic reaction to amphetamine products, lisdexamfetamine dimesylate, its excipients, and/or related substances
  - Food allergies
  - Presence of any dietary restrictions unless deemed by the PI/Sub-I as "Not Clinically Significant"
  - Severe allergic reactions (e.g., anaphylactic reactions, angioedema).

- Females who had used implanted, injected, intravaginal, or intrauterine hormonal contraceptive within 6 months prior to first study drug administration.
- Females who had taken oral or transdermal hormonal contraceptives within 30 days prior to first study drug administration.
- Use of any enzyme-modifying drugs and/or other products, including strong inhibitors of cytochrome P450 (CYP) enzymes (e.g., cimetidine, fluoxetine, quinidine, erythromycin, ciprofloxacin, fluconazole, ketoconazole, diltiazem and HIV antivirals) and strong inducers of CYP enzymes (e.g., barbiturates, carbamazepine, glucocorticoids, phenytoin, St. John´s Wort, and rifampicin) within 30 days prior to first study drug administration.
- Use of any monoamine oxidase (MAO) inhibitors (e.g., phenelzine, tranylcypromine) within 30 days prior to first study drug administration.
- Use of serotonergic drugs such as SSRIs, SNRIs, triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, or busipirone within 30 days prior to first study drug administration.
- Use of any urinary alkalinizing agents (e.g., sodium bicarbonate, acetazolamide), or urinary acidifying agents (e.g., ammonium chloride, sodium acid phosphate, methenamine salts) within 30 days prior to first study drug administration.
- Use of any prescription medication within 14 days prior to first study drug administration.

- Use of any over-the-counter medications (including oral multivitamins, herbal and/or dietary supplements) within 14 days prior to first study drug administration (except for spermicidal/barrier contraceptive products).

- Consumption of food or beverages containing grapefruit and/or pomelo within 10 days prior to first study drug administration.

- Consumption of food or beverages containing caffeine/methylxanthines, poppy seeds and/or alcohol within 48 hours before dosing in each study period.

Screening assessments are outlined in Table 5.

Participants were discontinued from the study if they experienced emesis within 7 hours after dosing. Participants experiencing three or more episodes of loose stool (diarrhea) after dosing were to be evaluated for discontinuation on a case-by-case basis by the PI/Sub-Investigator, Pharmacokinetics staff and the Sponsor.

***Clinical Reviewer Comment:*** *The study eligibility criteria are appropriate for the objectives of this phase 1 study.*

**Study Endpoints**

Pharmacokinetic endpoints for concentration of lisdexamfetamine and dextroamphetamine included $AUC_{0\text{-}1.5h}$, $AUC_{0\text{-}4h}$, $AUC_{1.5\text{-}4h}$, $AUC_{4\text{-}13h}$, $AUC_{4\text{-}t}$, $AUC_{13\text{-}24h}$, $C_{max}$, $T_{max}$, $AUC_t$, $AUC_{inf}$, $T_{1/2}$, and λ/Kel/Lambda.

Taste was evaluated via a five-item questionnaire immediately after dosing and at 10 ± 2 minutes after the dose of lisdexamfetamine dimesylate oral solution 10 mg/mL.

Safety assessments included vital signs measurement (seated BP, HR, RR, and temperature), clinical laboratory tests (including hematology, urine analysis, serum chemistry), pregnancy test (females only), physical examinations and adverse events. A schedule of study assessments is outlined in Table 5.

**Table 5. Study 2793 Schedule of Events**

| Procedure/Activity | Time points | | | |
|---|---|---|---|---|
| | **Screening** | **Period 1** | **Period 2** | **Post-Study** |
| Study ICF | X | | | |
| Medical History | X | | | |
| BMI | X | | | |
| ECG | X | | | |
| Vital Signs (BP, HR, RR and temperature) | X | | | X |
| Physical Exam | X | | | X |
| Laboratory Testing | X | | | X |
| Drugs of Abuse | X | $X_a$ | $X_a$ | |
| Breath Alcohol Test | X | $X_a$ | $X_a$ | |
| Urine Cotinine | X | $X_a$ | $X_a$ | |
| Pregnancy Test[#] | X | $X_a$ | $X_a$ | |
| Inclusion/Exclusion Assessment | X | | | |
| Vital Signs (BP & HR) | | $X_b$ | $X_b$ | |
| Restrictions Compliance Check | | $X_c$ | $X_c$ | |
| Study Drug Administration | | X | X | |
| PK Blood Sampling | | $X_d$ | $X_d$ | |
| Organoleptic Evaluation | | $X_e$ | $X_e$ | |
| Adverse Event Reporting | | $X_f$ | $X_f$ | X |
| Meals | | $X_g$ | $X_g$ | |
| Safety Screening for COVID-19 | $X_h$ | $X_h$ | $X_h$ | $X_h$ |

#- Serum pregnancy at screening and Urine pregnancy at check-in.

a. At check-in only.
b. Vital signs measurements (BP and HR) were obtained at pre-dose, and at 2, 6, 13, 24, 36, 48 and 72 after dosing in each study period.

c. Confirmed at check-in and each ambulatory blood draw, if applicable.
d. PK sampling - At pre-dose (within 90 minutes prior to dosing), and at 0.08, 0.17, 0.33, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.33, 2.67, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 7.00, 8.00, 10.00, 13.00, 16.00, 24.00, 36.00, 48.00 and 72.00 hours post-dose.
e. An Organoleptic Evaluation questionnaire was conducted immediately after dosing and at 10 ± 2 minutes after administration of test drug in each study period
f. Pre-dose conditions at Period 1 check-in and confirmed at each check-in and each ambulatory blood draw, if applicable.
g. Meals were served at check-in and approximately at 4.5, 9.5 and 13.5 hours after dosing.
h. COVID-19 screening questionnaire was completed, and temperature was checked on each study visit.

ICF=informed consent document; BMI=body mass index; ECG=electrocardiogram; BP=blood pressure; HR=heart rate; RR=respiratory rate
*Source:* (b) (4) *2793 Study Report, Table 9-2, pp. 40-41.*

**Statistical Analysis Plan**

The Applicant calculated descriptive statistics of all pharmacokinetic parameters (min, max, median, mean, standard deviation, and coefficient of variability) for the test and reference products. The Applicant transformed parameters for $AUC_{0\text{-}1.5h}$, $AUC_{1.5\text{-}4h}$, $AUC_{4\text{-}13h}$, $AUC_{13\text{-}24h}$, $AUC_{0\text{-}4h}$, $AUC_{4\text{-}t}$, $AUC_{inf}$, $AUC_t$, and $C_{max}$ prior to analysis using a natural logarithmic transformation. The Applicant performed ANOVA including sequence, subjects nested within sequence, period and treatment on the ln-transformed data for $AUC_{0\text{-}1.5}$, $AUC_{1.5\text{-}4}$, $AUC_{4\text{-}13}$, $AUC_{13\text{-}24}$, $AUC_{0\text{-}4}$, $AUC_{4\text{-}t}$, $AUC_{inf}$, $AUC_t$, and $C_{max}$ and analyzed $T_{max}$ using an additional non-parametric test (Wilcoxon test). The 90% confidence intervals (CIs) of the test/reference ratios of geometric means for $AUC_{0\text{-}1.5}$, $AUC_{1.5\text{-}4}$, $AUC_{4\text{-}13}$, $AUC_{13\text{-}24}$, $AUC_{0\text{-}4}$, $AUC_{4\text{-}t}$, $AUC_{inf}$, $AUC_t$, and $C_{max}$ were calculated based on the least square means and estimate of the ANOVA.

Comparative bioavailability was concluded if the 90% CIs for test/reference geometric mean ratios for $AUC_{0\text{-}4}$, $AUC_{4\text{-}t}$, $AUC_{inf}$, and $C_{max}$ were within the range of 80% to 125%.

No interim analyses were performed on the data. No subgroup analyses were performed. See Section 6 Clinical Pharmacology for discussion of PK methodology.

**Protocol Amendments**

There were no major protocol amendments, only minor updates to the protocol (i.e., typographical edits).

### 8.1.2. Study Results

**Compliance with Good Clinical Practices**

In their clinical study report, the Applicant states that the study was conducted in compliance with the applicable parts of the United States Code of Federal Regulations, Guidelines for Good Clinical Practice (21 CFR Parts 50 and 56), Good Clinical Practices and International Conference on Harmonization (ICH) Guidelines, Division 5 of the Canadian Food and Drug Regulations, as

well as Company Policies, Protocols, Standard Operating Procedures and study designs.

**Financial Disclosure**

See 15.2 of this review for detailed financial disclosure information. There are no disclosed financial interests or arrangements or missing disclosures that raise questions about the integrity of study data.

**Patient Disposition**

The Applicant enrolled 32 subjects (16 subjects per treatment sequence). In Period 1, 32 subjects were dosed; 28 subjects were dosed in Period 2. Only the 28 subjects who completed both treatment periods were included in the pharmacokinetic and statistical analyses. Of the four subjects excluded from the analysis, one subject withdrew due to an adverse event (arthralgia); two were withdrawn due to being "no show"; and one was dismissed by the primary investigator due to an adverse event (urinary retention).

**Protocol Violations/Deviations**

There were several protocol violations/deviations, all of which involved vital signs being measured outside of the ±30-minute window. These protocol violations are not expected to impact the PK results.

**Table of Demographic Characteristics**

See Table 6 for a summary of demographic and baseline characteristics among subjects who received treatment.

**Table 6. Baseline Demographic Characteristics of Subjects Completing Study 2793**

| **Demographic Parameters** | **Treatment Group** (N=28) |
|---|---|
| **Sex** | |
| Male | 17 |
| Female | 11 |
| **Age** | |
| Mean years (SD) | 39 (10) |
| Median (years) | 36 |
| Min, max (years) | 24, 55 |
| **Age Group** | |
| < 65 years | 28 |
| ≥ 65 years | 0 |
| **Race** | |
| White | 15 |
| Black or African American | 9 |
| Asian | 4 |
| American Indian or Alaska Native | 0 |

| | |
|---|---|
| Native Hawaiian or Other Pacific Islander | 0 |
| **Ethnicity** | |
| Hispanic or Latino | 5 |
| Not Hispanic or Latino | 23 |

*Source: Clinical Study Report, Study 2793.*

**Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)**

Subjects were excluded for health conditions or use of concomitant medications within various timeframes of dosing, as described above.

**Treatment Compliance, Concomitant Medications, and Rescue Medication Use**

According to the Applicant, all subjects were dosed in the presence of the investigator. No concomitant or rescue medications were administered.

**Efficacy Results – Primary Endpoint**

Efficacy data were not collected in this study. The Applicant proposes to rely on the Agency's prior findings of effectiveness and safety for the LD with a PK bridge to lisdexamfetamine dimesylate capsules; see Section 6 for PK results.

Based on the PK and statistical analysis, the Applicant was able to demonstrate that the 90% confidence intervals for the geometric mean ratios of PK parameters of dextroamphetamine ($C_{max}$, $AUC_{last}$, and $AUC_{inf}$) across treatments are within the regulatory criteria of 80% to 125% under fed conditions. Lisdexamfetamine dimesylate oral solution 10mg/mL (Test Product) and Vyvanse capsules (Reference Product) demonstrate comparable bioavailability under fasted conditions.

**Data Quality and Integrity**

The data quality was acceptable for review.

### 8.1.3. Study (b) (4) 2794

**Trial Design**

(b) (4) 2794 (Study 2794) was conducted with a randomized, single-dose, open-label, two-way, crossover design to assess the comparative bioavailability of dexamphetamine from lisdexamfetamine dimesylate oral solution 10 mg/mL and lisdexamfetamine dimesylate capsules 70 mg (Vyvanse) under fed conditions. The study was designed to expose all participants to each condition: 7 mL of 10mg/mL lisdexamfetamine dimesylate oral solution (Treatment A) and 70 mg lisdexamfetamine dimesylate (Vyvanse) capsules (Treatment B). Participants were randomly assigned to a treatment sequence (i.e., AB or BA). Participants served as their own controls in the study. The lisdexamfetamine dimesylate dose administered

in each treatment condition was 70 mg once daily. Participants remained in the study facility from at least 10 hours prior to each drug administration until after the 24-hour blood sample collection in each study period. Participants were asked to come back to the clinical facility for return visits. The treatment phases were separated by a washout interval of at least 7 (± 3 hours) days.

Healthy, male and non-pregnant, non-lactating female non-smokers (for at least 6 months prior to first drug administration) between 18 to 55 years of age (inclusive) were eligible to participate in the study.

Select inclusion criteria:

- SBP between 95 and 140 mmHg, inclusive, and DBP between 55 and 90 mmHg, inclusive, and HR between 50 and 100 bpm, inclusive

- BMI between 18.5 and 30.0 kg/m2 (inclusive).

Select exclusion criteria:

- Clinically significant history or presence of any clinically significant gastrointestinal pathology (e.g., chronic diarrhea, inflammatory bowel disease), unresolved gastrointestinal symptoms (e.g., diarrhea, vomiting), or other conditions known to interfere with the absorption, distribution, metabolism or excretion of the drug experienced within 7 days prior to first study drug administration, as determined by the PI/Sub-Investigator.

- Known history or presence of:

    - Alcohol abuse or dependence within 1 year prior to first study drug administration

    - Drug abuse or dependence

    - Family history of sudden death or ventricular arrhythmia

    - Hypersensitivity or idiosyncratic reaction to amphetamine products, lisdexamfetamine dimesylate, its excipients, and/or related substances

    - Food allergies

    - Presence of any dietary restrictions unless deemed by the PI/Sub-I as “Not Clinically Significant”

    - Severe allergic reactions (e.g., anaphylactic reactions, angioedema)

- Females who had used implanted, injected, intravaginal, or intrauterine hormonal contraceptive within 6 months prior to first study drug administration.

- Females who had taken oral or transdermal hormonal contraceptives within 30 days prior to first study drug administration.

- Use of any enzyme-modifying drugs and/or other products, including strong inhibitors of cytochrome P450 (CYP) enzymes (e.g., cimetidine, fluoxetine, quinidine, erythromycin, ciprofloxacin, fluconazole, ketoconazole, diltiazem and HIV antivirals) and strong inducers of CYP enzymes (e.g., barbiturates, carbamazepine, glucocorticoids, phenytoin, St. John´s Wort, and rifampicin) within 30 days prior to first study drug administration.

- Use of any monoamine oxidase (MAO) inhibitors (e.g., phenelzine, tranylcypromine) within 30 days prior to first study drug administration.

- Use of serotonergic drugs such as SSRIs, SNRIs, triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, or busipirone within 30 days prior to first study drug administration.

- Use of any urinary alkalinizing agents (e.g., sodium bicarbonate, acetazolamide), or urinary acidifying agents (e.g., ammonium chloride, sodium acid phosphate, methenamine salts) within 30 days prior to first study drug administration.

- Use of any prescription medication within 14 days prior to first study drug administration.

- Use of any over-the-counter medications (including oral multivitamins, herbal and/or dietary supplements) within 14 days prior to first study drug administration (except for spermicidal/barrier contraceptive products).

- Consumption of food or beverages containing grapefruit and/or pomelo within 10 days prior to first study drug administration.

- Consumption of food or beverages containing caffeine/methylxanthines, poppy seeds and/or alcohol within 48 hours before dosing in each study period.

Screening assessments are outlined in Table 7.

Participants were discontinued from the study if they experienced emesis within 7 hours after dosing. Participants experiencing three or more episodes of loose stool (diarrhea) after dosing were to be evaluated for discontinuation on a case-by-case basis by the PI/Sub-Investigator, Pharmacokinetics staff and the Sponsor.

***Clinical Reviewer Comment****: The study eligibility criteria are appropriate for the objectives of this phase 1 study.*

**Study Endpoints**

Pharmacokinetic endpoints for concentration of lisdexamfetamine and dextroamphetamine included $AUC_{0\text{-}1.5}$, $AUC_{0\text{-}4}$ , $AUC_{1.5\text{-}4}$, $AUC_{4\text{-}13}$, $AUC_{4\text{-}t}$, $AUC_{13\text{-}24}$, $C_{max}$, $T_{max}$, $AUC_t$, $AUC_{inf}$, $T_{1/2}$, and λ/Kel/Lambda.

Taste was evaluated via a five-item questionnaire immediately after dosing and at 10 ± 2 minutes after the dose of lisdexamfetamine dimesylate oral solution 10 mg/mL.

Safety assessments included vital signs measurement (seated BP, HR, respiratory rate (RR), and temperature), clinical laboratory tests (including hematology, urine analysis, serum chemistry), pregnancy test (females only), physical examinations, and adverse events. A schedule of study assessments is outlined in Table 7.

**Table 7. Study 2794 Schedule of Events**

| Procedure/Activity | Time points | | | |
|---|---|---|---|---|
| | **Screening** | **Period 1** | **Period 2** | **Post-Study** |
| Study ICF | X | | | |
| Medical History | X | | | |
| BMI | X | | | |
| ECG | X | | | |
| Vital Signs (BP, HR, RR and temperature) | X | | | X |
| Physical Exam | X | | | X |
| Laboratory Testing | X | | | X |
| Drugs of Abuse | X | $X_a$ | $X_a$ | |
| Breath Alcohol Test | X | $X_a$ | $X_a$ | |
| Urine Cotinine | X | $X_a$ | $X_a$ | |
| Pregnancy Test[#] | X | $X_a$ | $X_a$ | |
| Inclusion/Exclusion Assessment | X | | | |
| Vital Signs (BP & HR) | | $X_b$ | $X_b$ | |
| Restrictions Compliance Check | | $X_c$ | $X_c$ | |
| Study Drug Administration | | X | X | |
| PK Blood Sampling | | $X_d$ | $X_d$ | |
| Organoleptic Evaluation | | $X_e$ | $X_e$ | |
| Adverse Event Reporting | | $X_f$ | $X_f$ | X |
| Meals | | $X_g$ | $X_g$ | |
| Safety Screening for COVID-19 | $X_h$ | $X_h$ | $X_h$ | $X_h$ |

#- Serum pregnancy at screening and Urine pregnancy at check-in.

a. At check-in only.
b. Vital signs measurements (BP and HR) were obtained at pre-dose, and at 2, 6, 13, 24, 36, 48 and 72 after dosing in each study period.

c. Confirmed at check-in and each ambulatory blood draw, if applicable.
d. PK sampling: At pre-dose (within 90 minutes prior to dosing), and at 0.08, 0.17, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 13, 16, 24, 36, 48, and 72 hours post-dose.
e. An Organoleptic Evaluation questionnaire was conducted immediately after dosing and at 10 ± 2 minutes after administration of test drug in each study period
f. Pre-dose conditions at Period 1 check-in and confirmed at each check-in and each ambulatory blood draw, if applicable.
g. Meals were served at check-in and approximately at 4.5, 9.5, and 13.5 hours after dosing.
h. COVID-19 screening questionnaire was completed, and temperature was checked on each study visit.

ICF=informed consent document; BMI=body mass index; ECG=electrocardiogram; BP=blood pressure; HR=heart rate; RR=respiratory rate
*Source: (b) (4) 2794 Study Report, Table 9-3, pp. 42-43.*

**Statistical Analysis Plan**

The Applicant calculated descriptive statistics of all pharmacokinetic parameters (min, max, median, mean, standard deviation, and coefficient of variability) for the test and reference products. The Applicant transformed parameters for $AUC_{0\text{-}1.5}$, $AUC_{1.5\text{-}4}$, $AUC_{4\text{-}13}$, $AUC_{13\text{-}24}$, $AUC_{0\text{-}4}$, $AUC_{4\text{-}t}$, $AUC_{inf}$, $AUC_t$, and $C_{max}$ prior to analysis using a natural logarithmic transformation. The Applicant performed ANOVA including sequence, subjects nested within sequence, period and treatment on the ln-transformed data for $AUC_{0\text{-}1.5h}$, $AUC_{1.5\text{-}4h}$, $AUC_{4\text{-}13h}$, $AUC_{13\text{-}24h}$, $AUC_{0\text{-}4h}$, $AUC_{4\text{-}t}$, $AUC_{inf}$, $AUC_t$, and $C_{max}$ and analyzed $T_{max}$ using an additional non-parametric test (Wilcoxon test). The 90% confidence intervals (CIs) of the test/reference ratios of geometric means for $AUC_{0\text{-}1.5h}$, $AUC_{1.5\text{-}4h}$, $AUC_{4\text{-}13h}$, $AUC_{13\text{-}24h}$, $AUC_{0\text{-}4h}$, $AUC_{4\text{-}t}$, $AUC_{inf}$, $AUC_t$, and $C_{max}$ were calculated based on the least square means and estimate of the ANOVA.

Comparative bioavailability was concluded if the 90% CIs for test/reference geometric mean ratios for $AUC_{0\text{-}4}$, $AUC_{4\text{-}t}$, $AUC_{inf}$, and $C_{max}$ were within the range of 80% to 125%.

No interim analyses were performed on the data. No subgroup analyses were performed. See Section 6 Clinical Pharmacology for discussion of PK methodology.

**Protocol Amendments**

There were no major protocol amendments.

### 8.1.4. Study (b) (4) 2794

**Compliance with Good Clinical Practices**

In their clinical study report, the Applicant states that the study was conducted in compliance with the applicable parts of the United States Code of Federal Regulations, Guidelines for Good Clinical Practice (21 CFR Parts 50 and 56), Good Clinical Practices and International Conference on Harmonization (ICH) Guidelines, Division 5 of the Canadian Food and Drug Regulations, as well as Company Policies, Protocols, Standard Operating Procedures and study designs.

**Financial Disclosure**

See Section 15.2 of this review for detailed financial disclosure information. There are no disclosed financial interests or arrangements or missing disclosures that raise questions about the integrity of study data.

**Patient Disposition**

The Applicant enrolled 32 subjects (16 subjects per treatment sequence). All subjects completed the study.

**Protocol Violations/Deviations**

Several protocol violations/deviations occurred. Two subjects missed blood sample collections due to being "no show" (36 hours for one subject and 36 and 72 hours for the other). Multiple subjects had vital signs measured beyond the ±30-minute window. During Period 2, one subject spilled approximately 10 to 15 ml of the dosing water on his shirt while drinking the dosing water. One subject completed the taste evaluation out of the ± 2 minutes time window (1 minute late), 10 minutes after dosing.

Most of these protocol violations are not expected to impact the PK results. The protocol violations involving missed blood draws would be most likely to impact PK results, compared with the other violations. However, these time points lie beyond the absorption phase of the study drug lisdexamfetamine and its metabolite dextroamphetamine; therefore, they would not impact the $C_{max}$/$T_{max}$ estimation. The Applicant states that the missing samples may have slightly impacted AUCs estimation in these subjects in Period 1, but states the results are still within the reported variability. The Applicant believes that despite these missed blood draws, the PK profiles were still sufficiently characterized, and there was no impact on the overall study outcome.

***Clinical Reviewer Comment****: These protocol deviations are unlikely to have significantly impacted the study results.*

**Table of Demographic Characteristics**

See Table 8 for a summary of demographic and baseline characteristics among subjects who received treatment.

**Table 8. Baseline Demographic Characteristics of Subjects Who Completed Study 2794**

| Demographic Parameters | **Treatment Group** (N=32) |
|---|---|
| **Sex** | |
| Male | 22 |
| Female | 10 |
| **Age** | |
| Mean years (SD) | 41 (11) |
| Median (years) | 43 |
| Min, max (years) | 22, 55 |
| **Age Group** | |
| < 65 years | 32 |
| ≥ 65 years | 0 |
| **Race** | |
| White | 18 |
| Black or African American | 9 |
| Asian | 5 |
| American Indian or Alaska Native | 0 |
| Native Hawaiian or Other Pacific Islander | 0 |
| **Ethnicity** | |
| Hispanic or Latino | 8 |
| Not Hispanic or Latino | 24 |

*Source: Clinical Study Report, Study 2794.*

**Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)**

Subjects were excluded for health conditions or use of concomitant medications within various timeframes of dosing, as described above.

**Treatment Compliance, Concomitant Medications, and Rescue Medication Use**

According to the Applicant, all subjects were dosed in the presence of the investigator. There were no concomitant or rescue medications.

**Efficacy Results – Primary Endpoint**

Efficacy data were not collected in this study. The Applicant proposes to rely on the Agency's prior findings of effectiveness and safety for the LD with a PK bridge to lisdexamfetamine dimesylate capsules; see Section 6 for PK results.

Based on the PK and statistical analysis, the Applicant was able to demonstrate that the 90% confidence intervals for the geometric mean ratios of PK parameters of dextroamphetamine ($C_{max}$, $AUC_{last}$, and $AUC_{inf}$) across treatments are within the regulatory criteria of 80% to 125% under fed conditions. Lisdexamfetamine dimesylate oral solution 10 mg/mL (Test Product) and

Vyvanse capsules (Reference Product) demonstrate comparable bioavailability under fed conditions.

**Data Quality and Integrity**

The data quality was acceptable for review.

## 8.2. Review of Safety

### 8.2.1. Safety Review Approach

The Applicant proposes to rely on the Agency's prior findings for safety for the LD with a scientific bridge to lisdexamfetamine dimesylate capsules. The safety review is based on data from the two submitted bioavailability studies, (b) (4) 2793 and (b) (4) 2794. This review assesses whether the collected safety data are consistent with lisdexamfetamine dimesylate's known safety profile. Post-treatment safety assessments included vital signs measurement, clinical laboratory tests, physical examinations, and adverse events.

### 8.2.2. Review of the Safety Database

**Overall Exposure**

A total of 64 subjects were enrolled in the study and treated with at least one dose of lisdexamfetamine dimesylate 70 mg (either as an oral capsule or solution). Therefore, all subjects contributed tothe safety analysis population.

**Adequacy of the safety database**

The safety population included all participants who received a dose of study medication. The dose and duration of exposure to lisdexamfetamine dimesylate oral solution are considered adequate to obtain accurate assessment of bioequivalence and comparative bioavailability. The sample sizes for these BA studies are adequate for assessing formulation-specific safety issues.

### 8.2.3. Adequacy of Applicant's Clinical Safety Assessments

**Issues Regarding Data Integrity and Submission Quality**

The application was submitted in eCTD format. From a safety perspective, there are no issues regarding data integrity and submission quality.

**Categorization of Adverse Events**

The Applicant categorized adverse events (AEs) by system organ class and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA) Version 26.0. The Applicant collected AEs throughout each study period. The Applicant defined AEs as "any untoward

medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment." The Applicant also appropriately defined severity of AEs and serious AEs. All unresolved AEs were followed until resolution or for up to 1 week following completion of the study, after which the PI/Sub-investigator will decide the course of action. The protocol also including appropriate guidelines for reporting serious AEs. There were no specified AEs of special interest.

**Routine Clinical Tests**

Investigators assessed blood pressure and heart rate at screening; pre-dose; at 2, 6, 13, 24, 36, 48, and 72 after dosing in each study period; and post-study. Clinical safety laboratory tests (i.e., chemistry, hematology, urinalysis) were collected at screening and post-study. An electrocardiogram (ECG) was performed at baseline.

### 8.2.4. Safety Results

**Deaths**

The Applicant reported no deaths.

**Serious Adverse Events**

The Applicant reported no serious adverse events (SAEs).

**Dropouts and/or Discontinuations Due to Adverse Effects**

In Study 2793, two subjects discontinued the study due to AEs. One subject experienced arthralgia 73.5 hours after dosing with lisdexamfetamine dimesylate oral solution in Period 1 and withdrew due to arthralgia prior to Period 2. Another subject experienced the AE urinary retention 20.3 hours after dosing with lisdexamfetamine mesylate oral solution in Period 1. The investigator assessed this AE as moderate in severity and as possibly related to the study drug. The subject was assessed by an emergency physician at a local hospital and had a catheter placed for urine drainage. Subsequently, subject was also seen by a urologist and prescribed dutasteride 0.5 mg once a day. The AE resolved, but the subject was lost to follow up.

In Study 2794, no subjects withrew or were discontinued.

***Clinical Reviewer Comment*:** *The LD label does not list urinary retention as an adverse reaction. However, there are case reports of urinary retention associated with methamphetamine, another CNS stimulant (Ojo 2021). Increased sympathomimetic action may lead to induction of spinal reflex potentiation of urethral constriction, causing resistance against voiding of urine. Therefore, it is possible that this AE could be related to the study drug. However, the subject's prescription suggests that the urologist's evaluation identified an underlying cause other than an acute drug effect.*

**Significant Adverse Events**

The Applicant reported no significant adverse events.

**Treatment Emergent Adverse Events and Adverse Reactions (TEAEs)**

In Study 2793, 18 subjects (56%) reported a total of 52 adverse events. The Investigator rated 51 of these adverse events as mild and one (the event of urinary retention described above) as moderate. Thirteen subjects reported 25 AEs with lisdexamfetamine dimesylate oral solution; 13 subjects reported 27 adverse events with lisdexamfetamine dimesylate capsules.

**Table 9. Treatment Emergent Adverse Events in Study 2793**

| | | TRT | |
|---|---|---|---|
| **Body System or Organ Class** | **Dictionary-Derived Term** | **A (N=30) n (%)** | **B (N=30) n (%)** |
| Cardiac disorders | PALPITATIONS | 3 (10) | 1 (3) |
| Gastrointestinal disorders | ABDOMINAL PAIN | 0 | 1 (3) |
| | DRY MOUTH | 0 | 1 (3) |
| | NAUSEA | 0 | 1 (3) |
| Investigations | BLOOD PRESSURE INCREASED | 8 (26.7) | 8 (26.7) |
| | HEART RATE INCREASED | 10 (33.3) | 7 (23.3) |
| Musculoskeletal and connective tissue disorders | ARTHRALGIA | 1 (3) | 0 |
| Nervous system disorders | DIZZINESS | 0 | 2 (6.7) |
| | HEADACHE | 1 (3) | 3 (10) |
| | PARAESTHESIA | 0 | 1 (3) |
| Renal and urinary disorders | URINARY RETENTION | 1 (3) | 0 |

N = Number of subjects dosed for respective treatment; n = Number of subjects reporting at least one incidence of the respective adverse event
(%) = Percentage of subjects reporting at least one incidence of the respective adverse event
*Source: ADAE.xpt.*

In Study 2794, 16 subjects (%) reported a total of 36 adverse events. The Investigator rated all of these adverse events as mild. 11 subjects reported 20 AEs with lisdexamfetamine dimesylate oral solution; 10 subjects reported 16 adverse events with lisdexamfetamine dimesylate capsules.

**Table 10. Treatment Emergent Adverse Events in Study 2794**

| | | TRT | |
|---|---|---|---|
| **Body System or Organ Class** | **Dictionary-Derived Term** | **A (N=32) n (%)** | **B (N=32) n (%)** |
| Cardiac disorders | PALPITATIONS | 0 | 1 (3) |
| Gastrointestinal disorders | ABDOMINAL DISTENSION | 1 (3) | 0 |
| | DRY MOUTH | 1 (3) | 0 |
| General disorders and administration site conditions | CATHETER SITE PAIN | 1 (3) | 0 |
| | FEELING HOT | 1 (3) | 0 |
| Investigations | BLOOD BILIRUBIN INCREASED | 0 | 1 (3) |
| | BLOOD PRESSURE INCREASED | 7 (21.9) | 6 (18.8) |

| | | TRT | |
|---|---|---|---|
| **Body System or Organ Class** | **Dictionary-Derived Term** | **A (N=32) n (%)** | **B (N=32) n (%)** |
| | HEART RATE INCREASED | 3 (9.4) | 2 (6.3) |
| Metabolism and nutrition disorders | DECREASED APPETITE | 1 (3) | 0 |
| Nervous system disorders | DIZZINESS | 2 (6.3) | 0 |
| | HEADACHE | 0 | 3 (9.4) |
| | SOMNOLENCE | 2 (6.3) | 0 |
| Psychiatric disorders | EUPHORIC MOOD | 1 (3) | 0 |
| Renal and urinary disorders | URINARY HESITATION | 0 | 1 (3) |
| Respiratory, thoracic and mediastinal disorders | COUGH | 1 (3) | 0 |
| | RHINORRHOEA | 1 (3) | 0 |

N = Number of subjects dosed for respective treatment
n = Number of subjects reporting at least one incidence of the respective adverse event
(%) = Percentage of subjects reporting at least one incidence of the respective adverse event
*Source: ADAE.xpt.*

**Laboratory Findings**

The Applicant reported no AEs related to abnormal laboratory findings and no screening, or post-study laboratory results outside of normal range that were deemed clinically significant by the Investigator in Study 2793. In Study 2794, one subject experienced increased levels of total bilirubin (38 umol/L) after receiving the LD in Period 2. Repeat testing 5 days later showed showed a reduced bilirubin level, though still outside of normal range (27 umol/L). The Applicant reports no other screening or post-study laboratory results outside of normal range that were deemed clinically significant by the Investigator.

**Vital Signs**

Several subjects in both studies experienced AEs related to vital sign abnormalities.

Study 2793

In Study 2793, 8 subjects (26.7%) experienced "blood pressure increased" after dosing with lisdexamfetamine dimesylate oral solution; the same number (and percent) experienced this AE after dosing with the LD. More subjects experienced "heart rate increased" after taking lisdexamfetamine dimesylate oral solution (10 or 33.3%) than after the LD (7 or 23.3%). Both of these AEs occurred at higher rates in this study compared with what is described in the label of the LD (3% of adults with ADHD in a 4 week clinical trial). This may be due to the fact that in phase 3 clinical trials (and in practice), the LD is initiated at 30 mg and increased by 10 or 20 mg each week to reach 70 mg. In contrast, in this study (and in Study 2794), a single dose of 70 mg was administered to treatment naïve subjects.

The Applicant did not define abnormal vital signs or analyze shifts in vital signs. The protocol required subjects to have SBP between 95 and 140 mmHg; DBP between 55 and 90 mmHg; and heart rate between 50 and 100 bpm (all ranges inclusive).

Eleven subjects experienced DBP >90 mmHg during the study: seven subjects after receiving lisdexamfetamine dimesylate oral solution and ten subjects after the LD (six subjects after both). The highest measured DBP was 101 mmHg. Five subjects experienced DBP of 100 or 101 mmHg; two after dosing with lisdexamfetamine dimesylate oral solution and three after receiving the LD.

Twelve subjects experienced SBP >140 mmHg during the study: ten subjects after receiving lisdexamfetamine dimesylate oral solution and eight after the LD (six subjects after both). One subject experienced SBP >180 (consistent with hypertensive urgency, defined by SBP >180 mmHg or DBP >120 mmHg). That subject experienced SBP up to 205 mmHg 2 hours after receiving the LD. The same subject experienced SBP of 201 mmHg 2 hours after receiving lisdexamfetamine dimesylate oral solution. That subject had SBP of 139 mmHg at screening and 146 mmHg pre-dose in period 1 (prior to receiving any study drug).

Fifteen subjects experienced HR >100 bpm during the study: ten subjects after receiving lisdexamfetamine dimesylate oral solution and ten after the LD (five subjects after both). Twenty-seven subjects experienced an increase in HR ≥20 bpm between a pre-dose and post-dose timepoint: 21 subjects after receiving lisdexamfetamine dimesylate oral solution and 22 subjects after the LD (16 after both).

Study 2794

In Study 2794, 7 subjects (21.9%) experienced “blood pressure increased” after dosing with lisdexamfetamine dimesylate oral solution; six subjects (18.8%) experienced this AE after dosing with the LD. Three subjects experienced heart rate increased after taking lisdexamfetamine dimesylate oral solution (9.4%) compared with two after the LD (6.3%).

As in Study 2793, the Applicant did not define abnormal vital signs or analyze shifts in vital signs. The protocol for Study 2794 also required subjects to have SBP between 95 and 140 mmHg; DBP between 55 and 90 mmHg; and HR between 50 and 100 bpm (all ranges inclusive).

Six subjects experienced DBP >90 mmHg during the study: six subjects after receiving lisdexamfetamine dimesylate oral solution and four subjects after the LD (four subjects after both). The highest measured DBP was 108 mmHg. Two subjects experienced DBP >100 mmHg: one only after dosing with lisdexamfetamine dimesylate oral solution and one after dosing with both products.

Seven subjects experienced SBP >140 mmHg during the study: five subjects after receiving lisdexamfetamine dimesylate oral solution and four after the LD (two subjects after both). The highest measured SBP was 176 mmHg pre-dose in period 2, prior to dosing with lisdexamfetamine dimesylate oral solution. The same subject experienced SBP of 162 mmHg pre-dose in Period 1 and 173 mmHg at 13 hours post-dose with the LD in Period 1.

Seven subjects experienced HR >100 beats bpm during the study: five subjects after receiving lisdexamfetamine dimesylate oral solution and four after the LD (two subjects after both). Seventeen subjects experienced an increase in HR ≥20 bpm between a pre-dose and post-dose timepoint: twelve subjects after receiving lisdexamfetamine dimesylate oral solution and nine subjects after the LD (four after both).

**Electrocardiograms (ECGs)**

The Applicant did not report any abnormalities related to ECGs performed at screening. ECGs were not conducted at the end of the study.

**Immunogenicity**

The Applicant did not report any potentially immunogenicity-related AEs.

### 8.2.5. Analysis of Submission-Specific Safety Issues

The primary submission-specific safety issue was formulation-specific toxicity. There was no indication of AEs related to the formulation.

### 8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Not applicable.

### 8.2.7. Safety Analyses by Demographic Subgroups

The sample size was not large enough to perform subgroup analyses.

### 8.2.8. Specific Safety Studies/Clinical Trials

Not applicable.

### 8.2.9. Additional Safety Explorations

**Human Carcinogenicity or Tumor Development**

No new information about human carcinogenicity or tumor development was submitted in this application.

**Human Reproduction and Pregnancy**

No new information about human reproduction and pregnancy was submitted in this application. No participants became pregnant during the course of the studies.

**Pediatrics and Assessment of Effects on Growth**

No pediatric data were submitted with this application; see Section 10 for more information.

**Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

No analyses or assessments regarding overdose, drug abuse potential, withdrawal, or rebound were conducted in these studies. Our understanding of these areas are informed by the LD.

### 8.2.10. Safety in the Postmarket Setting

**Safety Concerns Identified Through Postmarket Experience**

The following adverse reactions have been identified and added to product labeling since the initial approval of the LD in 2007: cardiomyopathy, mydriasis, diplopia, difficulties with visual accommodation, blurred vision, eosinophilic hepatitis, anaphylactic reaction, hypersensitivity, dyskinesia, dysgeusia, motor and verbal tics, bruxism, depression, dermatillomania, alopecia, aggression, Stevens-Johnson syndrome, chest pain, angioedema, urticaria, seizures, libido changes, frequent or prolonged erections, constipation, rhabdomyolysis, and intestinal ischemia.

**Expectations on Safety in the Postmarket Setting**

The Applicant has demonstrated that lisdexamfetamine dimesylate oral solution has comparable bioavailability to the LD, Vyvanse (lisdexamfetamine dimesylate capsules). The postmarket safety profile is anticipated to be similar to that of the LD. Studies 2793 and 2794 were conducted in healthy volunteers with no experience taking CNS stimulants. With regard to vital signs, a more favorable profile would be expected in individuals with previous experience taking CNS stimulants and also with the titration schedule recommended in the label**.**

### 8.2.11. Integrated Assessment of Safety

The determination of safety for this product relies almost entirely on investigations conducted with lisdexamfetamine dimesylate capsules (the LD). A smaller amount of safety data was derived from bioavailability studies for this product. These data were analyzed for potential safety issues specific to the oral solution formulation that might differ from the LD. There were no apparent formulation-specific toxicities. There were high rates of vital sign elevation in both studies compared to what is described in the label of the LD. This is likely due to the lack of titration and the population of stimulant naïve subjects. The single case of urinary retention could not be adequately evaluated as the subject was lost to follow-up. However, the prescription given to the patient suggests that this AE may have been related to an underlying condition rather than an acute drug effect. Overall, this safety review has not identified any safety issues related to the oral solution formulation that would preclude the approval of this NDA or suggest a different safety risk than the LD.

## 8.3. Statistical Issues

This development program did not include efficacy studies that would be subject to statistical review. See Section 6 for a discussion of statistical issues related to PK comparison.

## 8.4. Conclusions and Recommendations

Results of the submitted studies indicate that lisdexamfetamine dimesylate oral solution has comparable bioavailability to the LD, lisdexamfetamine dimesylate capsules. The safety profile of lisdexamfetamine dimesylate oral solution is also consistent with that of lisdexamfetamine dimesylate capsules. Therefore, we recommend approval of this application.

# 9 Advisory Committee Meeting and Other External Consultations

This 505(b)(2) application relies on the findings of safety and efficacy of the LD. There were no questions for an Advisory Committee. No external consultations were needed for review of this application.

# 10 Pediatrics

No new pediatric data were submitted with this application; this application relies on the Agency's findings of safety and effectiveness for the LD, lisdexamfetamine dimesylate capsules. The LD has been adequately studied in well-controlled clinical trials in the following pediatric age groups: 4 to 5 years old, 6 to 12 years old, and 13 to 17 years old. This application triggered PREA because of the proposed new formulation (oral solution). The Applicant's iPSP was reviewed by the Pediatric Review Committee in October 2023. No additional pediatric trials will be required for this formulation. Pediatric labeling for the treatment of ADHD will be consistent with the LD. For more information, see Section 3.2: Summary of Presubmission/Submission Regulatory Activity.

# 11 Labeling Recommendations

## 11.1. Prescription Drug Labeling

Prescribing information

Labeling for lisdexamfetamine dimesylate oral solution is generally consistent with that of the LD. Dosage and administration guidelines have been expanded to account for new modes of administration. Pertinent differences between the labels for this product and the LD are described below.

Section 7 DRUG INTERACTIONS

- For Section 7.1, the order of information (prevention/management and mechanism/clinical effects) is revised for clarity. However, the contents are unchanged.

- For Section (b) (4), we removed this section. Only clinically significant drug interactions are described in Section 7.

12.3 PHARMACOKINETICS

- Contents in this section have been reorganized and revised to include relevant PK measures and parameters that are important for the safe and effective use of lisdexamfetamine dimesylate oral solution per the clinical pharmacology labeling guidance.

- The (b) (4) is replaced by the "Effect of Food" subheading and the effect of food on dextroamphetamine's PK is described inder this subheading.

14 CLINICAL STUDIES

The following paragraph was added to the beginning of this section to explain the basis for approval of this product:

> The efficacy of ARYNTA has been established based on adequate and well-controlled studies of oral lisdexamfetamine dimesylate in the treatment of adults and pediatric patients 6 years and older with ADHD and adults with moderate-to-severe binge eating disorder (BED). The information below describes the results of the adequate and well-controlled studies of oral lisdexamfetamine dimesylate in patients with ADHD and BED.

# 12 Risk Evaluation and Mitigation Strategies (REMS)

Not applicable. There were no findings in the clinical review of this application that suggested the need for REMS.

# 13 Postmarketing Requirements and Commitment

None.

# 14 Division Deputy Director (Clinical) Comments

This review reflects my edits and feedback. I agree with the findings as described by the review team and concur with the approval decision.

# 15 Appendices

## 15.1. References

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.).

Erskine HE, Whiteford HA. Epidemiology of binge eating disorder. Curr Opin Psychiatry 2018; 31:462–70.

Giel KE, Bulik CM, Fernandez-Aranda F, Hay P, Keski-Rahkonen A, Schag K, Schmidt U, Zipfel S. Binge eating disorder. Nature Reviews Disease Primers. 2022;8(1):16.

Keski-Rahkonen A. Epidemiology of binge eating disorder: prevalence, course, comorbidity, and risk factors. Curr Opin Psychiatry. 2021;34(6):525-31.

Ojo AO, Ajasa AL, Oladipupo, RB, and Aderinto, NO. Urinary retention concomitant with methamphetamine use: a case report. J Med Case Rep. 2021;15(1):183. doi:10.1186/s13256-021-02705-9

Streatfeild J, Hickson J, Austin SB, et al. Social and economic cost of eating disorders in the United States: evidence to inform policy action. Int J Eat Disord 2021; 54:851–68.

## 15.2. Financial Disclosure

**Covered Clinical Study (Name and/or Number):** (b) (4) 2793 and (b) (4) 2794

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ (Request list from Applicant) |
| Total number of investigators identified: 7 | | |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0 | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0 | | |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ | | |

| | | |
|---|---|---|
| Significant payments of other sorts: _____<br>Proprietary interest in the product tested held by investigator: _____<br>Significant equity interest held by investigator in S<br>Sponsor of covered study: _____ | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes ☐ | No ☐ (Request details from Applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes ☐ | No ☐ (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____ | | |
| Is an attachment provided with the reason: | Yes ☐ | No ☐ (Request explanation from Applicant) |

## 15.3. Nonclinical Pharmacology/Toxicology

Not applicable.

## 15.4. Clinical Pharmacology

**Bioanalytical Methods**

A liquid chromatography tandem mass spectrometry in positive ion mode (LC-MS/MS) method for determination of lisdexamfetamine and dextroamphetamine in human plasma was developed and validated for (b) (4)

**Table 11. Sample Analysis Results for Lisdexamfetamine**

| Analyte | | Lisdexamfetamine |
|---|---|---|
| Internal Standard (IS) | | Lisdexamfetamine-D4 (ISA) |
| Matrix | | Human plasma |
| Incurred Sample Reproducibility (ISR) | | ISR was performed using 194 subject samples. ISR showed 99.47% reproducibility for all calculable samples |
| Calibration | Range (ng/mL) | 0.15 to 60.00 ng/mL |
| | #Conc. points | 0.15, 0.30, 1.50, 3.00, 6.00, 12.00, 36.00, 54.00 and 60.00 ng/mL |
| | %CV (precision) | 2.2 to 6.7% |
| | %RE (bias) | -2.2 to 2.4% |

| | | |
|---|---|---|
| Quality Control | Concentrations | 0.45, 7.20, 14.40, 30.00 and 48.00 ng/mL<br>DQC 120.00 ng/mL |
| | %CV | 1.7 to 4.4% |
| | %Bias | -2.4 to 3.7% |
| Carryover effect | | No significant carryover was observed |
| Long-term Stability in Matrix Validated | | 181 days at -70°C ± 10°C |
| Short-term Stability in Matrix Validated | | LQC (0.45 ng/ml) and HQC (48 ng/ml)in ice-cold water bath and room temperature after 08 hrs and 03 mins, and 21 hrs and 49 mins, respectively. |
| Longest storage period | | 57 days at -70°C ± 10°C |
| Date Range of Bioanalytical Assays | | 32 days (22 December 2022 to 22nd January 2023) |

DQC = diluted quality control; LQC = low quality control; HQC = high quality control.
*Source: Adapted from the bioanalytical report for study 2793 and 2794.*

**Table 12. Sample Analysis Results for Dextroamphetamine (D-Amphetamine)**

| Analyte | | D-Amphetamine |
|---|---|---|
| Internal Standard (IS) | | (±)-Amphetamine-D5 (ISB) |
| Matrix | | Human plasma |
| Incurred Sample Reproducibility (ISR) | | ISR was performed using 194 subject samples. ISR showed 98.96% reproducibility for all calculable samples |
| Calibration | Range (ng/mL) | 0.40 to 160.00 ng/mL |
| | #Conc. points | 0.40, 0.80, 4.00, 8.00, 16.00, 32.00, 96.00, 144.00 and 160.00 ng/mL |
| | %CV (precision) | 1.8 to 7.5% |
| | %RE (bias) | -1.4 to 2.3% |
| Quality Control | Concentrations | 1.20, 19.20, 38.40, 80.00 and 128.00 ng/mL<br>DQC 320.00 ng/mL |
| | %CV | 1.4 to 6.9% |
| | %Bias | -3.3 to 1.5% |
| Carryover effect | | No significant carryover was observed |
| Long-term Stability in Matrix Validated | | 181 days at -70°C ± 10°C |

| | |
|---|---|
| Short-term Stability in Matrix Validated | LQC (1.20 ng/ml) and HQC (128.00 ng/ml) in room temperature after 2 hours followed by 93 hours at 5°C ± 3°C. |
| Longest storage period | 57 days at -70°C ± 10°C |
| Date Range of Bioanalytical Assays | 32 days (22 December 2022 to 22nd January 2023) |

*Source: Adapted from the bioanalytical report for study 2793 and 2794.*

The bioanalytical methods satisfy the criteria for "method validation" and "application to routine analysis" set by the Guidance for Industry, Bioanalytical Method Development (May 2018), and are acceptable.

**Summary of Clinical Pharmacology Study**

**Clinical study report 2793**

***Title:*** A Pivotal, Single-Dose, Randomized, Open-Label, Two-Way Crossover, Comparative Bioavailability Study of Lisdexamfetamine Didimesylate Oral Solution 10 mg/mL (Adalvo Limited) and Vyvanse (Lisdexamfetamine Didimesylate) Capsule 70 mg (Takeda Pharmaceuticals USA Inc.) in Healthy, Male and Non-Pregnant and Non-Lactating Female Volunteers under Fasting Conditions.

***Primary Objectives:***

- Assess the comparative bioavailability of dextroamphetamine from lisdexamfetamine didimesylate oral solution 10 mg/mL and lisdexamfetamine didimesylate capsules 70 mg (Vyvanse) – RLD Sample in healthy, non-smoking, males and non-pregnant, non-lactating female volunteers under fasting conditions.

***Secondary Objectives:***

- Assess the safety and tolerability of both the formulations on the basis of clinical and laboratory examination, documentation of the Adverse Events (AEs) and/or Adverse Drug Reactions (ADRs).
- Evaluate palatability/organoleptic properties of the Test product.

***Study Design***:

- A pivotal, single-dose, randomized, open-label, two-period, two-sequence, two-treatment, single-center, crossover study.
- The study scheme was as follows:

| | Period 1 | Period 2 |
|---|---|---|
| Sequence 1 | A | B |
| Sequence 2 | B | A |

*Source: Clinical study protocol for Study 2973, p. 23.*

***Treatments Administered:***

- **Treatment A (Test):** 7 mL of lisdexamfetamine didimesylate oral solution 10 mg/mL (Adalvo Limited)
- **Treatment B (Reference):** 1 x Vyvanse (lisdexamfetamine didimesylate) Capsule 70 mg (Takeda Pharmaceuticals USA Inc.)

***Pharmacokinetic Sampling:*** PK sampling at pre-dose (within 90 minutes prior to dosing), and at 0.08, 0.17, 0.33, 0.5, 0.75, 1, 1.25, 1.50, 1.75, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 13, 16, 24, 36, 48, and 72 hours post-dose.

***Results:***

*Subject Disposition*

**Table 13. Demographic for Subjects Included in the Dataset**

| | Age (years) | Height (cm) | Height (in) | Weight (kg) | Weight (lb) | BMI (Kg/m²) | Ethnicity | Race | |
|---|---|---|---|---|---|---|---|---|---|
| **Mean** | 39 | 170.9 | 67.3 | 75.1 | 165.6 | 25.6 | Hispanic/ Latino | White | 5 |
| **+/- SD** | 10 | 9.3 | 3.6 | 12.6 | 27.8 | 3.0 | Not Hispanic/ Latino | White | 10 |
| **Median** | 36 | 170.7 | 67.2 | 75.0 | 165.2 | 25.9 | | Black/ African American | 9 |
| **Range** | 24-55 | 153.0-188.5 | 60.2-74.2 | 52.4-97.0 | 115.5-213.8 | 18.6-29.9 | | Asian | 4 |

*Source: Study 2793 report, Table 11-2, p. 56.*

- The study enrolled 32 subjects and 28 subjects completed the study and had PK blood sampling for both periods.
- Among the 28 subjects that completed the study, there were 11 females and 17 males.
- Four subjects were discontinued during the study period. Two of them were discontinued because of AEs and two of them withdrew from the study (details shown in table below).

**Table 14. Discontinued Subjects**

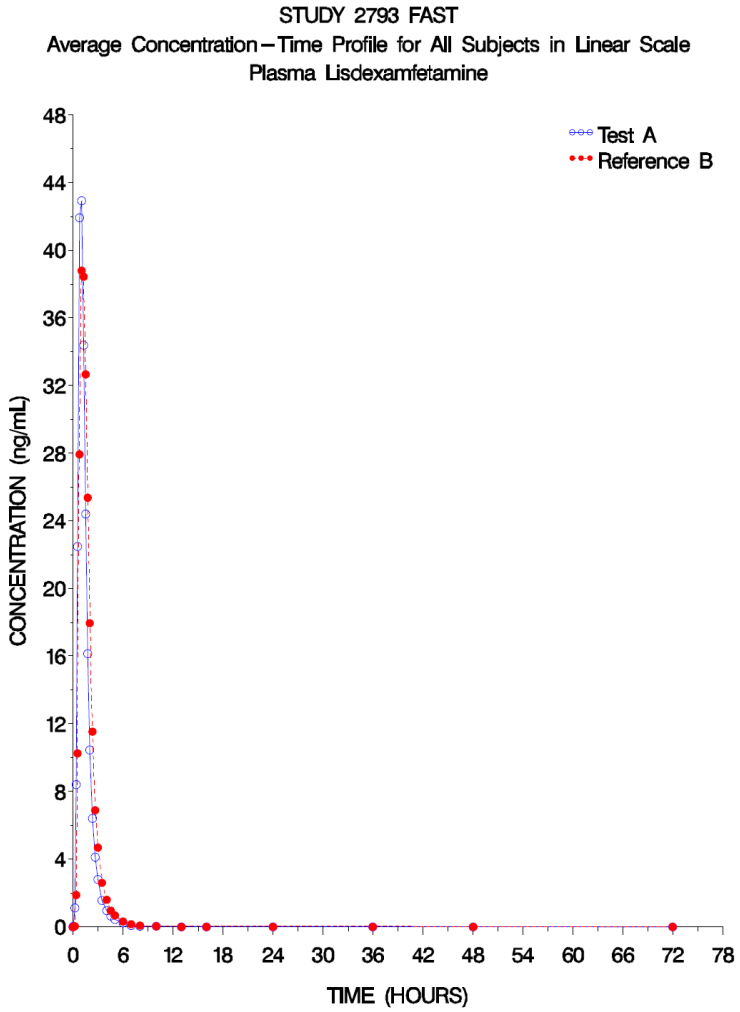
| Subject | Sequence | Last Treatment Administered | Reason | Phase of Dropout |
|---|---|---|---|---|
| (b) (6) | AB | A | Withdrew due to AE (arthralgia) | Prior to Period 2 check-in |
| | BA | B | Withdrew due to being No show | Period 2 check-in |
| | AB | A | Dismissed by PI due to AE (urinary retention) | Period1 |
| | BA | B | Withdrew due to being No show | P2 check-in |

In this relative bioavailability study under fasted conditions, the geometric mean ratios (GMRs) and 90% confidence intervals (CI) around GMRs of PK parameters of lisdexamfetamine and

dextroamphetamine are within the regulatory criteria of 80% to 125%. For lisdexamfetamine, the GMRs (90% CI) of peak plasma concentration ($C_{max}$) and area under the plasma concentration-time curve ($AUC_{inf}$) are 1.01 (0.96 – 1.08) and 0.93 (0.89 – 1.01)), respectively. The median time to reach $C_{max}$ ($T_{max}$) of lisdexamfetamine following administration of lisdexamfetamine oral solution and the LD under fasted condition is approximately 0.89 hours and 1.13 hours, respectively. The median $T_{max}$ of lisdexamfetamine following administration of lisdexamfetamine oral solution and the LD under fasted condition is approximately 1.59 hours and 2.54 hours, respectively.

The mean concentration-time profile and PK parameters of lisdexamfetamine are presented below (Figure 3 and Table 15). The PK parameters of dextroamphetamine are presented in Table 16.

**Figure 3. Mean Plasma Concentration Profile for Lisdexamfetamine Following the Administration of 70 mg Lisdexamfetamine Didimesylate Capsule and 70 mg Lisdexamfetamine Didimesylate Oral Solution Under Fasted Condition.**




*Source: Study 2793 report, Figure 14-1, p. 85.*

**Table 15. Plasma Pharmacokinetic Parameters of Lisdexamfetamine Following Single Oral Dose Administration of Lisdexamfetamine Oral Solution vs Vyvanse Capsule under Fasted Conditions**

| PK Parameters (unit) | Treatment A (Test) | Treatment B (Reference) |
|---|---|---|
| **$C_{max}$ (ng/mL)** | 46.31 (44.63) | 45.73 (39.68) |
| **$T_{max}$* (h)** | 0.89 (0.50 – 1.27) | 1.13 (0.75 – 1.75) |
| **$AUC_t$ (ng.h/mL)** | 56.08 (39.90) | 60.05 (43.84) |
| **$AUC_{inf}$ (ng.h/mL)** | 56.60 (39.91) | 60.57 (43.95) |
| **$AUC_{0\text{-}1.5h}$ (ng.h/mL)** | 39.05 (45.33) | 32.85 (37.51) |
| **$AUC_{1.5\text{-}4h}$ (ng.h/mL)** | 15.82 (46.03) | 26.15 (63.58) |
| **$AUC_{0\text{-}4h}$ (ng.h/mL)** | 54.87 (38.68) | 59.69 (34.71) |
| **$AUC_{4\text{-}t}$ (ng.h/mL)** | 1.21 (77.21) | 1.89 (114.05) |

[1] Reported as geometric mean (geometric CV%)
[2] Reported as median (range)
[3] Values are displayed as geometric mean ratios (GMR, T/R) and 90% CIs around GMRs.
AUC=area under the curve; $C_{max}$=peak plasma concentration; $T_{max}$=time post dose to reach peak plasma concentration.
*Source: Reviewer's analysis and Applicant's study report for Study 2973, Appendix 16.2.6.1.5, p. 43.*

**Table 16. Plasma Pharmacokinetic Parameters of Dextroamphetamine Following Single Oral Dose Administration of Lisdexamfetamine Oral Solution vs Vyvanse Capsule Under Fasted Conditions**

| PK Parameters (unit) | Treatment A (Test)[1] | Treatment B (Reference)[1] | T/R Ratio[3] |
|---|---|---|---|
| **$C_{max}$ (ng/mL)** | 72.61 (18.69) | 71.75 (15.84) | 1.01 (0.970. – 1.04) |
| **$T_{max}$[2] (h)** | 3.42 (2.00 – 6.00) | 3.70 (1.75 – 6.00) | - |
| **$AUC_t$ (ng.h/mL)** | 1444.17 (27.60) | 1456.98 (26.05) | 0.98 (0.95 – 1.02) |
| **$AUC_{inf}$ (ng.h/mL)** | 1479.12 (27.61) | 1492.39 (26.04) | 0.98 (0.95 – 1.02) |
| **$AUC_{0\text{-}1.5h}$ (ng.h/mL)** | 24.09 (42.75) | 15.63 (61.70) | 1.66 (1.33 – 2.06) |
| **$AUC_{1.5\text{-}4h}$ (ng.h/mL)** | 158.37 (21.49) | 147.77 (18.43) | 1.06 (1.01 – 1.12) |
| **$AUC_{0\text{-}4h}$ (ng.h/mL)** | 182.46 (23.24) | 163.40 (20.97) | 1.10 (1.04 – 1.18) |
| **$AUC_{4\text{-}t}$ (ng.h/mL)** | 1261.71 (29.96) | 1293.58 (28.16) | 0.97 (0.93 – 1.01) |

[1] Reported as geometric mean (geometric CV%)
[2] Reported as median (range)
[3] Values are displayed as geometric mean ratios (GMR, T/R) and 90% CIs around GMRs.
AUC=area under the curve; $C_{max}$=peak plasma concentration; $T_{max}$=time post dose to reach peak plasma concentration.
*Source: Reviewer's analysis and Applicant's study report for Study 2973, Appendix 16.2.6.1.5, p. 43.*

Partial AUCs for lisdexamfetamine and dextroamphetamine were assessed as part of the exploratory analysis. Previous clinical study suggested that dextroamphetamine achieves its maximum efficacy in adults at around 4 hours post-dose (NDA 208510 Vyvanse label). Given that the $AUC_{0\text{-}4h}$ of dextroamphetamine is approximately 10% relatve to the $AUC_t$ and the T/R ratio of $AUC_{0\text{-}4h}$ falls within the regulatory criteria, the differences in the initial partial AUCs are not considered clinically significant.

**Clinical study report 2794**

***Title:*** A Pivotal, Single-Dose, Randomized, Open-Label, Two-Way Crossover, Comparative Bioavailability Study of Lisdexamfetamine Didimesylate Oral Solution 10 mg/mL (Adalvo Limited) and Vyvanse (Lisdexamfetamine Didimesylate) Capsule 70 mg (Takeda Pharmaceuticals USA Inc.) in Healthy, Male and Non-Pregnant and Non-Lactating Female Volunteers under Fed Conditions.

***Primary Objectives:***

- Assess the comparative bioavailability of dextroamphetamine from lisdexamfetamine didimesylate oral solution 10 mg/mL and lisdexamfetamine didimesylate capsules 70 mg (Vyvanse) – RLD Sample in healthy, non-smoking, males and non-pregnant, non-lactating female volunteers under fed conditions.

***Secondary Objectives:***

- Assess the safety and tolerability of both the formulations on the basis of clinical and laboratory examination, documentation of the Adverse Events (AEs) and/or Adverse Drug Reactions (ADRs);
- Evaluate palatability/organoleptic properties of the Test product.

***Study Design***:

- A pivotal, single-dose, randomized, open-label, two-period, two-sequence, two-treatment, single-center, crossover study.
- The study scheme was as follows:

| | Period 1 | Period 2 |
|---|---|---|
| Sequence 1 | A | B |
| Sequence 2 | B | A |

*Source: Clinical study protocol for Study 2974, p. 27.*

***Treatments Administered:***

**Treatment A (Test):** 7 mL of lisdexamfetamine dimesylate oral solution 10 mg/mL (Adalvo Limited)
**Treatment B (Reference):** 1 x Vyvanse (lisdexamfetamine dimesylate) capsule 70 mg (Takeda Pharmaceuticals USA Inc.)

***Pharmacokinetic Sampling:*** PK sampling at pre-dose (within 90 minutes prior to dosing), and at 0.08, 0.17, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 13, 16, 24, 36, 48, and 72 hours post-dose.

***Results:***

*Subject Disposition*

**Table 17. Demographic for Subjects Included in the Dataset**

| | Age (years) | Height (cm) | Height (in) | Weight (kg) | Weight (lb) | BMI ($Kg/m^2$) | Ethnicity | Race | |
|---|---|---|---|---|---|---|---|---|---|
| **Mean** | 41 | 171.3 | 67.5 | 75.9 | 167.3 | 25.7 | Hispanic/ Latino | White | 8 |
| **+/- SD** | 11 | 9.5 | 3.7 | 13.8 | 30.4 | 2.7 | Not Hispanic/ Latino | White | 10 |
| **Median** | 43 | 170.8 | 67.2 | 78.0 | 171.8 | 25.6 | | Black/ African American | 9 |
| **Range** | 22-55 | 153.5-197.5 | 60.4-77.8 | 55.5-109.5 | 122.4-241.4 | 20.0-29.9 | | Asian | 5 |

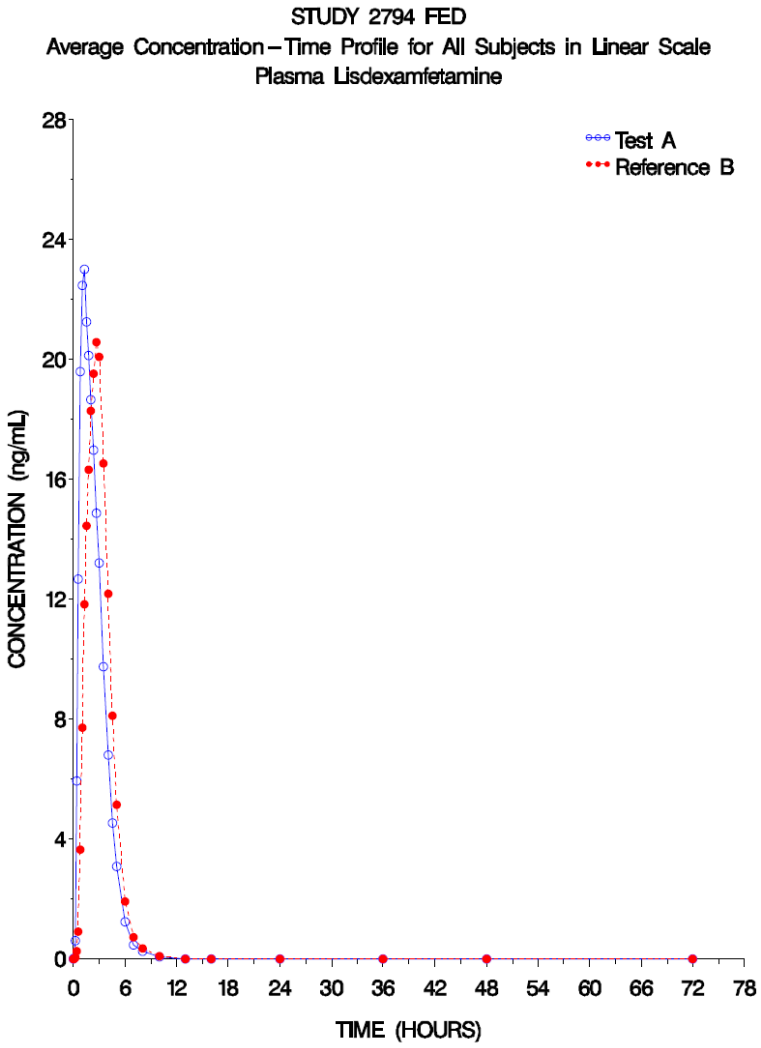
*Source: Study 2794 report, Table 11-2, p. 61.*

- The study enrolled 32 subjects and 32 subjects completed the study and had PK blood sampling for both periods.
- Among the 32 subjects that completed the study, there were 10 females and 22 males.

Similar to the results under fasted condition, a relative bioavailability study conducted under fed conditions showed similar exposures for lisdexamfetamine between lisdexamfetamine dimesylate solution and lisdexamfetamine dimesylate capsule. The GMRs (90% CI) for lisdexamfetamine of $C_{max}$ and $AUC_{inf}$ are 1.01 (0.98 – 1.04) and 1.02 (0.98 – 1.06), respectively.

The mean concentration-time profile and PK parameters of lisdexamfetamine are presented in Figure 4 and Table 18. The PK parameters of dextroamphetamine are presented in Table 19.

**Figure 4. Mean Plasma Concentration Profile for Lisdexamfetamine Following the Administration of 70 mg Lisdexamfetamine Dimesylate Capsule and 70 mg Lisdexamfetamine Dimesylate Oral Solution Under Fed Condition.**




*Source: Study 2794 report, Figure 14-1, p. 85.*

**Table 18. Plasma Pharmacokinetic Parameters of Lisdexamfetamine Following Single Oral Dose Administration of Lisdexamfetamine Oral Solution vs Vyvanse Capsule**

| PK Parameters (unit) | Treatment A (Test)[1] | Treatment B (Reference)[1] |
|---|---|---|
| **$C_{max}$ (ng/mL)** | 29.23 (38.92) | 28.91 (30.33) |
| **$T_{max}$[2] (h)** | 1.59 (0.50 – 3.50) | 2.54 (1.00 – 4.50) |
| **$AUC_t$ (ng.h/mL)** | 66.67 (34.11) | 66.06 (29.66) |
| **$AUC_{inf}$ (ng.h/mL)** | 67.07 (34.03) | 65.52 (29.65) |
| **$AUC_{0\text{-}1.5h}$ (ng.h/mL)** | 22.62 (55.22) | 7.78 (98.07) |
| **$AUC_{1.5\text{-}4h}$ (ng.h/mL)** | 35.78 (41.00) | 44.44 (34.56) |
| **$AUC_{0\text{-}4h}$ (ng.h/mL)** | 58.40 (37.23) | 51.91 (33.07) |
| **$AUC_{4\text{-}t}$ (ng.h/mL)** | 8.27 (93.23) | 14.10 (81.68) |

[1] Reported as geometric mean (geometric CV%)
[2] Reported as median (range)
AUC=area under the curve; $C_{max}$=peak plasma concentration; $T_{max}$=time post dose to reach peak plasma concentration.
*Source: Reviewer's analysis and Applicant's study report for Study 2974, Appendix 16.2.6.1.5, p. 43.*

**Table 19. Plasma Pharmacokinetic Parameters of Dextroamphetamine Following Single Oral Dose Administration of Lisdexamfetamine Oral Solution vs Vyvanse Capsule**

| PK Parameters (unit) | Treatment A (Test)[1] | Treatment B (Reference)[1] | T/R Ratio[3] |
|---|---|---|---|
| $C_{max}$ (ng/mL) | 68.04 (19.69) | 68.92 (19.69) | 0.98 (0.96 – 1.01) |
| $T_{max}$[2] (h) | 4.45 (3.00 – 6.00) | 4.88 (2.00 – 7.03) | - |
| $AUC_t$ (ng.h/mL) | 1260.10 (26.20) | 1261.65 (25.72) | 0.99 (0.97 – 1.02) |
| $AUC_{inf}$ (ng.h/mL) | 1296.12 (26.19) | 1296.66 (25.74) | 0.99 (0.97 – 1.02) |
| $AUC_{0\text{-}1.5h}$ (ng.h/mL) | 16.57 (41.89) | 2.79 (117.70) | 5.93 (4.29 – 8.21) |
| $AUC_{1.5\text{-}4h}$ (ng.h/mL) | 124.73 (21.57) | 87.61 (38.81) | 1.42 (1.27 – 1.60) |
| $AUC_{0\text{-}4h}$ (ng.h/mL) | 142.63 (22.06) | 91.71 (41.74) | 1.55 (1.37 – 1.76) |
| $AUC_{4\text{-}t}$ (ng.h/mL) | 1069.22 (33.98) | 1119.91 (30.94) | 0.95 (0.93 – 0.98) |

[1] Reported as geometric mean (geometric CV%)
[2] Reported as median (range)
[3] Values are displayed as geometric mean ratios (GMR, T/R) and 90% CIs around GMRs.
AUC=area under the curve; Cmax=peak plasma concentration; Tmax=time post dose to reach peak plasma concentration.
*Source: Reviewer's analysis and Applicant's study report for Study 2974, Appendix 16.2.6.2.5, p. 158.*

Partial AUCs for lisdexamfetamine and dextroamphetamine were assessed as part of the exploratory analysis. The results for the fed state are similar to the fasted state. Given that the $AUC_{0\text{-}4h}$ of dextroamphetamine is approximately 10% relatve to the $AUC_t$ and the T/R raio of $AUC_{0\text{-}4h}$ falls within the regulatory criteria, the differences in the initial partial AUCs are not considered clinically significant.

## 15.5. Additional Clinical Outcome Assessment Analyses

Not applicable.

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