CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

202827Orig1s000

Trade Name:	Lisdexamfetamine Dimesylate Capsules, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg.
Sponsor:	Hikma Pharmaceuticals USA Inc
Approval Date:	August 25, 2023

CENTER FOR DRUG EVALUATION AND RESEARCH

202827Orig1s000

CONTENTS

Reviews / Information Included in this ANDA Review.

Approval Letter	**X**
Other Action Letters	**X**
Labeling	**X**
Labeling Review(s)	**X**
Bioequivalence Review(s)	**X**
Chemistry Review(s)	**X**
Clinical Pharmacology/Biopharmaceutics Review(s)	
Other Reviews	
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202827Orig1s000

APPROVAL LETTER

ANDA 202827

ANDA APPROVAL

Hikma Pharmaceuticals USA Inc.
1809 Wilson Road
Columbus, OH 43228
Attention: George E. Prestash IV
Associate Director, Regulatory Affairs

Dear George E. Prestash IV:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on February 23, 2011, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Lisdexamfetamine Dimesylate Capsules, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg.

Reference is also made to the tentative approval letter issued by this office on June 23, 2014, the complete response letter issued by this office on December 15, 2022, and to any amendments thereafter.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug meets the requirements for approval under the FD&C Act. Accordingly the ANDA is **approved**, effective on the date of this letter. We have determined your Lisdexamfetamine Dimesylate Capsules, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg, to be bioequivalent and therapeutically equivalent to the reference listed drug (RLD), Vyvanse Capsules, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg, of Takeda Pharmaceuticals U.S.A., Inc.

Please note that if FDA requires a Risk Evaluation and Mitigation Strategy (REMS) for a listed drug, an ANDA referencing that listed drug also will be required to have a REMS. See section 505-1(i) of the FD&C Act.

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standard for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise

official USP monographs. More information on the USP-NF is available on USP's website at: https://www.uspnf.com/.

REQUIREMENTS AND RECOMMENDATIONS POST APPROVAL

Under applicable statutes, regulations, and guidances, your ANDA may be subject to certain requirements and recommendations post approval, including requirements regarding changes to approved ANDAs, postmarketing reporting, promotional materials, and annual facility fees, among others. For information on post-approval requirements and recommendations for ANDAs and a list of resources for ANDA holders, we refer you to: https://www.fda.gov/drugs/abbreviated-new-drug-application-anda/requirements-and-resources-approved-andas.

Sincerely yours,

{See appended electronic signature page}

For Edward M. Sherwood
Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

Catherine Poole

Digitally signed by Catherine Poole
Date: 8/25/2023 08:49:11AM
GUID: 5407887a000a1c0c26055eafb8e3258a

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205692Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 202827

Roxane Laboratories, Inc.
Attention: Anton Amann, Ph.D.
Executive Director, Drug Regulatory Affairs
1809 Wilson Road
Columbus, OH 43228

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated February 23, 2011, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Lisdexamfetamine Dimesylate Capsules, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg.

Reference is made to the Complete Response letter issued by this office on October 24, 2013, and to your amendments dated February 13, April 4, May 22, May 23, and June 18, 2014.

We have completed the review of this ANDA, and based upon the information you have presented to date we have concluded that the drug is safe and effective for use as recommended in the submitted labeling. However, we are unable to grant final approval to your ANDA at this time because of the patent issue noted below. Therefore, the ANDA is **tentatively approved**. This determination is based upon information available to the agency at this time (i.e., information in your ANDA and the status of current good manufacturing practice (cGMP) at the facilities used in the manufacturing and testing of the drug product) and is therefore subject to change on the basis of new information that may come to our attention. This letter does not address issues related to the 180-day exclusivity provisions under section 505(j)(5)(B)(iv) of the Act.

The reference listed drug (RLD) upon which you have based your ANDA, Vyvanse Capsules, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg, of Shire Development Inc., is subject to periods of patent protection. The following patents and expiration dates are currently listed in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"):

U.S. Patent Number	Expiration Date
7,105,486 (the '486 patent)	June 29, 2023
7,223,735 (the '735 patent)	June 29, 2023
7,655,630 (the '630 patent)	February 24, 2023
7,659,253 (the '253 patent)	February 24, 2023
7,659,254 (the '254 patent)	February 24, 2023
7,662,787 (the '787 patent)	February 24, 2023
7,662,788 (the '788 patent)	February 24, 2023
7,671,030 (the '030 patent)	February 24, 2023
7,671,031 (the '031 patent)	February 28, 2023
7,674,774 (the '774 patent)	March 18, 2023
7,678,770 (the '770 patent)	March 25, 2023
7,678,771 (the '771 patent)	March 25, 2023
7,687,466 (the '466 patent)	February 24, 2023
7,687,467 (the '467 patent)	April 8, 2023
7,700,561 (the '561 patent)	June 29, 2023
7,713,936 (the '936 patent)	February 24, 2023
7,718,619 (the '619 patent)	February 24, 2023
7,723,305 (the '305 patent)	February 24, 2023

With respect to the '788 and '936 patents, the agency notes that these patents were listed in the Orange Book after submission of your ANDA for all strengths.

Your ANDA contains paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the Act stating that each of these patents is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Lisdexamfetamine Dimesylate Capsules 20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg under this ANDA. You have notified the agency that Roxane Laboratories, Inc. (Roxane) complied with the requirements of section 505(j)(2)(B) of the Act, and that litigation was brought against Roxane for infringement of the '486, '735, '630, '253, '254, '787, '030, '031, '774, '770, '771, '466, '467, '561, '619, and '305 patents in the United States District Court for the District of New Jersey [Shire LLC, and Shire Development Inc. v. Roxane Laboratories, Inc., Civil Action No. 2:2011-cv-03866].

Therefore, final approval cannot be granted until:

1. a. the expiration of the 7½-year period provided for in sections 505(j)(5)(B)(iii) and 505(j)(5)(F)(ii)[1],

[1] The agency notes that the '030, '619, '305, '774, '771, and '467 patents were listed in the Orange Book for the 20 mg strength after submission of your ANDA and therefore cannot serve as the basis for a stay of approval for the 20 mg strength.

b. the date the court decides[2] that the '486, '735, '630, '253, '254, '787, '030, '031, '774, '770, '771, '466, '467, '561, '619, and '305 patents are invalid or not infringed (see sections 505(j)(5)(B)(iii)(I), (II), and (III) of the Act), or

c. the listed patents have expired, and

2. The agency is assured there is no new information that would affect whether final approval should be granted.

Please note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the Act.

To reactivate your ANDA prior to final approval, please submit a "MINOR AMENDMENT – FINAL APPROVAL REQUESTED" 90 days prior to the date you believe that your ANDA will be eligible for final approval. This amendment should provide the legal/regulatory basis for your request for final approval and should include a copy of a court decision, or a settlement or licensing agreement, as appropriate. It should also identify changes, if any, in the conditions under which the ANDA was tentatively approved, i.e., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made, and it should be designated clearly in your cover letter as a MINOR AMENDMENT – FINAL APPROVAL REQUESTED.

In addition to the amendment requested above, the agency may request at any time prior to the date of final approval that you submit an additional amendment containing the requested information. Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your ANDA, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this ANDA as well as changes in the status of the manufacturing and testing facilities' cGMPs are subject to agency review before

[2] This decision may be either a decision of the district court or the court of appeals, whichever court is the first to decide that the patents (excluding the '030, '619, '305, '774, '771, and '467 patents for the 20 mg strength) are invalid or not infringed.

final approval of the ANDA will be made. Such changes should be categorized as representing either "major" or "minor" changes, and they will be reviewed according to OGD policy in effect at the time of receipt. The submission of multiple amendments prior to final approval may also result in a delay in the issuance of the final approval letter.

This drug product may not be marketed without final agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under section 301 of the Act. Also, until the agency issues the final approval letter, this drug product will not be deemed to be approved for marketing under section 505 of the Act, and will not be listed in the "Orange Book."

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self-identification or fee payment.

Additionally, we note that the failure of any facility referenced in the application to self-identify and pay applicable fees means that FDA will not consider the GDUFA application review goal dates to apply to that application.

For further information on the status of this ANDA, or prior to submitting additional amendments, please contact Andrew Kim, Project Manager, at (240) 402-8983.

Sincerely yours,

{See appended electronic signature page}

Kathleen Uhl, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT L WEST

06/23/2014

Deputy Director, Office of Generic Drugs, for
Kathleen Uhl, M.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202827Orig1s000

LABELING

Each capsule contains: Lisdexamfetamine dimesylate 20 mg (equivalent to 11.6 mg lisdexamfetamine).

SEE PACKAGE INSERT FOR DOSAGE INFORMATION.

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP.

Distributed by: **Hikma Pharmaceuticals USA Inc.**
Berkeley Heights, NJ 07922

NDC 0054-**0370**-13 30 Capsules

Lisdexamfetamine Dimesylate
Capsules

CII

20 mg

PHARMACIST: Medication Guide to be dispensed to patients.

℞ **only**

hikma.

3 N 0054-0370-13 8

c50001161/01

Each capsule contains: Lisdexamfetamine dimesylate 20 mg (equivalent to 11.6 mg lisdexamfetamine).

SEE PACKAGE INSERT FOR DOSAGE INFORMATION.

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP.

Distributed by: **Hikma Pharmaceuticals USA Inc.**
Berkeley Heights, NJ 07922

NDC 0054-**0370**-25 100 Capsules

Lisdexamfetamine Dimesylate C II

Capsules

20 mg

PHARMACIST: Medication Guide to be dispensed to patients.

℞ only

hikma.

3 N 0054-0370-25 1

c50001162/01

Each capsule contains:
Lisdexamfetamine dimesylate 30 mg (equivalent to 17.3 mg lisdexamfetamine).

SEE PACKAGE INSERT FOR DOSAGE INFORMATION.

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP.

Distributed by: **Hikma Pharmaceuticals USA Inc.**
Berkeley Heights, NJ 07922

NDC 0054-**0371**-13 30 Capsules

Lisdexamfetamine Dimesylate
Capsules

CII

30 mg

PHARMACIST: Medication Guide to be dispensed to patients.

R_x only

hikma.

3 N 0054-0371-13 5

c50001163/01

Each capsule contains:
Lisdexamfetamine dimesylate 30 mg (equivalent to 17.3 mg lisdexamfetamine).

SEE PACKAGE INSERT FOR DOSAGE INFORMATION.

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP.

Distributed by: **Hikma Pharmaceuticals USA Inc.**
Berkeley Heights, NJ 07922

NDC 0054-**0371**-25 100 Capsules

Lisdexamfetamine Dimesylate
Capsules

CII

30 mg

PHARMACIST: Medication Guide to be dispensed to patients.

℞ **only**

hikma.

3 N 0054-0371-25 8

c50001164/01

Each capsule contains: Lisdexamfetamine dimesylate 40 mg (equivalent to 23.1 mg lisdexamfetamine).

SEE PACKAGE INSERT FOR DOSAGE INFORMATION.

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP.

Distributed by: **Hikma Pharmaceuticals USA Inc.**
Berkeley Heights, NJ 07922

NDC 0054-**0372**-13 30 Capsules

Lisdexamfetamine Dimesylate
Capsules

CII

40 mg

PHARMACIST: Medication Guide to be dispensed to patients.

℞ only

hikma.

3 0054-0372-13 2

c50001165/01

Each capsule contains: Lisdexamfetamine dimesylate 40 mg (equivalent to 23.1 mg lisdexamfetamine).

SEE PACKAGE INSERT FOR DOSAGE INFORMATION.

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP.

Distributed by: **Hikma Pharmaceuticals USA Inc.**
Berkeley Heights, NJ 07922

NDC 0054-**0372**-25 100 Capsules

Lisdexamfetamine Dimesylate
Capsules

CII

40 mg

PHARMACIST: Medication Guide to be dispensed to patients.

℞ only

hikma.

3 N 0054-0372-25 5

c50001166/01

Each capsule contains: Lisdexamfetamine dimesylate 50 mg (equivalent to 28.9 mg lisdexamfetamine).

SEE PACKAGE INSERT FOR DOSAGE INFORMATION.

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled RoomTemperature].

Dispense in a tight, light-resistant container as defined in the USP.

Distributed by: **Hikma Pharmaceuticals USA Inc.**
Berkeley Heights, NJ 07922

NDC 0054-**0373**-13 30 Capsules

Lisdexamfetamine Dimesylate
Capsules

CII

50 mg

PHARMACIST: Medication Guide to be dispensed to patients.

R_x only

hikma.

3 N 0054-0373-13 9

c50001167/01

Each capsule contains: Lisdexamfetamine dimesylate 50 mg (equivalent to 28.9 mg lisdexamfetamine).

SEE PACKAGE INSERT FOR DOSAGE INFORMATION.

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP.

Distributed by: **Hikma Pharmaceuticals USA Inc.**
Berkeley Heights, NJ 07922

NDC 0054-**0373**-25 100 Capsules

Lisdexamfetamine Dimesylate

C II

Capsules

50 mg

PHARMACIST: Medication Guide to be dispensed to patients.

℞ only

hikma.

3 0054-0373-25 2

c50001168/01

Each capsule contains:
Lisdexamfetamine dimesylate 60 mg (equivalent to 34.7 mg lisdexamfetamine).

SEE PACKAGE INSERT FOR DOSAGE INFORMATION.

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP.

Distributed by: **Hikma Pharmaceuticals USA Inc.**
Berkeley Heights, NJ 07922

NDC 0054-**0374**-13 30 Capsules

Lisdexamfetamine Dimesylate
Capsules

CII

60 mg

PHARMACIST: Medication Guide to be dispensed to patients.

℞ **only**

hikma.

3 N 0054-0374-13 9

c50001169/01

Each capsule contains: Lisdexamfetamine dimesylate 60 mg (equivalent to 34.7 mg lisdexamfetamine).

SEE PACKAGE INSERT FOR DOSAGE INFORMATION.

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP.

Distributed by: **Hikma Pharmaceuticals USA Inc.**
Berkeley Heights, NJ 07922

NDC 0054-**0374**-25 100 Capsules

Lisdexamfetamine Dimesylate CII

Capsules

60 mg

PHARMACIST: Medication Guide to be dispensed to patients.

℞ only

hikma.

c50001170/01

Each capsule contains:
Lisdexamfetamine dimesylate 70 mg (equivalent to 40.5 mg lisdexamfetamine).

SEE PACKAGE INSERT FOR DOSAGE INFORMATION.

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP.

Distributed by: **Hikma Pharmaceuticals USA Inc.**
Berkeley Heights, NJ 07922

NDC 0054-**0375**-13 30 Capsules

Lisdexamfetamine Dimesylate
Capsules

CII

70 mg

PHARMACIST: Medication Guide to be dispensed to patients.

℞ **only**

hikma.

3 N 0054-0375-13 3

c50001171/01

Each capsule contains: Lisdexamfetamine dimesylate 70 mg (equivalent to 40.5 mg lisdexamfetamine).

SEE PACKAGE INSERT FOR DOSAGE INFORMATION.

Store a at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP.

Distributed by: **Hikma Pharmaceuticals USA Inc.**
Berkeley Heights, NJ 07922

NDC 0054-**0375**-25 100 Capsules

Lisdexamfetamine Dimesylate CII

Capsules

70 mg

PHARMACIST: Medication Guide to be dispensed to patients.

℞ only

hikma.

3 N 0054-0375-25 9

c50001172/01

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LISDEXAMFETAMINE DIMESYLATE CAPSULES safely and effectively. See full prescribing information for LISDEXAMFETAMINE DIMESYLATE CAPSULES.

LISDEXAMFETAMINE DIMESYLATE capsules, for oral use, CII
Initial U.S. Approval: 2007

WARNING: ABUSE AND DEPENDENCE

See full prescribing information for complete boxed warning.

- **CNS stimulants, including lisdexamfetamine dimesylate, other amphetamine-containing products, and methylphenidate have a high potential for abuse and dependence (5.1, 9.3)**
- **Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy (5.1, 9.2)**

---------- RECENT MAJOR CHANGES ----------

Indications and Usage (1)	7/2021
Warnings and Precautions (5.5)	7/2021

---------- INDICATIONS AND USAGE ----------

Lisdexamfetamine dimesylate capsules are a central nervous system (CNS) stimulant indicated for the treatment of (1):

- Attention Deficit Hyperactivity Disorder (ADHD) in adults and pediatric patients 6 years and older
- Moderate to severe binge eating disorder (BED) in adults

Limitations of Use:

- Pediatric patients with ADHD younger than 6 years of age experienced more long-term weight loss than patients 6 years and older (8.4)
- Lisdexamfetamine dimesylate capsules are not indicated for weight loss. Use of other sympathomimetic drugs for weight loss has been associated with serious cardiovascular adverse events. The safety and effectiveness of lisdexamfetamine dimesylate capsules for the treatment of obesity have not been established (5.2)

---------- DOSAGE AND ADMINISTRATION ----------

Indicated Population	Initial Dose	Titration Schedule	Recommended Dose	Maximum Dose
ADHD (Adults and pediatric patients 6 years and older) (2.2)	30 mg every morning	10 mg or 20 mg weekly	30 mg to 70 mg per day	70 mg per day
BED (Adults) (2.3)	30 mg every morning	20 mg weekly	50 mg to 70 mg per day	70 mg per day

- Prior to treatment, assess for presence of cardiac disease (2.4)
- Severe renal impairment: Maximum dose is 50 mg/day (2.5)
- End stage renal disease (ESRD): Maximum dose is 30 mg/day (2.5)

---------- DOSAGE FORMS AND STRENGTHS ----------

- Capsules: 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg (3)

---------- CONTRAINDICATIONS ----------

- Known hypersensitivity to amphetamine products or other ingredients in lisdexamfetamine dimesylate capsules (4)
- Use with monoamine oxidase (MAO) inhibitor, or within 14 days of the last MAO inhibitor dose (4, 7.2)

---------- WARNINGS AND PRECAUTIONS ----------

- *Serious Cardiovascular Reactions*: Sudden death has been reported in association with CNS stimulant treatment at recommended doses in pediatric patients with structural cardiac abnormalities or other serious heart problems. In adults, sudden death, stroke, and myocardial infarction have been reported. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmia, or coronary artery disease (5.2)
- *Blood Pressure and Heart Rate Increases*: Monitor blood pressure and pulse. Consider benefits and risks before use in patients for whom blood pressure increases may be problematic (5.3)
- *Psychiatric Adverse Reactions*: May cause psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychosis. Evaluate for bipolar disorder prior to stimulant use (5.4)
- *Suppression of Growth*: Monitor height and weight in pediatric patients during treatment (5.5)
- *Peripheral Vasculopathy, including Raynaud's phenomenon*: Stimulants are associated with peripheral vasculopathy, including Raynaud's phenomenon. Careful observation for digital changes is necessary during treatment with stimulants (5.6)
- *Serotonin Syndrome:* Increased risk when co-administered with serotonergic agents (e.g., SSRIs, SNRIs, triptans), but also during overdosage situations. If it occurs, discontinue lisdexamfetamine dimesylate capsules and initiate supportive treatment (4, 5.7, 10)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions (incidence ≥5% and at a rate at least twice placebo) in pediatric patients ages 6 to 17 years, and/or adults with ADHD were anorexia, anxiety, decreased appetite, decreased weight, diarrhea, dizziness, dry mouth, irritability, insomnia, nausea, upper abdominal pain, and vomiting (6.1)

Most common adverse reactions (incidence ≥ 5% and at a rate at least twice placebo) in adults with BED were dry mouth, insomnia, decreased appetite, increased heart rate, constipation, feeling jittery, and anxiety (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Hikma Pharmaceuticals USA Inc. at 1-800-962-8364 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

---------- DRUG INTERACTIONS ----------

Acidifying and Alkalinizing Agents: Agents that alter urinary pH can alter blood levels of amphetamine. Acidifying agents decrease amphetamine blood levels, while alkalinizing agents increase amphetamine blood levels. Adjust lisdexamfetamine dimesylate dosage accordingly (2.6, 7.1)

---------- USE IN SPECIFIC POPULATIONS ----------

- *Pregnancy*: May cause fetal harm (8.1)
- *Lactation*: Breastfeeding not recommended (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 06/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: ABUSE AND DEPENDENCE
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Pre-treatment Screening
2.2 General Instructions for Use
2.3 Dosage for Treatment of ADHD
2.4 Dosage for Treatment of Moderate to Severe BED in Adults
2.5 Dosage in Patients with Renal Impairment
2.6 Dosage Modification due to Drug Interaction
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Potential for Abuse and Dependence
5.2 Serious Cardiovascular Reactions
5.3 Blood Pressure and Heart Rate Increases
5.4 Psychiatric Adverse Reactions
5.5 Suppression of Growth
5.6 Peripheral Vasculopathy, including Raynaud's Phenomenon
5.7 Serotonin Syndrome
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Drugs Having Clinically Important Interactions with Amphetamines
7.2 Drugs Having No Clinically Important Interactions with Lisdexamfetamine Dimesylate
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
14.1 Attention Deficit Hyperactivity Disorder (ADHD)
14.2 Binge Eating Disorder (BED)
16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
16.2 Storage and Handling
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: ABUSE AND DEPENDENCE

CNS stimulants, including lisdexamfetamine dimesylate, other amphetamine-containing products, and methylphenidate, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy *[see Warnings and Precautions (5.1), and Drug Abuse and Dependence (9.2, 9.3)]*.

1 INDICATIONS AND USAGE

Lisdexamfetamine Dimesylate Capsules are indicated for the treatment of:

- Attention Deficit Hyperactivity Disorder (ADHD) in adults and pediatric patients 6 years and older *[see Clinical Studies (14.1)]*
- Moderate to severe binge eating disorder (BED) in adults *[see Clinical Studies (14.2)]*

Limitations of Use:

- Pediatric patients with ADHD younger than 6 years of age experienced more long-term weight loss than patients 6 years and older *[see Use in Specific Populations (8.4)]*.
- Lisdexamfetamine dimesylate capsules are not indicated or recommended for weight loss. Use of other sympathomimetic drugs for weight loss has been associated with serious cardiovascular adverse events. The safety and effectiveness of lisdexamfetamine dimesylate capsules for the treatment of obesity have not been established *[see Warnings and Precautions (5.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Pre-treatment Screening

Prior to treating patients with CNS stimulants, including lisdexamfetamine dimesylate capsules, assess for the presence of cardiac disease (e.g., a careful history, family history of sudden death or ventricular arrhythmia, and physical exam) *[see Warnings and Precautions (5.2)]*.

To reduce the abuse of CNS stimulants including lisdexamfetamine dimesylate capsules, assess the risk of abuse, prior to prescribing. After prescribing, keep careful prescription records, educate patients about abuse, monitor for signs of abuse and overdose, and re-evaluate the need for lisdexamfetamine dimesylate capsules use *[see Warnings and Precautions (5.1), Drug Abuse and Dependence (9)]*.

2.2 General Instructions for Use

Take lisdexamfetamine dimesylate capsules by mouth in the morning with or without food; avoid afternoon doses because of the potential for insomnia. Lisdexamfetamine dimesylate capsules may be administered in one of the following ways:

Information for lisdexamfetamine dimesylate capsules:

- Swallow lisdexamfetamine dimesylate capsules whole, or
- Open capsules, empty and mix the entire contents with yogurt, water, or orange juice. If the contents of the capsule include any compacted powder, a spoon may be used to break apart the powder. The contents should be mixed until completely dispersed. Consume the entire mixture immediately. It should not be stored. The active ingredient dissolves completely once dispersed; however, a film containing the inactive ingredients may remain in the glass or container once the mixture is consumed.

Do not take anything less than one capsule per day. A single dose should not be divided.

2.3 Dosage for Treatment of 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 *[see Clinical Studies (14.1)]*.

2.4 Dosage for Treatment of Moderate to Severe BED in Adults

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 *[see Clinical Studies (14.2)]*. Discontinue lisdexamfetamine dimesylate if binge eating does not improve.

2.5 Dosage in Patients with Renal Impairment

In patients with severe renal impairment (GFR 15 to < 30 mL/min/1.73 m^2), the maximum dosage should not exceed 50 mg once daily. In patients with end stage renal disease (ESRD, GFR < 15 mL/min/1.73 m^2), the maximum recommended dosage is 30 mg once daily *[see Use in Specific Populations (8.6)]*.

2.6 Dosage Modification due to Drug Interaction

Agents that alter urinary pH can impact urinary excretion and alter blood levels of amphetamine. Acidifying agents (e.g., ascorbic acid) decrease blood levels, while alkalinizing agents (e.g., sodium bicarbonate) increase blood levels. Adjust lisdexamfetamine dimesylate dosage accordingly *[see Drug Interactions (7.1)]*.

3 DOSAGE FORMS AND STRENGTHS

Lisdexamfetamine dimesylate capsules 20 mg: ivory body/ivory cap (imprinted with 54 990)

Lisdexamfetamine dimesylate capsules 30 mg: white body/orange cap (imprinted with 54 682)

Lisdexamfetamine dimesylate capsules 40 mg: white body/light green cap (imprinted with 54 098)

Lisdexamfetamine dimesylate capsules 50 mg: white body/blue cap (imprinted with 54 296)

Lisdexamfetamine dimesylate capsules 60 mg: blue body/blue cap (imprinted with 54 338)

Lisdexamfetamine dimesylate capsules 70 mg: orange body/blue cap (imprinted with 54 818)

4 CONTRAINDICATIONS

Lisdexamfetamine dimesylate capsules are contraindicated in patients with:

- Known hypersensitivity to amphetamine products or other ingredients of lisdexamfetamine dimesylate capsules. Anaphylactic reactions, Stevens-Johnson Syndrome, angioedema, and urticaria have been observed in postmarketing reports *[see Adverse Reactions (6.2)]*.

- 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 *[see Warnings and Precautions (5.7) and Drug Interactions (7.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Potential for Abuse and Dependence

CNS stimulants, including lisdexamfetamine dimesylate capsules, other amphetamine-containing products and methylphenidate, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy *[see Drug Abuse and Dependence (9.2, 9.3)]*.

5.2 Serious Cardiovascular Reactions

Sudden death, stroke and myocardial infarction have been reported in adults with CNS stimulant treatment at recommended doses. Sudden death has been reported in pediatric patients with structural cardiac abnormalities and other serious heart problems taking CNS stimulants at recommended doses for ADHD. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmia, coronary artery disease, and other serious heart problems. Further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias during lisdexamfetamine dimesylate capsules treatment.

5.3 Blood Pressure and Heart Rate Increases

CNS stimulants cause an increase in blood pressure (mean increase about 2 to 4 mm Hg) and heart rate (mean increase about 3 to 6 bpm). Monitor all patients for potential tachycardia and hypertension.

5.4 Psychiatric Adverse Reactions

Exacerbation of Pre-existing Psychosis: CNS stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychotic disorder.

Induction of a Manic Episode in Patients with Bipolar Disorder: CNS stimulants may induce a mixed/manic episode in patients with bipolar disorder. Prior to initiating treatment, screen patients for risk factors for developing a manic episode (e.g., comorbid or history of depressive symptoms or a family history of suicide, bipolar disorder, and depression).

New Psychotic or Manic Symptoms: CNS stimulants, at recommended doses, may cause psychotic or manic symptoms (e.g., hallucinations, delusional thinking, or mania) in patients without a prior history of psychotic illness or mania. If such symptoms occur, consider discontinuing lisdexamfetamine dimesylate capsules. In a pooled analysis of multiple short-term, placebo-controlled studies of CNS stimulants, psychotic or manic symptoms occurred in 0.1% of CNS stimulant-treated patients compared to 0% in placebo-treated patients.

5.5 Suppression of Growth

CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients. Closely monitor growth (weight and height) in pediatric patients treated with CNS stimulants, including lisdexamfetamine dimesylate capsules. In a 4-week, placebo-controlled trial of lisdexamfetamine dimesylate capsules in pediatric patients ages 6 to 12 years old with ADHD, there was a dose-related decrease in weight in the lisdexamfetamine dimesylate capsules groups compared to weight gain in the placebo group. Additionally, in studies of another stimulant, there was slowing of the increase in height *[see Adverse Reactions (6.1)]*.

Patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted. Lisdexamfetamine dimesylate capsules are not approved for use in pediatric patients below 6 years of age *[see Use in Specific Populations (8.4)]*.

5.6 Peripheral Vasculopathy, including Raynaud's Phenomenon

Stimulants, including lisdexamfetamine dimesylate capsules, are associated with peripheral vasculopathy, including Raynaud's phenomenon. Signs and symptoms are usually intermittent and mild; however, very rare sequelae include digital ulceration and/or soft tissue breakdown. Effects of peripheral vasculopathy, including Raynaud's phenomenon, were observed in post-marketing reports at different times and at therapeutic doses in all age groups throughout the course of treatment. Signs and symptoms generally improve after reduction in dose or discontinuation of drug. Careful observation for digital changes is necessary during treatment with stimulants. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients.

5.7 Serotonin Syndrome

Serotonin syndrome, a potentially life-threatening reaction, may occur when amphetamines are used in combination with other drugs that affect the serotonergic neurotransmitter systems such as monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort *[see Drug Interactions (7.1)]*. The co-administration with cytochrome P450 2D6 (CYP2D6) inhibitors may also increase the risk with increased exposure to the active metabolite of lisdexamfetamine dimesylate capsules (dextroamphetamine). In these situations, consider an alternative non-serotonergic drug or an alternative drug that does not inhibit CYP2D6 *[see Drug Interactions (7.1)]*.

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

Concomitant use of lisdexamfetamine dimesylate capsules with MAOI drugs is contraindicated *[see Contraindications (4)]*.

Discontinue treatment with lisdexamfetamine dimesylate capsules and any concomitant serotonergic agents immediately if symptoms of serotonin syndrome occur, and initiate supportive symptomatic treatment. If concomitant use of lisdexamfetamine dimesylate capsules with other serotonergic drugs or CYP2D6 inhibitors is clinically warranted, initiate lisdexamfetamine dimesylate capsules with lower doses, monitor patients for the emergence of serotonin syndrome during drug initiation or titration, and inform patients of the increased risk for serotonin syndrome.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Known hypersensitivity to amphetamine products or other ingredients of lisdexamfetamine dimesylate capsules *[see Contraindications (4)]*
- Hypertensive Crisis When Used Concomitantly with Monoamine Oxidase Inhibitors *[see Contraindications (4) and Drug Interactions (7.1)]*
- Drug Dependence *[see Boxed Warning, Warnings and Precautions (5.1), and Drug Abuse and Dependence (9.2, 9.3)]*
- Serious Cardiovascular Reactions *[see Warnings and Precautions (5.2)]*
- Blood Pressure and Heart Rate Increases *[see Warnings and Precautions (5.3)]*
- Psychiatric Adverse Reactions *[see Warnings and Precautions (5.4)]*
- Suppression of Growth *[see Warnings and Precautions (5.5)]*

- Peripheral Vasculopathy, including Raynaud's phenomenon *[see Warnings and Precautions (5.6)]*
- Serotonin Syndrome *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Attention Deficit Hyperactivity Disorder

The safety data in this section is based on data from the 4-week controlled parallel-group clinical studies of lisdexamfetamine dimesylate in pediatric and adult patients with ADHD *[see Clinical Studies (14.1)]*.

Adverse Reactions Associated with Discontinuation of Treatment in ADHD Clinical Trials: In the controlled trial in pediatric patients ages 6 to 12 years (Study 1), 8% (18/218) of lisdexamfetamine dimesylate-treated patients discontinued due to adverse reactions compared to 0% (0/72) of placebo-treated patients. The most frequently reported adverse reactions (1% or more and twice rate of placebo) were ECG voltage criteria for ventricular hypertrophy, tic, vomiting, psychomotor hyperactivity, insomnia, decreased appetite and rash [2 instances for each adverse reaction, i.e., 2/218 (1%)]. Less frequently reported adverse reactions (less than 1% or less than twice rate of placebo) included abdominal pain upper, dry mouth, weight decreased, dizziness, somnolence, logorrhea, chest pain, anger and hypertension.

In the controlled trial in pediatric patients ages 13 to 17 years (Study 4), 3% (7/233) of lisdexamfetamine dimesylate-treated patients discontinued due to adverse reactions compared to 1% (1/77) of placebo-treated patients. The most frequently reported adverse reactions (1% or more and twice rate of placebo) were decreased appetite (2/233; 1%) and insomnia (2/233; 1%). Less frequently reported adverse reactions (less than 1% or less than twice rate of placebo) included irritability, dermatillomania, mood swings, and dyspnea.

In the controlled adult trial (Study 7), 6% (21/358) of lisdexamfetamine dimesylate -treated patients discontinued due to adverse reactions compared to 2% (1/62) of placebo-treated patients. The most frequently reported adverse reactions (1% or more and twice rate of placebo) were insomnia (8/358; 2%), tachycardia (3/358; 1%), irritability (2/358; 1%), hypertension (4/358; 1%), headache (2/358; 1%), anxiety (2/358; 1%), and dyspnea (3/358; 1%). Less frequently reported adverse reactions (less than 1% or less than twice rate of placebo) included palpitations, diarrhea, nausea, decreased appetite, dizziness, agitation, depression, paranoia and restlessness.

Adverse Reactions Occurring at an Incidence of ≥5% or More Among Lisdexamfetamine dimesylate Treated Patients with ADHD in Clinical Trials: The most common adverse reactions (incidence ≥5% and at a rate at least twice placebo) reported in pediatric patients ages 6 to 17 years, and/or adults were anorexia, anxiety, decreased appetite, decreased weight, diarrhea, dizziness, dry mouth, irritability, insomnia, nausea, upper abdominal pain, and vomiting.

Adverse Reactions Occurring at an Incidence of 2% or More Among Lisdexamfetamine dimesylate Treated Patients with ADHD in Clinical Trials: Adverse reactions reported in the controlled trials in pediatric patients ages, 6 to 12 years (Study 1), pediatric patients ages 13 to 17 years (Study 4), and adult patients (Study 7) treated with lisdexamfetamine dimesylate or placebo are presented in Tables 1, 2 and 3 below.

Table 1 Adverse Reactions Reported by 2% or More of Pediatric Patients Ages 6 to 12 Years with ADHD Taking Lisdexamfetamine Dimesylate and Greater than or Equal to Twice the Incidence in Patients Taking Placebo in a 4-Week Clinical Trial (Study 1)

	Lisdexamfetamine Dimesylate	**Placebo**
	(n=218)	**(n=72)**
Decreased Appetite	39%	4%

Insomnia	22%	3%
Abdominal Pain Upper	12%	6%
Irritability	10%	0%
Vomiting	9%	4%
Weight Decreased	9%	1%
Nausea	6%	3%
Dry Mouth	5%	0%
Dizziness	5%	0%
Affect Lability	3%	0%
Rash	3%	0%
Pyrexia	2%	1%
Somnolence	2%	1%
Tic	2%	0%
Anorexia	2%	0%

Table 2 Adverse Reactions Reported by 2% or More of Pediatric Patients Ages 13 to 17 Years with ADHD Taking Lisdexamfetamine Dimesylate and Greater than or Equal to Twice the Incidence in Patients Taking Placebo in a 4-Week Clinical Trial (Study 4)

	Lisdexamfetamine Dimesylate	**Placebo**
	(n=233)	**(n=77)**
Decreased Appetite	34%	3%
Insomnia	13%	4%
Weight Decreased	9%	0%
Dry Mouth	4%	1%
Palpitations	2%	1%
Anorexia	2%	0%
Tremor	2%	0%

Table 3 Adverse Reactions Reported by 2% or More of Adult Patients with ADHD Taking Lisdexamfetamine Dimesylate and Greater than or Equal to Twice the Incidence in Patients Taking Placebo in a 4-Week Clinical Trial (Study 7)

	Lisdexamfetamine Dimesylate	**Placebo**
	(n=358)	**(n=62)**
Decreased Appetite	27%	2%
Insomnia	27%	8%
Dry Mouth	26%	3%
Diarrhea	7%	0%
Nausea	7%	0%
Anxiety	6%	0%
Anorexia	5%	0%
Feeling Jittery	4%	0%
Agitation	3%	0%
Increased Blood Pressure	3%	0%
Hyperhidrosis	3%	0%
Restlessness	3%	0%
Decreased Weight	3%	0%
Dyspnea	2%	0%
Increased Heart Rate	2%	0%
Tremor	2%	0%
Palpitations	2%	0%

In addition, in the adult population erectile dysfunction was observed in 2.6% of males on lisdexamfetamine dimesylate and 0% on placebo; decreased libido was observed in 1.4% of subjects on lisdexamfetamine dimesylate and 0% on placebo.

Weight Loss and Slowing Growth Rate in Pediatric Patients with ADHD: In a controlled trial of lisdexamfetamine dimesylate capsules in pediatric patients ages 6 to 12 years (Study 1), mean weight loss from baseline after 4 weeks of therapy was -0.9, -1.9, and -2.5 pounds, respectively, for patients receiving 30 mg, 50 mg, and 70 mg of lisdexamfetamine dimesylate, compared to a 1 pound weight gain for patients receiving placebo. Higher doses were associated with greater weight loss with 4 weeks of treatment. Careful follow-up for weight in pediatric patients ages 6 to 12 years who received lisdexamfetamine dimesylate capsules over 12 months suggests that consistently medicated pediatric patients (i.e., treatment for 7 days per week throughout the year) have a slowing in growth rate, measured by body weight as demonstrated by an age-and sex-normalized mean change from baseline in percentile, of -13.4 over 1 year (average percentiles at baseline and 12 months were 60.9 and 47.2, respectively). In a 4-week controlled trial of lisdexamfetamine dimesylate in pediatric patients ages 13 to 17 years, mean weight loss from baseline to endpoint was -2.7, -4.3, and -4.8 lbs., respectively, for patients receiving 30 mg, 50 mg, and 70 mg of lisdexamfetamine dimesylate, compared to a 2.0 pound weight gain for patients receiving placebo.

Careful follow-up of weight and height in pediatric patients ages 7 to 10 years who were randomized to either methylphenidate or non-medication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and non-medication treated pediatric patients over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated pediatric patients ages 7 to 13 years (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development. In a controlled trial of amphetamine (d- to l-enantiomer ratio of 3:1) in pediatric patients ages 13 to 17 years, mean weight change from baseline within the initial 4 weeks of therapy was -1.1 pounds and -2.8 pounds, respectively, for patients receiving 10 mg and 20 mg of amphetamine. Higher doses were associated with greater weight loss within the initial 4 weeks of treatment *[see Warnings and Precautions (5.5)]*.

Weight Loss in Adults with ADHD: In the controlled adult trial (Study 7), mean weight loss after 4 weeks of therapy was 2.8 pounds, 3.1 pounds, and 4.3 pounds, for patients receiving final doses of 30 mg, 50 mg, and 70 mg of lisdexamfetamine dimesylate capsules, respectively, compared to a mean weight gain of 0.5 pounds for patients receiving placebo.

Binge Eating Disorder

The safety data in this section is based on data from two 12-week parallel group, flexible-dose, placebo-controlled studies in adults with BED *[see Clinical Studies 14.2]*. Patients with cardiovascular risk factors other than obesity and smoking were excluded.

Adverse Reactions Associated with Discontinuation of Treatment in BED Clinical Trials: In controlled trials of patients ages 18 to 55 years, 5.1% (19/373) of lisdexamfetamine dimesylate-treated patients discontinued due to adverse reactions compared to 2.4% (9/372) of placebo-treated patients. No single adverse reaction led to discontinuation in 1% or more of lisdexamfetamine dimesylate-treated patients. Less commonly reported adverse reactions (less than 1% or less than twice rate of placebo) included increased heart rate, headache, abdominal pain upper, dyspnea, rash, insomnia, irritability, feeling jittery and anxiety.

Adverse Reactions Occurring at an Incidence of 5% or More and At Least Twice Placebo Among Lisdexamfetamine dimesylate Treated Patients with BED in Clinical Trials: The most common adverse reactions (incidence ≥5% and at a rate at least twice placebo) reported in adults were dry mouth, insomnia, decreased appetite, increased heart rate, constipation, feeling jittery, and anxiety.

Adverse Reactions Occurring at an Incidence of 2% or More and At Least Twice Placebo Among Lisdexamfetamine dimesylate Treated Patients with BED in Clinical Trials: Adverse reactions reported in the pooled controlled trials in adult patients (Study 11 and 12) treated with lisdexamfetamine dimesylate or placebo are presented in Table 4 below.

Table 4 Adverse Reactions Reported by 2% or More of Adult Patients with BED Taking Lisdexamfetamine Dimesylate and Greater than or Equal to Twice the Incidence in Patients Taking Placebo in 12-Week Clinical Trials (Study 11 and 12)

	Lisdexamfetamine Dimesylate (N=373)	Placebo (N=372)
Dry Mouth	36%	7%
Insomnia[1]	20%	8%
Decreased Appetite	8%	2%
Increased Heart Rate[2]	7%	1%
Feeling Jittery	6%	1%
Constipation	6%	1%
Anxiety	5%	1%
Diarrhea	4%	2%
Decreased Weight	4%	0%
Hyperhidrosis	4%	0%
Vomiting	2%	1%
Gastroenteritis	2%	1%
Paresthesia	2%	1%
Pruritus	2%	1%
Upper Abdominal Pain	2%	0%
Energy Increased	2%	0%
Urinary Tract Infection	2%	0%
Nightmare	2%	0%
Restlessness	2%	0%
Oropharyngeal Pain	2%	0%

1. Includes all preferred terms containing the word “insomnia.”
2. Includes the preferred terms “heart rate increased” and “tachycardia.”

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of lisdexamfetamine dimesylate capsules. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events are as follows: cardiomyopathy, mydriasis, diplopia, difficulties with visual accommodation, blurred vision, eosinophilic hepatitis, anaphylactic reaction, hypersensitivity, dyskinesia, dysgeusia, 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.

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with Amphetamines

Table 5 Drugs having clinically important interactions with amphetamines.

MAO Inhibitors (MAOI)

Clinical Impact	MAOI antidepressants slow amphetamine metabolism, increasing amphetamines effect on the release of norepinephrine and other monoamines from adrenergic nerve endings causing headaches and other signs of hypertensive crisis. Toxic neurological effects and malignant hyperpyrexia can occur, sometimes with fatal results.
Intervention	Do not administer lisdexamfetamine dimesylate during or within 14 days following the administration of MAOI *[see Contraindications (4)]*.
Serotonergic Drugs	
Clinical Impact	The concomitant use of lisdexamfetamine dimesylate and serotonergic drugs increases the risk of serotonin syndrome.
Intervention	Initiate with lower doses and monitor patients for signs and symptoms of serotonin syndrome, particularly during lisdexamfetamine dimesylate initiation or dosage increase. If serotonin syndrome occurs, discontinue lisdexamfetamine dimesylate and the concomitant serotonergic drug(s) *[see Warnings and Precautions (5.7)]*.
CYP2D6 Inhibitors	
Clinical Impact	The concomitant use of lisdexamfetamine dimesylate and CYP2D6 inhibitors may increase the exposure of dextroamphetamine, the active metabolite of lisdexamfetamine dimesylate compared to the use of the drug alone and increase the risk of serotonin syndrome.
Intervention	Initiate with lower doses and monitor patients for signs and symptoms of serotonin syndrome particularly during lisdexamfetamine dimesylate initiation and after a dosage increase. If serotonin syndrome occurs, discontinue lisdexamfetamine dimesylate and the CYP2D6 inhibitor *[see Warnings and Precautions (5.7) and Overdosage (10)]*.
Alkalinizing Agents	
Clinical Impact	Urinary alkalinizing agents can increase blood levels and potentiate the action of amphetamine.
Intervention	Co-administration of lisdexamfetamine dimesylate and urinary alkalinizing agents should be avoided.
Acidifying Agents	
Clinical Impact	Urinary acidifying agents can lower blood levels and efficacy of amphetamines.
Intervention	Increase dose based on clinical response.
Tricyclic Antidepressants	
Clinical Impact	May enhance the activity of tricyclic or sympathomimetic agents causing striking and sustained increases in the concentration of d-amphetamine in the brain; cardiovascular effects can be potentiated.
Intervention	Monitor frequently and adjust or use alternative therapy based on clinical response.

7.2 Drugs Having No Clinically Important Interactions with Lisdexamfetamine Dimesylate

From a pharmacokinetic perspective, no dose adjustment of lisdexamfetamine dimesylate is necessary when lisdexamfetamine dimesylate is co-administered with guanfacine, venlafaxine, or omeprazole. In addition, no dose adjustment of guanfacine or venlafaxine is needed when lisdexamfetamine dimesylate is co-administered *[see Clinical Pharmacology (12.3)]*.

From a pharmacokinetic perspective, no dose adjustment for drugs that are substrates of CYP1A2 (e.g., theophylline, duloxetine, melatonin), CYP2D6 (e.g., atomoxetine, desipramine, venlafaxine), CYP2C19 (e.g., omeprazole, lansoprazole, clobazam), and CYP3A4 (e.g., midazolam, pimozide, simvastatin) is necessary when lisdexamfetamine dimesylate is co-administered *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ADHD medications during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Psychostimulants at 1-866-961-2388 or visiting online at https://womensmentalhealth.org/clinical-and researchprograms/pregnancyregistry/adhdmedications/.

Risk Summary

The limited available data from published literature and postmarketing reports on use of lisdexamfetamine dimesylate in pregnant women are not sufficient to inform a drug-associated risk for major birth defects and miscarriage. Adverse pregnancy outcomes, including premature delivery and low birth weight, have been seen in infants born to mothers dependent on amphetamines *[see Clinical Considerations]*. In animal reproduction studies, lisdexamfetamine dimesylate (a prodrug of d-amphetamine) had no effects on embryo-fetal morphological development or survival when administered orally to pregnant rats and rabbits throughout the period of organogenesis. Pre-and postnatal studies were not conducted with lisdexamfetamine dimesylate. However, amphetamine (d-to l-ratio of 3:1) administration to pregnant rats during gestation and lactation caused a decrease in pup survival and a decrease in pup body weight that correlated with a delay in developmental landmarks at clinically relevant doses of amphetamine. In addition, adverse effects on reproductive performance were observed in pups whose mothers were treated with amphetamine. Long-term neurochemical and behavioral effects have also been reported in animal developmental studies using clinically relevant doses of amphetamine *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Amphetamines, such as lisdexamfetamine dimesylate, cause vasoconstriction and thereby may decrease placental perfusion. In addition, amphetamines can stimulate uterine contractions increasing the risk of premature delivery. Infants born to amphetamine-dependent mothers have an increased risk of premature delivery and low birth weight.

Monitor infants born to mothers taking amphetamines for symptoms of withdrawal such as feeding difficulties, irritability, agitation, and excessive drowsiness.

Data

Animal Data

Lisdexamfetamine dimesylate had no apparent effects on embryo-fetal morphological development or survival when administered orally to pregnant rats and rabbits throughout the period of organogenesis at doses of up to 40 and 120 mg/kg/day, respectively. These doses are approximately 5.5 and 33 times, respectively, the maximum recommended human dose (MRHD) of 70 mg/day given to adults, on a mg/m2 body surface area basis.

A study was conducted with amphetamine (d-to l-enantiomer ratio of 3:1) in which pregnant rats received daily oral doses of 2, 6, and 10 mg/kg from gestation day 6 to lactation day 20. All doses caused hyperactivity and decreased weight gain in the dams. A decrease in pup survival was seen at all doses. A decrease in pup body weight was seen at 6 and 10 mg/kg which correlated with delays in developmental landmarks, such as preputial separation and vaginal opening. Increased pup locomotor activity was seen at 10 mg/kg on day 22 postpartum but not at 5 weeks postweaning. When pups were

tested for reproductive performance at maturation, gestational weight gain, number of implantations, and number of delivered pups were decreased in the group whose mothers had been given 10 mg/kg.

A number of studies from the literature in rodents indicate that prenatal or early postnatal exposure to amphetamine (d- or d, l-) at doses similar to those used clinically can result in long term neurochemical and behavioral alterations. Reported behavioral effects include learning and memory deficits, altered locomotor activity, and changes in sexual function.

8.2 Lactation

Risk Summary

Lisdexamfetamine is a pro-drug of dextroamphetamine. Based on limited case reports in published literature, amphetamine (d-or d, l-) is present in human milk, at relative infant doses of 2% to 13.8% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 1.9 and 7.5. There are no reports of adverse effects on the breastfed infant. Long-term neurodevelopmental effects on infants from amphetamine exposure are unknown. It is possible that large dosages of dextroamphetamine might interfere with milk production, especially in women whose lactation is not well established. Because of the potential for serious adverse reactions in nursing infants, including serious cardiovascular reactions, blood pressure and heart rate increase, suppression of growth, and peripheral vasculopathy, advise patients that breastfeeding is not recommended during treatment with lisdexamfetamine dimesylate.

8.4 Pediatric Use

ADHD

Safety and effectiveness of lisdexamfetamine dimesylate have been established in pediatric patients with ADHD ages 6 to 17 years *[see Dosage and Administration (2.3), Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.1)]*.

Safety and effectiveness of lisdexamfetamine dimesylate have not been established in pediatric patients below the age of 6 years.

Safety and efficacy of lisdexamfetamine dimesylate were evaluated in a double-blind, randomized, parallel-group, placebo-controlled, fixed-dose study in pediatric patients ages 4 to 5 years with ADHD, followed by a 1-year open-label extension study. In these studies, patients experienced elevated rates of adverse reactions, including weight loss, decreased BMI, decreased appetite, insomnia, infections (upper respiratory and nasopharyngitis), irritability, and affect lability.

With the same lisdexamfetamine dimesylate dose, mean steady state exposure of dextroamphetamine was approximately 44% higher in pediatric patients ages 4 to 5 years compared to the pediatric patients ages 6 to 11 years.

BED

Safety and effectiveness of lisdexamfetamine dimesylate have not been established in patients less than 18 years of age.

Growth Suppression

Growth should be monitored during treatment with stimulants, including lisdexamfetamine dimesylate, and pediatric patients who are not growing or gaining weight as expected may need to have their treatment interrupted *[see Warnings and Precautions (5.5) and Adverse Reactions (6.1)]*.

Juvenile Animal Data

Studies conducted in juvenile rats and dogs at clinically relevant doses showed growth suppression that partially or fully reversed in dogs and female rats but not in male rats after a four-week drug-free recovery period.

A study was conducted in which juvenile rats received oral doses of 4, 10, or 40 mg/kg/day of lisdexamfetamine dimesylate from day 7 to day 63 of age. These doses are approximately 0.3, 0.7, and 3 times the maximum recommended human daily dose of 70 mg on a mg/m2 basis for a child. Dose-related decreases in food consumption, bodyweight gain,

and crown-rump length were seen; after a four-week drug-free recovery period, bodyweights and crown-rump lengths had significantly recovered in females but were still substantially reduced in males. Time to vaginal opening was delayed in females at the highest dose, but there were no drug effects on fertility when the animals were mated beginning on day 85 of age.

In a study in which juvenile dogs received lisdexamfetamine dimesylate for 6 months beginning at 10 weeks of age, decreased bodyweight gain was seen at all doses tested (2, 5, and 12 mg/kg/day, which are approximately 0.5, 1, and 3 times the maximum recommended human daily dose on a mg/m^2 basis for a child). This effect partially or fully reversed during a four-week drug-free recovery period.

8.5 Geriatric Use

Clinical studies of lisdexamfetamine dimesylate capsules did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience and pharmacokinetic data *[see Clinical Pharmacology (12.3)]* have not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should start at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Renal Impairment

Due to reduced clearance in patients with severe renal impairment (GFR 15 to < 30 mL/min/1.73 m^2), the maximum dose should not exceed 50 mg/day. The maximum recommended dose in ESRD (GFR < 15 mL/min/1.73 m^2) patients is 30 mg/day *[see Clinical Pharmacology (12.3)]*.

Lisdexamfetamine and d-amphetamine are not dialyzable.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Lisdexamfetamine dimesylate capsules contain lisdexamfetamine, a prodrug of amphetamine, a Schedule II controlled substance.

9.2 Abuse

CNS stimulants, including lisdexamfetamine dimesylate capsules, other amphetamine-containing products, and methylphenidate have a high potential for abuse. Abuse is the intentional non-therapeutic use of a drug, even once, to achieve a desired psychological or physiological effect. Abuse is characterized by impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence. Both abuse and misuse may lead to addiction, and some individuals may develop addiction even when taking lisdexamfetamine dimesylate capsules as prescribed.

Signs and symptoms of amphetamine abuse may include increased heart rate, respiratory rate, blood pressure, and/or sweating, dilated pupils, hyperactivity, restlessness, insomnia, decreased appetite, loss of coordination, tremors, flushed skin, vomiting, and/or abdominal pain. Anxiety, psychosis, hostility, aggression, suicidal or homicidal ideation have also been seen. Abusers of CNS stimulants may chew, snort, inject, or use other unapproved routes of administration which can result in overdose and death *[see Overdosage (10)]*.

To reduce the abuse of CNS stimulants, including lisdexamfetamine dimesylate capsules, assess the risk of abuse prior to prescribing. After prescribing, keep careful prescription records, educate patients and their families about abuse and on

proper storage and disposal of CNS stimulants. Monitor for signs of abuse while on therapy, and re-evaluate the need for lisdexamfetamine dimesylate capsules use.

Studies of Lisdexamfetamine Dimesylate Capsules in Drug Abusers:

A randomized, double-blind, placebo-control, cross-over, abuse liability study in 38 patients with a history of drug abuse was conducted with single-doses of 50, 100, or 150 mg of lisdexamfetamine dimesylate capsules, 40 mg of immediate-release d-amphetamine sulphate (a controlled II substance), and 200 mg of diethylpropion hydrochloride (a controlled IV substance). Lisdexamfetamine dimesylate capsules 100 mg produced significantly less “Drug Liking Effects” as measured by the Drug Rating Questionnaire-Subject score, compared to d-amphetamine 40 mg; and 150 mg of lisdexamfetamine dimesylate capsules demonstrated similar “Drug-Liking Effects” compared to 40 mg of d-amphetamine and 200 mg of diethylpropion.

Intravenous administration of 50 mg lisdexamfetamine dimesylate to individuals with a history of drug abuse produced positive subjective responses on scales measuring "Drug Liking", "Euphoria", "Amphetamine Effects", and "Benzedrine Effects" that were greater than placebo but less than those produced by an equivalent dose (20 mg) of intravenous d-amphetamine.

9.3 Dependence

Physical Dependence: Lisdexamfetamine dimesylate capsules may produce physical dependence from continued therapy. Physical dependence is a state of adaptation manifested by a withdrawal syndrome produced by abrupt cessation, rapid dose reduction, or administration of an antagonist. Withdrawal symptoms after abrupt cessation following prolonged high-dosage administration of CNS stimulants include extreme fatigue and depression.

Tolerance: lisdexamfetamine dimesylate capsules may produce tolerance from continued therapy. Tolerance is a state of adaptation in which exposure to a specific dose of a drug results in a reduction of the drug’s desired and/or undesired effects over time.

10 OVERDOSAGE

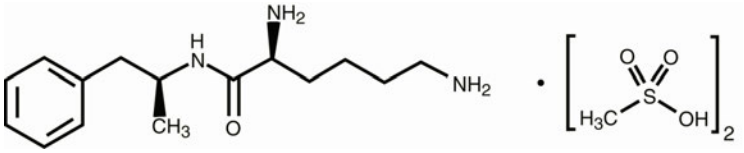
Consult with a Certified Poison Control Center (1-800-222-1222) for up-to-date guidance and advice for treatment of overdosage. Individual patient response to amphetamines varies widely. Toxic symptoms may occur idiosyncratically at low doses.

Manifestations of amphetamine overdose include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states, hyperpyrexia and rhabdomyolysis. Fatigue and depression usually follow the central nervous system stimulation. Serotonin syndrome has been reported with amphetamine use, including lisdexamfetamine dimesylate. Cardiovascular effects include arrhythmias, hypertension or hypotension and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma.

Lisdexamfetamine and d-amphetamine are not dialyzable.

11 DESCRIPTION

Lisdexamfetamine dimesylate capsules, a CNS stimulant, are capsules for once-a-day oral administration. The chemical designation for lisdexamfetamine dimesylate is (2S)-2,6-diamino-*N*-[(1*S*)-1-methyl-2-phenylethyl] hexanamide dimethanesulfonate. The molecular formula is $C_{15}H_{25}N_3O•(CH_4O_3S)_2$, which corresponds to a molecular weight of 455.60. The chemical structure is:



Lisdexamfetamine dimesylate is a white to off-white powder that is soluble in water (792 mg/mL). Lisdexamfetamine dimesylate capsules contain 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg of lisdexamfetamine dimesylate (equivalent to 11.6 mg, 17.3 mg, 23.1 mg, 28.9 mg, 34.7 mg, and 40.5 mg of lisdexamfetamine) and the following inactive ingredients: ammonium hydroxide, calcium phosphate, gelatin, iron oxide black, isopropyl alcohol, magnesium stearate, microcrystalline cellulose, n-butyl alcohol, propylene glycol, shellac glaze, sodium starch glycolate, and titanium dioxide. In addition, the 20 mg capsule also contains yellow iron oxide. The 30 mg capsule also contains FD&C yellow #6. The 40 mg capsule also contains FD&C blue #1 and FD&C green #3. The 50 mg and 60 mg capsules also contain D&C red #28 and FD&C blue #1. The 70 mg capsule also contains D&C red #28, FD&C blue #1, and FD&C yellow #6.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lisdexamfetamine is a prodrug of dextroamphetamine. Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The exact mode of therapeutic action in ADHD and BED is not known.

12.2 Pharmacodynamics

Amphetamines block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. The parent drug, lisdexamfetamine, does not bind to the sites responsible for the reuptake of norepinephrine and dopamine *in vitro*.

12.3 Pharmacokinetics

Pharmacokinetic studies after oral administration of lisdexamfetamine dimesylate have been conducted in healthy adult (capsule and chewable tablet formulations) and pediatric (6 to 12 years) patients with ADHD (capsule formulation). After single dose administration of lisdexamfetamine dimesylate, pharmacokinetics of dextroamphetamine was found to be linear between 30 mg and 70 mg in a pediatric study (6 to 12 years), and between 50 mg and 250 mg in an adult study. 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

Capsule formulation

Following single-dose oral administration of lisdexamfetamine dimesylate capsule (30 mg, 50 mg, or 70 mg) in patients ages 6 to 12 years with ADHD under fasted conditions, T_{max} of lisdexamfetamine and dextroamphetamine was reached at approximately 1 hour and 3.5 hours post dose, respectively. Weight/Dose normalized AUC and Cmax values were the same in pediatric patients ages 6 to 12 years as the adults following single doses of 30 mg to 70 mg lisdexamfetamine dimesylate capsule.

Effect of food on capsule formulation

Neither food (a high fat meal or yogurt) nor orange juice affects the observed AUC and Cmax of dextroamphetamine in healthy adults after single-dose oral administration of 70 mg of lisdexamfetamine dimesylate capsules. Food prolongs Tmax by approximately 1 hour (from 3.8 hours at fasted state to 4.7 hours after a high fat meal or to 4.2 hours with yogurt). After an 8-hour fast, the AUC for dextroamphetamine following oral administration of lisdexamfetamine dimesylate in solution and as intact capsules were equivalent.

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 one 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.

Specific Populations

Exposures of dextroamphetamine in specific populations are summarized in Figure 1.

Figure 1: Specific Populations*:

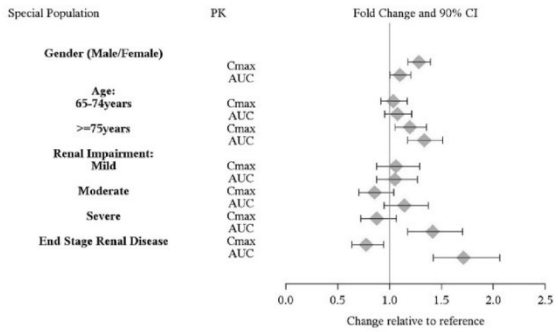
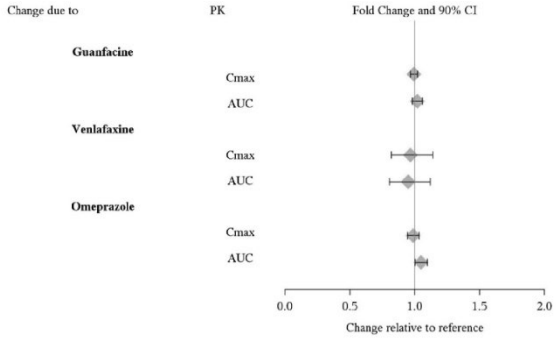


*Figure 1 shows the geometric mean ratios and the 90% confidence limits for Cmax and AUC of d-amphetamine. Comparison for gender uses males as the reference. Comparison for age uses 55-64 years as the reference

Drug Interaction Studies

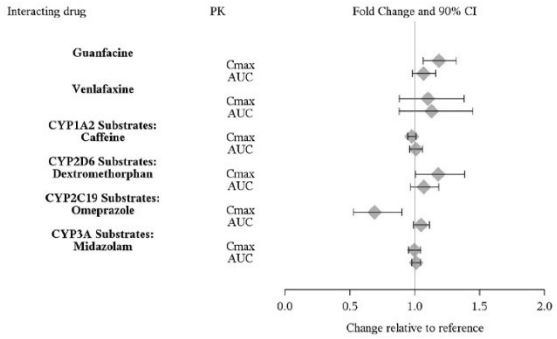
Effects of other drugs on the exposures of dextroamphetamine are summarized in Figure 2.

Figure 2: Effect of Other Drugs on Lisdexamfetamine Dimesylate:



The effects of Lisdexamfetamine dimesylate on the exposures of other drugs are summarized in Figure 3.

Figure 3: Effect of Lisdexamfetamine Dimesylate on Other Drugs:



13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis: Carcinogenicity studies of lisdexamfetamine dimesylate have not been performed. No evidence of carcinogenicity was found in studies in which d-, 1-amphetamine (enantiomer ratio of 1:1) was administered to mice and rats in the diet for 2 years at doses of up to 30 mg/kg/day in male mice, 19 mg/kg/day in female mice, and 5 mg/kg/day in male and female rats.

Mutagenesis: Lisdexamfetamine dimesylate was not clastogenic in the mouse bone marrow micronucleus test *in vivo* and was negative when tested in the *E. coli* and *S. typhimurium* components of the Ames test and in the L5178Y/TK$^{+/-}$ mouse lymphoma assay *in vitro*.

Impairment of Fertility: Amphetamine (d- to 1-enantiomer ratio of 3:1) did not adversely affect fertility or early embryonic development in the rat at doses of up to 20 mg/kg/day.

13.2 Animal Toxicology and/or Pharmacology

Acute administration of high doses of amphetamine (d- or d,1-) has been shown to produce long-lasting neurotoxic effects, including irreversible nerve fiber damage, in rodents. The significance of these findings to humans is unknown.

14 CLINICAL STUDIES

14.1 Attention Deficit Hyperactivity Disorder (ADHD)

Pediatric Patients Ages 6 to 12 Years with ADHD: A double-blind, randomized, placebo-controlled, parallel-group study (Study 1) was conducted in pediatric patients ages 6 to 12 years (N=290) who met DSM-IV criteria for ADHD (either the combined type or the hyperactive-impulsive type). Patients were randomized to receive final doses of 30 mg, 50 mg, or 70 mg of lisdexamfetamine dimesylate or placebo once daily in the morning for a total of four weeks of treatment. All

patients receiving lisdexamfetamine dimesylate were initiated on 30 mg for the first week of treatment. Patients assigned to the 50 mg and 70 mg dose groups were titrated by 20 mg per week until they achieved their assigned dose. The primary efficacy outcome was change in Total Score from baseline to endpoint in investigator ratings on the ADHD Rating Scale (ADHD-RS), an 18-item questionnaire with a score range of 0-54 points that measures the core symptoms of ADHD which includes both hyperactive/impulsive and inattentive subscales. Endpoint was defined as the last post-randomization treatment week (i.e., Weeks 1 through 4) for which a valid score was obtained. All lisdexamfetamine dimesylate dose groups were superior to placebo in the primary efficacy outcome. Mean effects at all doses were similar; however, the highest dose (70 mg/day) was numerically superior to both lower doses (Study 1 in Table 6). The effects were maintained throughout the day based on parent ratings (Conners' Parent Rating Scale) in the morning (approximately 10 am), afternoon (approximately 2 pm), and early evening (approximately 6 pm).

A double-blind, placebo-controlled, randomized, crossover design, analog classroom study (Study 2) was conducted in pediatric patients ages 6 to 12 years (N=52) who met DSM-IV criteria for ADHD (either the combined type or the hyperactive-impulsive type). Following a 3week open-label dose optimization with Adderall XR®, patients were randomly assigned to continue their optimized dose of Adderall XR (10 mg, 20 mg, or 30 mg), lisdexamfetamine dimesylate (30 mg, 50 mg, or 70 mg), or placebo once daily in the morning for 1 week each treatment. Efficacy assessments were conducted at 1, 2, 3, 4.5, 6, 8, 10, and 12 hours post-dose using the Swanson, Kotkin, Agler, M.Flynn, and Pelham Deportment scores (SKAMP-DS), a 4-item subscale of the SKAMP with scores ranging from 0 to 24 points that measures deportment problems leading to classroom disruptions. A significant difference in patient behavior, based upon the average of investigator ratings on the SKAMP-DS across the 8 assessments were observed between patients when they received lisdexamfetamine dimesylate compared to patients when they received placebo (Study 2 in Table 6). The drug effect reached statistical significance from hours 2 to 12 post-dose, but was not significant at 1 hour.

A second double-blind, placebo-controlled, randomized, crossover design, analog classroom study (Study 3) was conducted in pediatric patients ages 6 to 12 years (N=129) who met DSMIV criteria for ADHD (either the combined type or the hyperactive-impulsive type). Following a 4-week open-label dose optimization with lisdexamfetamine dimesylate (30 mg, 50 mg, 70 mg), patients were randomly assigned to continue their optimized dose of lisdexamfetamine dimesylate or placebo once daily in the morning for 1 week each treatment. A significant difference in patient behavior, based upon the average of investigator ratings on the SKAMP-Deportment scores across all 7 assessments conducted at 1.5, 2.5, 5.0, 7.5, 10.0, 12.0, and 13.0 hours post-dose, were observed between patients when they received lisdexamfetamine dimesylate compared to patients when they received placebo (Study 3 in Table 6, Figure 4).

Pediatric Patients Ages 13 to 17 Years with ADHD: A double-blind, randomized, placebo-controlled, parallel-group study (Study 4) was conducted in pediatric patients ages 13 to 17 years (N=314) who met DSM-IV criteria for ADHD. In this study, patients were randomized in a 1:1:1:1 ratio to a daily morning dose of lisdexamfetamine dimesylate (30 mg/day, 50 mg/day or 70 mg/day) or placebo for a total of four weeks of treatment. All patients receiving lisdexamfetamine dimesylate were initiated on 30 mg for the first week of treatment. Patients assigned to the 50 mg and 70 mg dose groups were titrated by 20 mg per week until they achieved their assigned dose. The primary efficacy outcome was change in Total Score from baseline to endpoint in investigator ratings on the ADHD Rating Scale (ADHD-RS). Endpoint was defined as the last post-randomization treatment week (i.e., Weeks 1 through 4) for which a valid score was obtained. All lisdexamfetamine dimesylate dose groups were superior to placebo in the primary efficacy outcome (Study 4 in Table 6).

Pediatric Patients Ages 6 to 17 Years: Short-Term Treatment in ADHD: A double-blind, randomized, placebo- and active-controlled parallel-group, dose-optimization study (Study 5) was conducted in pediatric patients ages 6 to 17 years (n=336) who met DSM-IV criteria for ADHD. In this eight-week study, patients were randomized to a daily morning dose of lisdexamfetamine dimesylate (30, 50 or 70 mg/day), an active control, or placebo (1:1:1). The study consisted of a Screening and Washout Period (up to 42 days), a 7-week Double-blind Evaluation Period (consisting of a 4-week Dose-Optimization Period followed by a 3-week Dose-Maintenance Period), and a 1-week Washout and Follow-up Period. During the Dose Optimization Period, subjects were titrated until an optimal dose, based on tolerability and investigator's judgment, was reached. Lisdexamfetamine dimesylate showed significantly greater efficacy than placebo. The placebo-

adjusted mean reduction from baseline in the ADHD-RS-IV total score was 18.6. Subjects on lisdexamfetamine dimesylate also showed greater improvement on the Clinical Global Impression-Improvement (CGI-I) rating scale compared to subjects on placebo (Study 5 in Table 6).

Pediatric Patients Ages 6 to 17 Years: Maintenance Treatment in ADHD: Maintenance of Efficacy Study (Study 6) - A double-blind, placebo-controlled, randomized withdrawal study was conducted in pediatric patients ages 6 to 17 years (N=276) who met the diagnosis of ADHD (DSM-IV criteria). A total of 276 patients were enrolled into the study, 236 patients participated in Study 5 and 40 subjects directly enrolled. Subjects were treated with open-label lisdexamfetamine dimesylate for at least 26 weeks prior to being assessed for entry into the randomized withdrawal period. Eligible patients had to demonstrate treatment response as defined by CGI-S <3 and Total Score on the ADHD-RS ≤22. Patients that maintained treatment response for 2 weeks at the end of the open label treatment period were eligible to be randomized to ongoing treatment with the same dose of lisdexamfetamine dimesylate (N=78) or switched to placebo (N=79) during the double-blind phase. Patients were observed for relapse (treatment failure) during the 6 week double blind phase. A significantly lower proportion of treatment failures occurred among lisdexamfetamine dimesylate subjects (15.8%) compared to placebo (67.5%) at endpoint of the randomized withdrawal period. The endpoint measurement was defined as the last post-randomization treatment week at which a valid ADHD-RS Total Score and CGI-S were observed. Treatment failure was defined as a ≥50% increase (worsening) in the ADHD-RS Total Score and a ≥2-point increase in the CGI-S score compared to scores at entry into the double-blind randomized withdrawal phase. Subjects who withdrew from the randomized withdrawal period and who did not provide efficacy data at their last on-treatment visit were classified as treatment failures (Study 6, Figure 5).

Adults: Short-Term Treatment in ADHD: A double-blind, randomized, placebo-controlled, parallel-group study (Study 7) was conducted in adults ages 18 to 55 (N=420) who met DSM-IV criteria for ADHD. In this study, patients were randomized to receive final doses of 30 mg, 50 mg, or 70 mg of lisdexamfetamine dimesylate or placebo for a total of four weeks of treatment. All patients receiving lisdexamfetamine dimesylate were initiated on 30 mg for the first week of treatment. Patients assigned to the 50 mg and 70 mg dose groups were titrated by 20 mg per week until they achieved their assigned dose. The primary efficacy outcome was change in Total Score from baseline to endpoint in investigator ratings on the ADHD Rating Scale (ADHD-RS). Endpoint was defined as the last post-randomization treatment week (i.e., Weeks 1 through 4) for which a valid score was obtained. All lisdexamfetamine dimesylate dose groups were superior to placebo in the primary efficacy outcome (Study 7 in Table 6).

The second study was a multi-center, randomized, double-blind, placebo-controlled, cross-over, modified analog classroom study (Study 8) of lisdexamfetamine dimesylate to simulate a workplace environment in 142 adults ages 18 to 55 who met DSM-IV-TR criteria for ADHD. There was a 4-week open-label, dose optimization phase with lisdexamfetamine dimesylate (30 mg/day, 50 mg/day, or 70 mg/day in the morning). Patients were then randomized to one of two treatment sequences: 1) lisdexamfetamine dimesylate (optimized dose) followed by placebo, each for one week, or 2) placebo followed by lisdexamfetamine dimesylate, each for one week. Efficacy assessments occurred at the end of each week, using the Permanent Product Measure of Performance (PERMP), a skill-adjusted math test that measures attention in ADHD. PERMP total score results from the sum of the number of math problems attempted plus the number of math problems answered correctly. Lisdexamfetamine dimesylate treatment, compared to placebo, resulted in a statistically significant improvement in attention across all post-dose time points, as measured by average PERMP total scores over the course of one assessment day, as well as at each time point measured. The PERMP assessments were administered at pre-dose (-0.5 hours) and at 2, 4, 8, 10, 12, and 14 hours post-dose (Study 8 in Table 6, Figure 6).

Adults: Maintenance Treatment in ADHD: A double-blind, placebo-controlled, randomized withdrawal design study (Study 9) was conducted in adults ages 18 to 55 (N=123) who had a documented diagnosis of ADHD or met DSM-IV criteria for ADHD. At study entry, patients must have had documentation of treatment with lisdexamfetamine dimesylate for a minimum of 6 months and had to demonstrate treatment response as defined by Clinical Global Impression Severity (CGI-S) ≤3 and Total Score on the ADHD-RS <22. ADHD-RS Total Score is a measure of core symptoms of ADHD. The CGI-S score assesses the clinician’s impression of the patient’s current illness state and ranges from 1 (not at all ill) to

7 (extremely ill). Patients that maintained treatment response at Week 3 of the open label treatment phase (N=116) were eligible to be randomized to ongoing treatment with the same dose of lisdexamfetamine dimesylate (N=56) or switched to placebo (N=60) during the double-blind phase. Patients were observed for relapse (treatment failure) during the 6-week double-blind phase. The efficacy endpoint was the proportion of patients with treatment failure during the double-blind phase. Treatment failure was defined as a ≥50% increase (worsening) in the ADHD-RS Total Score and ≥2-point increase in the CGI-S score compared to scores at entry into the double-blind phase. Maintenance of efficacy for patients treated with lisdexamfetamine dimesylate was demonstrated by the significantly lower proportion of patients with treatment failure (9%) compared to patients receiving placebo (75%) at endpoint during the double-blind phase (Study 9, Figure 7).

Table 6: Summary of Primary Efficacy Results from Short-term Studies of Lisdexamfetamine dimesylate in Pediatric Patients (Ages 6 to 17) and Adults with ADHD

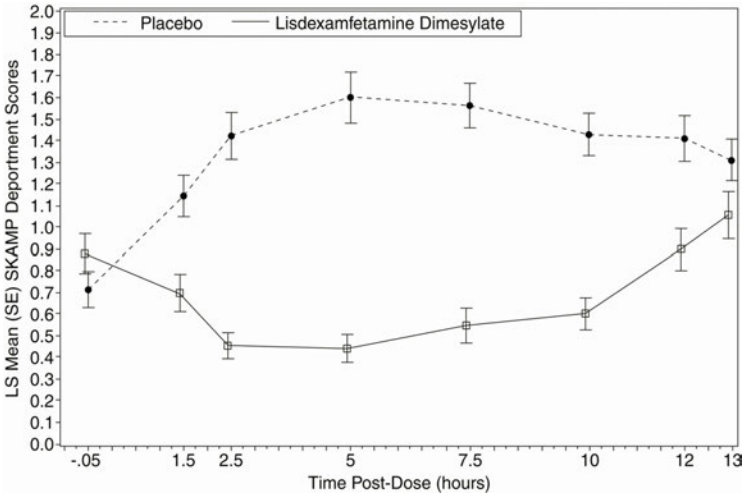
Study No. (Age range)	Primary Endpoint	Treatment Group	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Study 1 (6 -12 years)	ADHD-RSIV	lisdexamfetamine dimesylate (30 mg/day)[1]	43.2 (6.7)	-21.8 (1.6)	-15.6 (-19.9, -11.2)
		lisdexamfetamine dimesylate (50 mg/day)[1]	43.3 (6.7)	-23.4 (1.6)	-17.2 (-21.5, -12.9)
		lisdexamfetamine dimesylate (70 mg/day)[1]	45.1(6.8)	-26.7 (1.5)	-20.5 (-24.8, -16.2)
		Placebo	42.4 (7.1)	-6.2 (1.6)	--
Study 2 (6 -12 years)	Average SKAMP-DS	lisdexamfetamine dimesylate (30, 50 or 70 mg/day)[1]	--[b]	0.8 (0.1)[d]	-0.9 (-1.1, -0.7)
		Placebo	--[b]	1.7 (0.1)[d]	--
Study 3 (6 -12 years)	Average SKAMP-DS	lisdexamfetamine dimesylate (30, 50 or 70 mg/day)[1]	0.9 (1.0)[c]	0.7 (0.1)[d]	-0.7 (-0.9, -0.6)
		Placebo	0.7 (0.9)[c]	1.4 (0.1)[d]	--
Study 4 (13 -17 years)	ADHD-RS-IV	lisdexamfetamine dimesylate (30 mg/day)[1]	38.3 (6.7)	-18.3 (1.2)	-5.5 (-9.0, -2.0)
		lisdexamfetamine dimesylate (50 mg/day)[1]	37.3 (6.3)	-21.1 (1.3)	-8.3 (-11.8, -4.8)
		lisdexamfetamine dimesylate (70 mg/day)[1]	37.0 (7.3)	-20.7 (1.3)	-7.9 (-11.4, -4.5)
		Placebo	38.5 (7.1)	-12.8 (1.2)	--
Study 5 (6 -17 years)	ADHD-RS-IV	lisdexamfetamine dimesylate (30,	40.7 (7.3)	-24.3 (1.2)	-18.6 (-21.5, -15.7)

		50 or 70 mg/day)[1]			
		Placebo	41.0 (7.1)	-5.7 (1.1)	--
Study 7 (18 -55 years)	ADHD-RS-IV	lisdexamfetamine dimesylate (30 mg/day)[1]	40.5 (6.2)	-16.2 (1.1)	-8.0 (-11.5, -4.6)
		lisdexamfetamine dimesylate (50 mg/day)[1]	40.8 (7.3)	-17.4 (1.0)	-9.2 (-12.6, -5.7)
		lisdexamfetamine dimesylate (70 mg/day)[1]	41.0 (6.0)	-18.6 (1.0)	-10.4 (-13.9, -6.9)
		Placebo	39.4 (6.4)	-8.2 (1.4)	--
Study 8 (18 -55 years)	Average PERMP	lisdexamfetamine dimesylate (30, 50 or 70 mg/day)[1]	260.1 (86.2)[c]	312.9 (8.6)[d]	23.4 (15.6, 31.2)
		Placebo	261.4 (75.0)[c]	289.5 (8.6)[d]	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval.
[a] Difference (drug minus placebo) in least-squares mean change from baseline.
[b] Pre-dose SKAMP-DS was not collected.
[c] Pre-dose SKAMP-DS (Study 3) or PERMP (Study 8) total score, averaged over both periods.
[d] LS Mean for SKAMP-DS (Study 2 and 3) or PERMP (Study 8) is post-dose average score over all sessions of the treatment day, rather than change from baseline.

1. Doses statistically significantly superior to placebo.

Figure 4 LS Mean SKAMP Deportment Subscale Score by Treatment and Time-point for Pediatric Patients Ages 6 to 12 with ADHD after 1 Week of Double Blind Treatment (Study 3)



Higher score on the SKAMP-Deportment scale indicates more severe symptoms.

Figure 5 Kaplan-Meier Estimated Proportion of Patients with Treatment Failure for Pediatric Patients Ages 6 to 17 (Study 6)

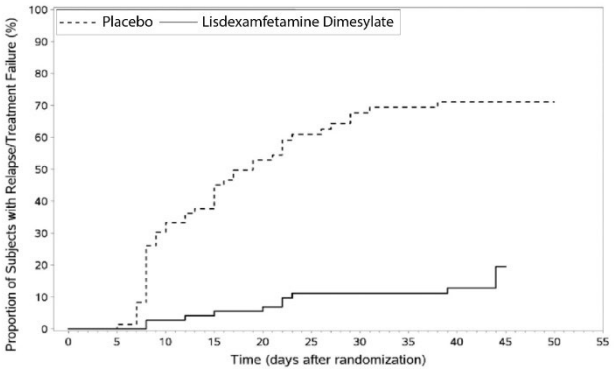
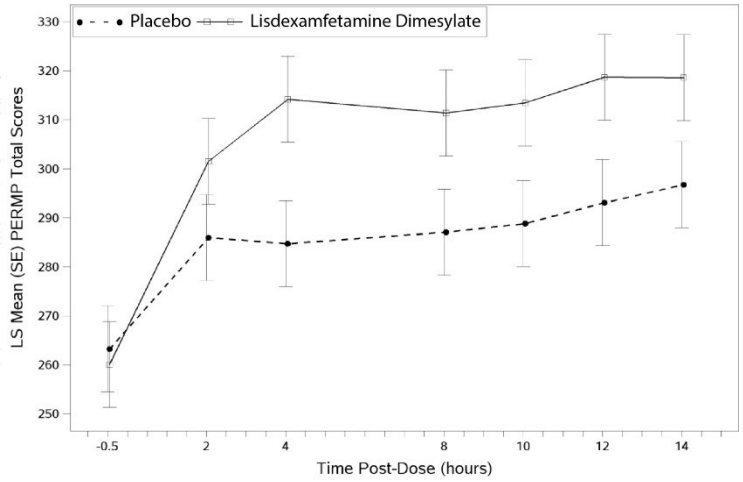
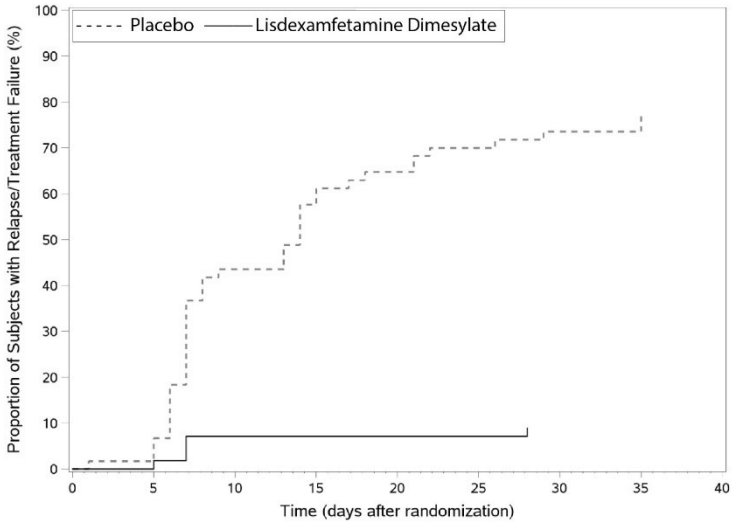


Figure 6 LS Mean (SE) PERMP Total Score by Treatment and Time-point for Adults Ages 18 to 55 with ADHD after 1 Week of Double Blind Treatment (Study 8)



Higher score on the PERMP scale indicates less severe symptoms.

Figure 7 Kaplan-Meier Estimated Proportion of Subjects with Relapse in Adults with ADHD (Study 9)



14.2 Binge Eating Disorder (BED)

A phase 2 study evaluated the efficacy of lisdexamfetamine dimesylate 30, 50 and 70 mg/day compared to placebo in reducing the number of binge days/week in adults with at least moderate to severe BED. This randomized, double-blind, parallel-group, placebo-controlled, forced-dose titration study (Study 10) consisted of an 11-week double-blind treatment period (3 weeks of forced-dose titration followed by 8 weeks of dose maintenance). Lisdexamfetamine dimesylate 30 mg/day was not statistically different from placebo on the primary endpoint. The 50 and 70 mg/day doses were statistically superior to placebo on the primary endpoint.

The efficacy of lisdexamfetamine dimesylate in the treatment of BED was demonstrated in two 12-week randomized, double-blind, multi-center, parallel-group, placebo-controlled, dose-optimization studies (Study 11 and Study 12) in adults aged 18-55 years (Study 11: N=374, Study 12: N=350) with moderate to severe BED. A diagnosis of BED was confirmed using DSM-IV criteria for BED. Severity of BED was determined based on having at least 3 binge days per week for 2 weeks prior to the baseline visit and on having a Clinical Global Impression Severity (CGI-S) score of ≥4 at the baseline visit. For both studies, a binge day was defined as a day with at least 1 binge episode, as determined from the subject's daily binge diary.

Both 12-week studies consisted of a 4-week dose-optimization period and an 8-week dose-maintenance period. During dose-optimization, subjects assigned to lisdexamfetamine dimesylate began treatment at the titration dose of 30 mg/day and, after 1 week of treatment, were subsequently titrated to 50 mg/day. Additional increases to 70 mg/day were made as tolerated and clinically indicated. Following the dose-optimization period, subjects continued on their optimized dose for the duration of the dose-maintenance period.

The primary efficacy outcome for the two studies was defined as the change from baseline at Week 12 in the number of binge days per week. Baseline is defined as the weekly average of the number of binge days per week for the 14 days prior to the baseline visit. Subjects from both studies on lisdexamfetamine dimesylate had a statistically significantly greater reduction from baseline in mean number of binge days per week at Week 12. In addition, subjects on lisdexamfetamine dimesylate showed greater improvement as compared to placebo across key secondary outcomes with higher proportion of subjects rated improved on the CGI-I rating scale, higher proportion of subjects with 4-week binge cessation, and greater reduction in the Yale-Brown Obsessive Compulsive Scale Modified for Binge Eating (Y-BOCS-BE) total score.

Table 7: Summary of Primary Efficacy Results in BED

Study	Treatment Group	Primary Efficacy Measure: Binge Days per Week at Week 12

Number		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Study 11	lisdexamfetamine dimesylate (50 or 70 mg/day)[1]	4.79 (1.27)	-3.87 (0.12)	-1.35 (-1.70, -1.01)
	Placebo	4.60 (1.21)	-2.51 (0.13)	--
Study 12	lisdexamfetamine dimesylate (50 or 70 mg/day)[1]	4.66 (1.27)	-3.92 (0.14)	-1.66 (-2.04, -1.28)
	Placebo	4.82 (1.42)	-2.26 (0.14)	--

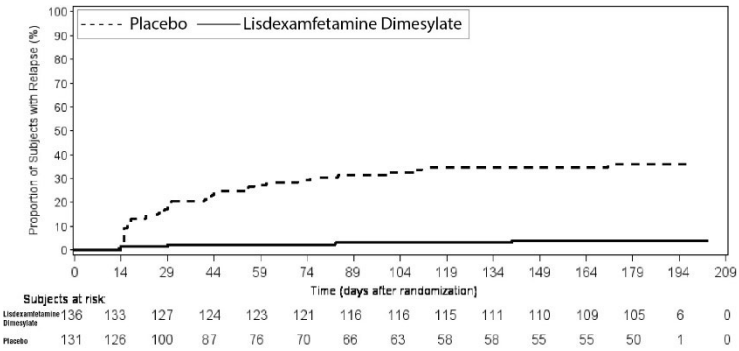
SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval.

[a] Difference (drug minus placebo) in least-squares mean change from baseline.

1. Doses statistically significantly superior to placebo.

A double-blind, placebo controlled, randomized withdrawal design study (Study 13) was conducted to evaluate maintenance of efficacy based on time to relapse between lisdexamfetamine dimesylate and placebo in adults aged 18 to 55 (N=267) with moderate to severe BED. In this longer-term study patients who had responded to lisdexamfetamine dimesylate in the preceding 12-week open-label treatment phase were randomized to continuation of lisdexamfetamine dimesylate or placebo for up to 26 weeks of observation for relapse. Response in the open-label phase was defined as 1 or fewer binge days each week for four consecutive weeks prior to the last visit at the end of the 12-week open-label phase and a CGIS score of 2 or less at the same visit. Relapse during the double-blind phase was defined as having 2 or more binge days each week for two consecutive weeks (14 days) prior to any visit and having an increase in CGI-S score of 2 or more points compared to the randomized-withdrawal baseline. Maintenance of efficacy for patients who had an initial response during the open-label period and then continued on lisdexamfetamine dimesylate during the 26-week double-blind randomized-withdrawal phase was demonstrated with lisdexamfetamine dimesylate being superior over placebo as measured by time to relapse.

Figure 8 Kaplan-Meier Estimated Proportions of Subjects with Relapse in Adults with BED (Study 13)



Examination of population subgroups based on age (there were no patients over 65), gender, and race did not reveal any clear evidence of differential responsiveness in the treatment of BED.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Lisdexamfetamine dimesylate capsules 20 mg: ivory body/ivory cap (imprinted with 54 990) Bottle of 30, NDC 0054-0370-13; Bottle of 100, NDC 0054-0370-25

Lisdexamfetamine dimesylate capsules 30 mg: white body/orange cap (imprinted with 54 682) Bottle of 30, NDC 0054-0371-13; Bottle of 100, NDC 0054-0371-25

Lisdexamfetamine dimesylate capsules 40 mg: white body/light green cap (imprinted with 54 098) Bottle of 30, NDC 0054-0372-13; Bottle of 100, NDC 0054-0372-25

Lisdexamfetamine dimesylate capsules 50 mg: white body/blue cap (imprinted with 54 296) Bottle of 30, NDC 0054-0373-13; Bottle of 100, NDC 0054-0373-25

Lisdexamfetamine dimesylate capsules 60 mg: blue body/blue cap (imprinted with 54 338) Bottle of 30, NDC 0054-0374-13; Bottle of 100, NDC 0054-0374-25

Lisdexamfetamine dimesylate capsules 70 mg: orange body/blue cap (imprinted with 54 818) Bottle of 30, NDC 0054-0375-13; Bottle of 100, NDC 0054-0375-25

16.2 Storage and Handling

Dispense in a tight, light-resistant container as defined in the USP.

Store at 20° to 25°C (68° to 77°F). Excursions permitted between 15º to 30ºC (59 to 86ºF) [See USP Controlled Room Temperature].

Disposal: Comply with local laws and regulations on drug disposal of CNS stimulants. Dispose of remaining, unused, or expired lisdexamfetamine dimesylate capsules by a medicine take-back program.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Controlled Substance Status/High Potential for Abuse and Dependence: Advise patients that lisdexamfetamine dimesylate is a controlled substance and it can be abused and lead to dependence and not to give lisdexamfetamine dimesylate to anyone else *[see Drug Abuse and Dependence (9.1, 9.2, and 9.3)]*. Advise patients to store lisdexamfetamine dimesylate in a safe place, preferably locked, to prevent abuse. Advise patients to dispose of remaining, unused, or expired lisdexamfetamine dimesylate by a medicine take-back program.

Serious Cardiovascular Risks: Advise patients that there is a potential serious cardiovascular risk including sudden death, myocardial infarction, stroke, and hypertension with lisdexamfetamine dimesylate use. Instruct patients to contact a healthcare provider immediately if they develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease *[see Warnings and Precautions (5.2)]*.

Hypertension and Tachycardia: Instruct patients that lisdexamfetamine dimesylate can cause elevations of their blood pressure and pulse rate and they should be monitored for such effects.

Psychiatric Risks: Advise patients that lisdexamfetamine dimesylate at recommended doses may cause psychotic or manic symptoms even in patients without prior history of psychotic symptoms or mania *[see Warnings and Precautions (5.4)]*.

Suppression of Growth: Advise patients that lisdexamfetamine dimesylate may cause slowing of growth including weight loss *[see Warnings and Precautions (5.5)]*.

Impairment in Ability to Operate Machinery or Vehicles: Advise patients that lisdexamfetamine dimesylate may impair their ability to engage in potentially dangerous activities such as operating machinery or vehicles. Instruct patients to find out how lisdexamfetamine dimesylate will affect them before engaging in potentially dangerous activities *[see Adverse Reactions (6.1, 6.2)]*.

Circulation problems in fingers and toes [Peripheral vasculopathy, including Raynaud's phenomenon]: Instruct patients beginning treatment with lisdexamfetamine dimesylate about the risk of peripheral vasculopathy, including Raynaud's phenomenon, and associated signs and symptoms: fingers or toes may feel numb, cool, painful, and/or may change from pale, to blue, to red. Instruct patients to report to their physician any new numbness, pain, skin color change, or sensitivity to temperature in fingers or toes. Instruct patients to call their physician immediately with any signs of unexplained wounds appearing on fingers or toes while taking lisdexamfetamine dimesylate. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients *[see Warnings and Precautions (5.6)]*.

Serotonin Syndrome: Caution patients about the risk of serotonin syndrome with concomitant use of lisdexamfetamine dimesylate and other serotonergic drugs including SSRIs, SNRIs, triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, St. John's Wort, and with drugs that impair metabolism of serotonin (in particular MAOIs, both those intended to treat psychiatric disorders and also others such as linezolid *[see Contraindications (4), Warnings and Precautions (5.7) and Drug Interactions (7.1)]*. Advise patients to contact their healthcare provider or report to the emergency room if they experience signs or symptoms of serotonin syndrome.

Concomitant Medications: Advise patients to notify their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs because there is a potential for interactions *[see Drug Interactions (7.1)]*.

Pregnancy: Advise patients of the potential fetal effects from the use of lisdexamfetamine dimesylate during pregnancy. Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with lisdexamfetamine dimesylate *[see Use in Specific Populations (8.1)]*.

Lactation: Advise women not to breastfeed if they are taking lisdexamfetamine dimesylate *[see Use in Specific Populations (8.2)]*.

Administration Instructions

- Capsules: Advise patients to take the capsules whole or empty and mix the entire contents with yogurt, water, or orange juice. Advise patients to consume the mixture immediately and not to store for future use *[see Dosage and Administration (2.2)]*.

Distributed by: **Hikma**
Pharmaceuticals USA Inc.
Berkeley Heights, NJ 07922

C50001173/01
Revised June 2023

MEDICATION GUIDE
LISDEXAMFETAMINE DIMESYLATE
(lis-DEX-am-FET-ah-meen) Capsules, CII

What is the most important information I should know about lisdexamfetamine dimesylate capsules?
Lisdexamfetamine dimesylate capsules may cause serious side effects, including:

- **Abuse and dependence.** Lisdexamfetamine dimesylate capsules, other amphetamine containing medicines, and methylphenidate have a high chance for abuse and may cause physical and psychological dependence. Your

healthcare provider should check you or your child for signs of abuse and dependence before and during treatment with lisdexamfetamine dimesylate capsules.
    - Tell your healthcare provider if you or your child have ever abused or been dependent on alcohol, prescription medicines, or street drugs.
    - Your healthcare provider can tell you more about the differences between physical and psychological dependence and drug addiction.
- **Heart-related problems including:**
    - sudden death, stroke, and heart attack in adults
    - sudden death in children who have heart problems or heart defects
    - increased blood pressure and heart rate

Your healthcare provider should check you or your child carefully for heart problems before starting treatment with lisdexamfetamine dimesylate capsules. Tell your healthcare provider if you or your child have any heart problems, heart defects, high blood pressure, or a family history of these problems.
Your healthcare provider should check your or your child's blood pressure and heart rate regularly during treatment with lisdexamfetamine dimesylate capsules.
Call your healthcare provider or go to the nearest hospital emergency room right away if you or your child have any signs of heart problems such as chest pain, shortness of breath, or fainting during treatment with lisdexamfetamine dimesylate capsules.

- **Mental (psychiatric) problems, including:**
    - new or worse behavior and thought problems
    - new or worse bipolar illness
    - new psychotic symptoms (such as hearing voices, or seeing or believing things that are not real) or new manic symptoms

Tell your healthcare provider about any mental problems you or your child have or about a family history of suicide, bipolar illness, or depression.
Call your healthcare provider right away if you or your child have any new or worsening mental symptoms or problems during treatment with lisdexamfetamine dimesylate capsules, especially hearing voices, seeing or believing things that are not real, or new manic symptoms.

What are lisdexamfetamine dimesylate capsules?
Lisdexamfetamine dimesylate capsules are central nervous system (CNS) stimulant prescription medicine used for the treatment of:

- Attention Deficit Hyperactivity Disorder (ADHD) in adults and children 6 years of age and older. Lisdexamfetamine dimesylate capsules may help increase attention and decrease impulsiveness and hyperactivity in people with ADHD.
- Moderate to severe binge eating disorder (BED) in adults. Lisdexamfetamine dimesylate **capsules** may help reduce the number of binge eating days in people with BED.

Lisdexamfetamine dimesylate capsules are not for use in children under 6 years of age with ADHD.
Lisdexamfetamine dimesylate capsules are not for weight loss. It is not known if lisdexamfetamine dimesylate capsules are safe and effective for the treatment of obesity. It is not known if lisdexamfetamine dimesylate capsules are safe and effective for use in children with BED.
Lisdexamfetamine dimesylate capsules are federally controlled substance (CII) because it contains lisdexamfetamine dimesylate that can be a target for people who abuse prescription medicines or street drugs.
Keep lisdexamfetamine dimesylate capsules in a safe place to protect it from theft. Never give your lisdexamfetamine dimesylate capsules to anyone else because it may cause death or harm them. Selling or giving away lisdexamfetamine dimesylate capsules may harm others and is against the law.

Do not take lisdexamfetamine dimesylate capsules if you or your child are:

- allergic to amphetamine products or any of the ingredients in lisdexamfetamine dimesylate capsules. See the end of this Medication Guide for a complete list of ingredients in lisdexamfetamine dimesylate capsules.

- taking, or have stopped taking in the last 14 days, a medicine called a Monoamine Oxidase Inhibitor (MAOI).
- being treated with the antibiotic linezolid or intravenous methylene blue.

Before taking lisdexamfetamine dimesylate capsules, tell your healthcare provider about all medical conditions, including if you or your child:

- have heart problems, heart defects, or high blood pressure
- have mental problems including psychosis, mania, bipolar illness, or depression or have a family history of suicide, bipolar illness, or depression
- have circulation problems in fingers and toes
- are pregnant or plan to become pregnant. Lisdexamfetamine dimesylate capsules may harm the unborn baby.
  o There is a pregnancy registry for females who are exposed to lisdexamfetamine dimesylate capsules during pregnancy. The purpose of the registry is to collect information about the health of females exposed to lisdexamfetamine dimesylate capsules and their baby. If you or your child becomes pregnant during treatment with lisdexamfetamine dimesylate capsules, talk to your healthcare provider about registering with the National Pregnancy Registry for Psychostimulants at 1-866-961-2388 or visit online at https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/adhd-medications/.
- are breastfeeding or plan to breastfeed. Lisdexamfetamine dimesylate capsules passes into breast milk. You should not breastfeed during treatment with lisdexamfetamine dimesylate capsules. Talk to your healthcare provider about the best way to feed the baby during treatment with lisdexamfetamine dimesylate capsules.

Tell your healthcare provider about all the medicines that you or your child take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Lisdexamfetamine dimesylate capsules can affect the way other medicines work and other medicines may affect how lisdexamfetamine dimesylate capsules works. Taking lisdexamfetamine dimesylate capsules with other medicines can cause serious side effects. Sometimes the doses of other medicines will need to be changed while taking lisdexamfetamine dimesylate capsules.

Especially tell your healthcare provider if you or your child take:

- selective serotonin reuptake inhibitors (SSRIs)
- medicines used to treat migraine headaches called triptans
- lithium
- tramadol
- buspirone
- serotonin norepinephrine reuptake inhibitors (SNRIs)
- tricyclic antidepressants
- fentanyl
- tryptophan
- St. John's Wort

Keep a list of all medicines to show your healthcare provider and pharmacist when you get a new medicine. Your healthcare provider will decide if lisdexamfetamine dimesylate capsules can be taken with other medicines.

Do not start any new medicine during treatment with lisdexamfetamine dimesylate capsules without talking to your healthcare provider first.

How should lisdexamfetamine dimesylate capsules be taken?

- Take lisdexamfetamine dimesylate capsules exactly as prescribed by your healthcare provider.
- Your healthcare provider may change the dose if needed.
- Take lisdexamfetamine dimesylate capsules 1 time each day in the morning with or without food.
- Your healthcare provider may sometimes stop lisdexamfetamine dimesylate capsules treatment for a while to check ADHD or BED symptoms.

- Lisdexamfetamine dimesylate comes in capsules.

Taking lisdexamfetamine dimesylate capsules:

- Lisdexamfetamine dimesylate capsules may be swallowed whole.
- If lisdexamfetamine dimesylate capsules cannot be swallowed whole, the capsule may be opened and the entire contents sprinkled onto yogurt, or poured into water or orange juice.
  - Using a spoon, break apart any powder that is stuck together. Stir the lisdexamfetamine dimesylate capsules powder and yogurt, water, or orange juice until they are completely mixed together.
  - Swallow all the yogurt, water, or orange juice mixture right away. **Do not** store the yogurt, water, or orange juice mixture.
  - It is normal to see a filmy coating on the inside of your glass or container after you eat or drink all the lisdexamfetamine dimesylate capsules mixture.

If you or your child take too much lisdexamfetamine amfetamine, call your healthcare provider or poison control center at 1-800-222-1222 or go to the nearest hospital emergency room right away.

What should I avoid while taking lisdexamfetamine dimesylate capsules?
Do not drive, operate machinery, or do other dangerous activities until you know how lisdexamfetamine dimesylate capsules affects you.

What are the possible side effects of lisdexamfetamine dimesylate capsules?
Lisdexamfetamine dimesylate capsules may cause serious side effects, including:

- See **"What is the most important information I should know about lisdexamfetamine dimesylate capsules?"**
- **Slowing of growth (height and weight) in children.** Children should have their height and weight checked often during treatment with lisdexamfetamine dimesylate capsules. Lisdexamfetamine dimesylate capsules treatment may be stopped if your child is not growing or gaining weight.
- **Circulation problems in fingers and toes (Peripheral vasculopathy, including Raynaud's phenomenon).**
  Signs and symptoms may include:
  - Fingers or toes may feel numb, cool, painful
  - Fingers or toes may change color from pale, to blue, to red

  Tell your healthcare provider if you or your child have numbness, pain, skin color change, or sensitivity to temperature in your fingers or toes.
  Call your healthcare provider right away if you or your child have any signs of unexplained wounds appearing on fingers or toes during treatment with lisdexamfetamine dimesylate capsules.
- **Serotonin Syndrome.** A potentially life-threatening problem called serotonin syndrome may happen when lisdexamfetamine dimesylate capsules are taken with certain other medicines. Stop taking lisdexamfetamine dimesylate capsules and call your healthcare provider or go to the nearest hospital emergency room right away if you or your child develop any of the following signs and symptoms of serotonin syndrome:
  - agitation
  - flushing
  - coma
  - loss of coordination
  - dizziness
  - seeing or hearing things that are not real (hallucination)
  - high body temperature (hyperthermia)
  - fast heartbeat
  - seizures
  - sweating
  - confusion
  - tremors, stiff muscles, or muscle twitching
  - changes in blood pressure
  - Nausea, vomiting, diarrhea

The most common side effects of lisdexamfetamine dimesylate capsules in children 6 to 17 years old and adults with ADHD include:

- loss of appetite (anorexia)
- decreased appetite
- diarrhea
- dry mouth
- trouble sleeping
- stomach pain
- anxiety
- weight loss
- dizziness
- irritability
- nausea
- vomiting

The most common side effects of lisdexamfetamine dimesylate capsules in adults with BED include:

- dry mouth
- decreased appetite
- constipation
- anxiety
- trouble sleeping
- increased heart rate
- feeling jittery

These are not all the possible side effects of lisdexamfetamine dimesylate capsules.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store lisdexamfetamine dimesylate capsules?

- Store lisdexamfetamine dimesylate capsules in a safe place (like a locked cabinet) and in a tightly closed container at room temperature between 68°F to 77°F (20°C to 25°C).
- Protect lisdexamfetamine dimesylate capsules from light.
- Dispose of remaining, unused, or expired lisdexamfetamine dimesylate capsules by a medicine take-back program at authorized collection sites such as retail pharmacies, hospital or clinic pharmacies, and law enforcement locations. If no take-back program or authorized collector is available, mix lisdexamfetamine dimesylate capsules with an undesirable, nontoxic substance such as dirt, cat litter, or used coffee grounds to make it less appealing to children and pets. Place the mixture in a container such as a sealed plastic bag and throw away (discard) lisdexamfetamine dimesylate capsules in the household trash.

Keep lisdexamfetamine dimesylate capsules and all medicines out of the reach of children.

General information about the safe and effective use of lisdexamfetamine dimesylate capsules.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use lisdexamfetamine dimesylate capsules for a condition for which it was not prescribed. Do not give lisdexamfetamine dimesylate capsules to other people, even if they have the same symptoms that you have. It may harm them and it is against the law. You can ask your pharmacist or healthcare provider for information about lisdexamfetamine dimesylate capsules that is written for health professionals.

What are the ingredients in lisdexamfetamine dimesylate capsules?
Active Ingredient: lisdexamfetamine dimesylate
Inactive Ingredients: ammonium hydroxide, calcium phosphate, gelatin, iron oxide black, isopropyl alcohol, magnesium stearate, microcrystalline cellulose, n-butyl alcohol, propylene glycol, shellac glaze, sodium starch glycolate, and titanium dioxide. In addition, the 20 mg capsule also contains yellow iron oxide. The 30 mg capsule also contains FD&C yellow #6. The 40 mg capsule also contains FD&C blue #1 and FD&C green #3. The 50 mg and 60 mg capsules also contains D&C red #28 and FD&C blue #1. The 70 mg capsule also contains D&C red #28, FD&C blue #1, and FD&C yellow #6.

For more information about lisdexamfetamine dimesylate capsules, go to www.hikma.com or call 1-800-962-8364.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Distributed by: **Hikma**

Pharmaceuticals USA Inc.
Berkeley Heights, NJ 07922

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Revised June 2023

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA202090

LABELING REVIEW(s)

Labeling Review

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	June 13, 2023
ANDA Number(s)	202827
Review Number	8
Applicant Name	HIKMA PHARMACEUTICALS USA INC
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Lisdexamfetamine Dimesylate Capsules, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg
Proposed Proprietary Name	None
Submission Received Date	June 9, 2023
Primary Labeling Reviewer	Alison Park
Secondary Labeling Reviewer	Refer to signature page

Review Conclusion

☒ Acceptable - No Comments
☐ Acceptable - Include Post Approval Comments
☐ Minor Deficiency* - Refer to Labeling Deficiencies and Comments for Letter to Applicant
☐ Major Deficiency** - Refer to Labeling Deficiencies and Comments for Letter to Applicant

On Policy Alert List	☒ Yes	☐ No
Acceptable For Filing	☒ Yes	☐ No
Combined Insert/Outsert	☐ Yes	☒ No

TABLE OF CONTENTS

1 LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT
1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE
1.3 POST-APPROVAL REVISIONS

2 INSTRUCTIONS FOR ASSESSMENT
3 OVERALL ASSESSMENT OF MATERIALS REVIEWED
4 LABELING REVIEW INFORMATION

4.1 REGULATORY INFORMATION
4.2 MODEL PRESCRIBING INFORMATION
4.3 PATENTS AND EXCLUSIVITIES
4.4 UNITED STATES PHARMACOPEIA (USP)
4.5 MODEL CONTAINER LABELS

5 ASSESSMENT OF ANDA LABELING AND LABELS

5.1 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS)

5.1.1 DRUG PRODUCT REVIEW
5.1.2 DESCRIPTION
5.1.3 HOW SUPPLIED/STORAGE AND HANDLING
5.1.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER

5.2 CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS)

5.3 PRESCRIBING INFORMATION
5.4 MEDICATION GUIDE

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES

1 LABELING COMMENTS (C8)

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT (C8)

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE (C8)

The Division of Labeling has no further questions/comments at this time based on your labeling submission received June 9, 2023.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.3 POST-APPROVAL REVISIONS (C8)

These comments will be addressed post approval (in the first labeling supplement review).

2 INSTRUCTIONS FOR ASSESSMENT (C8)

General Comments:

Select the "no deficiency" or "deficiency" radio button as appropriate for each row. If a "Deficiency Comments" appears, ensure it is appropriate for your situation, edit, or enter "Reviewer Comments" if necessary.

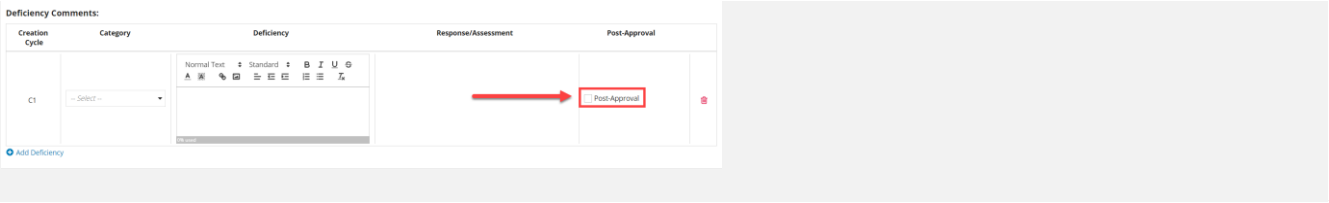
If there is no issue/concern, or if the question is not applicable. No "Deficiency Comments" will appear but reviewers can still enter "Reviewer Comments" if desired.

☐	☒	There is information in the Orange Book that the applicant needs to address.
☒	☐	Information in the Orange Book has **expired** and the applicant needs to revise labeling.

Reviewer Comments:
Enter free text in this section as necessary.

Deficiency Comments:

- Standardized comments/deficiencies are available for certain questions. For a complete list of standardized comments, reference the DLR Standardized Comments SharePoint.
- Reviewers can modify standardized comments/deficiencies for their situation.
- Deficiencies will have a review number, deficiency number, and roman numeral in the user interface. For first original reviews the review number and iteration numeral will align; however, older reviews may have review numbers and iteration numerals that differ due to some reviews being completed under past practices.
- Deficiency comments will populate by default to the Labeling Comments deficiency section unless you select the Post-Approval checkbox. Assessors also have the option to move all comments to the Post-Approval Revisions section or vice versa from the Labeling Comments tab.



3 OVERALL ASSESSMENT OF MATERIALS REVIEWED (C8)

Table 1: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Final	20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg - Bottles of 30 and 100 capsules	09/19/2022	Satisfactory
Blister	N/A	N/A		
Carton	N/A	N/A		

Table 2: Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	Revised June 2023	06/09/2023	Satisfactory
Medication Guide	Draft	Revised June 2023	06/09/2023	Satisfactory
Patient Information	N/A	N/A		
Instructions for Use	N/A	N/A		
SPL Data Elements				

4 LABELING REVIEW INFORMATION(C8)

4.1 REGULATORY INFORMATION (C8)

Yes	No	
☒	☐	Are there any applicable issues in DLR's SharePoint Drug Facts ? **CYCLE 7 COMMENT:** Posted 7/3/19 and updated 12/2/22 National Pregnancy Registry for Psychiatric Medications

Yes	No	
		Brief Description Updated 12/2/2022: • Unless required as part of REMS, PR appears to be a third party's PR ◦ Add comment for Cycle 1 or if the PR is new in the NDA labeling ◦ If ANDA included the PR in labeling, we should comment for the ANDA applicant to reach out to third party and verify that the data for the generic product will be accepted as part of the PR (data might be collected for some generic products but not others). If it is verified that the data for the generic product will be accepted, the ANDA applicant can continue to include the PR in labeling. If data for the generic product will not be accepted, the ANDA applicant should remove the PR in labeling. ▪ Example comment to include in SCD: *The reference listed drug (RLD) for your drug product contains third party pregnancy registry information in its labeling. Please reach out to the third party to verify if the data for your generic drug product will be accepted as part of their pregnancy registry. If it is verified that the data for your generic drug product will be accepted by the third party, you can continue including the pregnancy registry information in your labeling. If it is determined that the data for your generic drug product will not be accepted by the third party, please remove the pregnancy registry information in your labeling.* ◦ If ANDA did not include PR in labeling, we should comment for the ANDA applicant to reach out to third party and determine if the data for the generic product will be accepted as part of the PR. If it is verified that the data for the generic product will be accepted, the ANDA applicant should include the PR in labeling. If data for the generic product will not be accepted, the ANDA applicant can continue to exclude the PR. ▪ Example comment to include in SCD: *The reference listed drug (RLD) for your drug product contains third party pregnancy registry information in its labeling. Please reach out to the third party to verify if the data for your generic drug product will be accepted as part of their pregnancy registry. If it is verified that the data for your generic drug product will be accepted by the third party, please include the pregnancy registry information in your labeling. If it is determined that the data for your generic drug product will not be accepted by the third party, you can continue excluding the pregnancy registry information in your labeling.* --- There is a pregnancy registry established by the Massachusetts General Hospital and Havard Medical school for the class of psychiatric medications. There are three different groups under the pregnancy registry but the phone number for the PR is the same for all three. 1. The National Pregnancy Registry for Atypical Antipsychotics 2. The National Pregnancy Registry for Antidepressants 3. The National Pregnancy Registry for ADHD Medications. Per DPMH, this NDA holders are required to list this PR in their insert labeling. We will request all ANDAs for psychiatric medications to list this PR in their labeling to be the same as the RLD. We do NOT need to ask the firm to confirm that they are registred with this organization to participate in the PR. **Updated 4/14/2021: Added active ingredients for Atypical Antipsychotics, Antidepressants, and ADHD Medication. Please update as needed.** The RLD, Vyvanse, includes a pregnancy registry information in section **8.1 Pregnancy**. Refer to **section 5.3** for detailed assessment and deficiency comment if applicable. **CYCLE 8 COMMENT:** Refer to **section 5.3** for applicant's response to C7 comment.
☒	☐	Is the drug product listed in the Policy Alert Tracker on **OGD's SharePoint**? Policy Alert Basis: Patent/Exclusivity; Docket #: Internal; Brand Name (or Drug Class): Vyvanse; Generic Name / Dosage Form / Strengths: Lisdexamfetamine Dimesylate capsules; Action Requested or Issue Description: 3-year exclusivity decision pending with CDER Exclusivity Board.; RLD#: 021977/S-046; Approval Actions (TA/AP): No Final Approval Actions can be issued while Exclusivity is being determined Policy Alert Basis: Patent/Exclusivity; Docket #: Internal; Brand Name (or Drug Class): Vyvanse; Generic Name / Dosage Form / Strengths: Lisdexamfetamine Dimesylate chewable tablets; Action Requested or Issue Description: 3-year exclusivity decision pending with CDER Exclusivity Board.; RLD#: 208510/S-003; Approval Actions (TA/AP): No Final Approval Actions can be issued while Exclusivity is being determined

Yes	No	

Communications (CRL, CC/IR/DRL)	Notes	Date Filed (~)	OGD Policy Lead
Application Communications can continue; Labeling affected if exclusivity is granted	Supplements that do not require updated labeling or labeling review are not affected.	7/29/2021	Kun Shen
Application Communications can continue; Labeling affected if exclusivity is granted	Supplements that do not require updated labeling or labeling review are not affected.	7/29/2021	Kun Shen

Primary discipline reviews may continue but NO final actions until final exclusivity determinations made.

4.2 MODEL PRESCRIBING INFORMATION (C8)

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling (Check the box used as the Model Labeling)

☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)

NDA#/Supplement# (S-000 if original): NDA 021977 / S-048

Supplement Approval Date: 02/25/2022

Proprietary Name: Vyvanse

Established Name: Lisdexamfetamine Dimesylate Capsules

Description of Supplement:

These supplemental new drug applications provide for revisions to the labeling for Vyvanse, Adderall XR and Mydayis consistent with the Agency's December 14, 2021, safety labeling change notification letter, notifying the Sponsor, under Section 505(o)(4) of the FDCA, of new safety information pertaining to the association between the use of amphetamines and intestinal ischemia, that the Agency believes should be included in the labeling for all amphetamines.

Link: https://analytics.fda.gov/workspace/hubble/external/object/v0/fda-communication?pk_communication=4943991_4538393_090140af80649ae3_NDA021977_3411801

☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**

☒ **OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out):**

The following labeling supplement is pending:

- **S-050, pending 6/9/23:** Reference is made to the Safety Labeling Change Notification received via email on 11 May 2023 requesting that the US Prescribing Information (USPI) for Vyvanse capsules be updated as part of a safety labeling change notification initiated for products belonging to the amphetamine class. As noted by the FDA in the 11 May 2023 email, this new information is important to include in labeling so prescribers provide appropriate counseling that may reduce the risk of diversion that contributes to the nonmedical use of CII stimulants and to the attendant risks of nonmedical use such as substance use disorder. Since the drug was approved, the Agency has also become aware of an association between amphetamine and motor and verbal tics, and worsening of Tourette's Syndrome. This information is derived from FAERS cases and medical literature.

(b) (4)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	ANDA is **up-to-date** with the RLD/Model labeling.

Reviewer Comments:

CYCLE 6 COMMENT:

Tentative Approval was granted on 6/23/2014.

A transfer of ANDA ownership was completed between Roxane Laboratories to West-Ward (2016) and then to Hikma (2019).

A gratuitous labeling amendment was submitted on 10/14/14 (reviewed under Labeling Review #5 (C5)) with the following minor deficiencies identified.

Labeling Deficiencies determined on September 28, 2015 based on your submission dated October 14, 2014:

1. GENERAL COMMENTS

   State how you will address the I-703 (Moderate to severe binge eating disorder (BED)) exclusivity and, if necessary, revise your labeling accordingly.

2. PRESCRIBING INFORMATION

   a. Revise your labeling to be in accordance with the most recently approved reference listed drug (RLD) labeling, Vyvanse® NDA 021977/S-039, approved April 17, 2015.

   b. HIGHLIGHTS OF PRESCRIBING INFORMATION

      i. **Limitation** statement: Revise both instances of the established name (which includes the dosage form) to use upper case letters as such:

         These highlights do not include all the information needed to use LISDEXAMFETAMINE DIMESYLATE CAPSULES safely and effectively. See full prescribing information for LISDEXAMFETAMINE DIMESYLATE CAPSULES.

      ii. **Title** section: Revise to use lower case for the dosage form as such:

         LISDEXAMFETAMINE DIMESYLATE capsules, for oral use, CII

   c. FULL PRESCRIBING INFORMATION

      8.1 Pregnancy subsection: Add the subheading '(b) (4)' We refer you to 21 CFR 201.57(c)(9)(i)(A).

3. MEDICATION GUIDE

   We refer you to PRESCRIBING INFORMATION comment 2.a.

However, it appears that the deficiency comments above were not issued to the applicant based on the 10/14/14 submission based on the lack of acknowledgement by the applicant in subsequent amendments.

Nevertheless, the 9/19/22 "minor amendment final approval requested" submission provides for revised container, prescribing information (PI) and Medication Guide (MG) labeling which supersedes any previously identified deficiencies.

Per 9/19/22 cover letter:

In accordance with the Agency's Guidance for Industry ANDA Submissions – Amendments and Requests for Final Approval to Tentatively Approved ANDAs (September 2020), when an application has been granted Tentative Approval (TA) Status 3 or More Years Before the Earliest Lawful Approval Date, the Agency recommends an ANDA applicant to consider the changes and updates made to the application and submit the Request for Final Approval with enough time to allow the Agency to assess these changes that have been made to the application. Therefore, Hikma is herein submitting our Request for Final Approval approximately 12 months before the date on which we seek final approval (August 24, 2023).

A summary of the changes that have been made to the application since receipt of Tentative Approval (June 23, 2014) is summarized below and further detailed, as applicable, in the respective module documents.

Labeling Updates

The labeling has been updated in accordance with the most recently approved labeling for the reference listed drug (RLD) VYVANSE® (lisdexamfetamine dimesylate) capsules (Rev. 01/2022), which was approved on February 25, 2022. Kindly note that our labeling has undergone corporate rebranding activities and the name of the company reflected on our labeling has also been changed from Roxane Laboratories to Hikma Pharmaceuticals USA Inc. as previously provided for in this application. The updated labeling documents and associated reference materials are provided in the following sections:

- Draft Container Labels (Section 1.14.1.1)
- Annotated Draft Labeling Text (Section 1.14.1.2)
- Draft Labeling Text (Insert) (Section 1.14.1.3)
- Annotated Comparison with Listed Drug (Section 1.14.3.1)
- Labeling Text for Reference Listed Drug (Section 1.14.3.3)

Refer to **sections 5.2, 5.3, and 5.4** for detailed assessments.

CYCLE 7 COMMENT:

The applicant submitted a point-by-point response to prescribing information (PI) labeling deficiencies identified in Labeling Review #6 (C6) based on the 9/19/22 submission.
Per 11/23/22 amendment cover letter:

Hikma Pharmaceuticals USA Inc. (Hikma) wishes to amend ANDA 202827 for Lisdexamfetamine Dimesylate Capsules, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg in response to receiving the Discipline Response Letter (DRL) dated November 18, 2022. Hikma is submitting our complete responses to the Agency's November 18, 2022 DRL inquiries in the attached Appendix.

The RLD model labeling remains the same in this review cycle as in C6.

Refer to **sections 5.3 and 5.4** for detailed assessment of the PI and MG labeling.

CYCLE 8 COMMENT:

The applicant submitted a point-by-point response to prescribing information (PI) labeling deficiencies identified in Labeling Review #7 (C7) based on the 11/23/22 submission.
Per 6/9/23 response cover letter:

Hikma Pharmaceuticals USA Inc. (Hikma) wishes to amend ANDA 202827, Lisdexamfetamine Dimesylate Capsules, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg, in response to receiving the Discipline Review Letter – Labeling dated June 2, 2023. Hikma is submitting our complete responses to the Agency's inquiry in the attached Appendix.

As noted in our Request for Final Approval Amendment dated September 19, 2022, Hikma is requesting that the Agency issue the Final Approval of the subject ANDA upon expiration of the listed patents (including pediatric exclusivity) on August 24, 2023. A copy of the final court decision was previously provided to the Agency in our Litigation Update submission dated November 16, 2015 (Sequence 0021).

.....

LABELING

The following labeling documents have been updated in response to the Agency's request and are provided herein:

Table 1. List of Documents Included in This Submission

eCTD Section	Document Name
1.14.1.3	pi-lisdexamfetamine-c50001173-01-k03-word
1.14.1.3	pi-lisdexamfetamine-c50001173-01-k03-pdf
1.14.1.3	spl-lisdexamfetamine-c50001173-01-k03
1.14.3.1	sbs-outsert-previous-vs-proposed

Refer to **sections 5.3 and 5.4** for detailed assessment of the PI and MG labeling.

Please note that the RLD model labeling remains the same in this review as in C7.

Deficiency Comments:

4.3 PATENTS AND EXCLUSIVITIES (C8)

The Orange Book was searched on 06/13/2023

Table 4 provides Orange Book patents for the Model Labeling (NDA 021977) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 4: Impact of Model Labeling Patents on ANDA Labeling

Strengths	Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
20 mg, 30 mg, 50 mg, 60 mg, 70 mg	7105486	02/24/2023	U-727	FOR THE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)	IV	08/20/2012	Expired
20 mg, 40 mg, 60 mg	7105486	02/24/2023	U-842	INDICATED FOR THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)	IV	08/20/2012	Expired
20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7105486*PED	08/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7223735	02/24/2023			IV	08/20/2012	Expired
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7223735*PED	08/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7655630	02/24/2023			IV	08/20/2012	Expired
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7655630*PED	08/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50	7659253	02/24/2023	U-727	FOR THE TREATMENT OF ATTENTION DEFICIT	IV	08/20/2012	Expired

Table 4: Impact of Model Labeling Patents on ANDA Labeling							
Strengths	**Patent Number**	**Patent Expiration**	**Patent Use Code**	**Patent Use Code Definition**	**Patent Certification**	**Date of Patent Cert Submission**	**Labeling Impact**
mg, 60 mg, 70 mg				HYPERACTIVITY DISORDER (ADHD)			
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7659253*PED	08/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7659254	02/24/2023	U-1034	TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN ADULTS	IV	08/20/2012	Expired
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7659254*PED	08/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7662787	02/24/2023			IV	08/20/2012	Expired
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7662787*PED	08/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7662788	02/24/2023	U-727	FOR THE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)	IV	08/20/2012	Expired
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7662788*PED	08/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7671030	02/24/2023	U-727	FOR THE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)	IV	08/20/2012	Expired
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7671030*PED	08/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg,	7671031	02/24/2023	U-727	FOR THE TREATMENT OF ATTENTION DEFICIT	IV	08/20/2012	Expired

Table 4: Impact of Model Labeling Patents on ANDA Labeling							
Strengths	**Patent Number**	**Patent Expiration**	**Patent Use Code**	**Patent Use Code Definition**	**Patent Certification**	**Date of Patent Cert Submission**	**Labeling Impact**
40 mg, 50 mg, 60 mg, 70 mg				HYPERACTIVITY DISORDER (ADHD)			
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7671031*PED	08/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7674774	02/24/2023	U-842	INDICATED FOR THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)	IV	08/20/2012	Expired
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7674774*PED	08/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7678770	02/24/2023	U-842	INDICATED FOR THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)	IV	08/20/2012	Expired
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7678770*PED	08/24/2023			IV	08/20/2012	None
10 mg	7678771	02/24/2023			IV	08/20/2012	Expired
20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7678771	02/24/2023	U-842	INDICATED FOR THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)	IV	08/20/2012	Expired
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7678771*PED	08/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7687466	02/24/2023			IV	08/20/2012	Expired
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7687466*PED	08/24/2023			IV	08/20/2012	None

Table 4: Impact of Model Labeling Patents on ANDA Labeling							
Strengths	**Patent Number**	**Patent Expiration**	**Patent Use Code**	**Patent Use Code Definition**	**Patent Certification**	**Date of Patent Cert Submission**	**Labeling Impact**
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7687467	02/24/2023	U-842	INDICATED FOR THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)	IV	08/20/2012	Expired
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7687467*PED	08/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7700561	02/24/2023			IV	08/20/2012	Expired
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7700561*PED	08/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7713936	02/24/2023	U-727	FOR THE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)	IV	08/20/2012	Expired
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7713936*PED	08/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7718619	02/24/2023	U-842	INDICATED FOR THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)	IV	08/20/2012	Expired
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7718619*PED	08/24/2023			IV	08/20/2012	None
20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7723305	02/24/2023	U-842	INDICATED FOR THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)	IV	08/20/2012	Expired
20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7723305*PED	08/24/2023			IV	08/20/2012	None

Table 5 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling						
Strengths	**Exclusivity Code**	**Exclusivity Expiration**	**Exclusivity Code Definition**	**Exclusivity Statement**	**Date of Exclusivity Submission**	**Labeling Impact**
	N/A					

Reviewer Assessment:

Deficiency	**No Deficiency**	
☐	☒	There is information in the Orange Book that the applicant needs to address.
☐	☒	Information in the Orange Book has **expired** and the applicant needs to revise labeling.

Reviewer Comments:

CYCLE 7 COMMENT:

No newly listed patents and no currently listed exclusivities. Note that expired patents above are retained in the table as they are still listed in the Orange Book at this time.

CYCLE 8 COMMENT:

No newly listed patents and no currently listed exclusivities since C7. Note that expired patents above are retained in the table as they are still listed in the Orange Book at this time.

Deficiency Comments:

4.4 UNITED STATES PHARMACOPEIA (USP) (C8)

The USP was searched on 06/13/2023

Table 6: USP				
	YES or NO	**Date**	**Monograph Title (N/A if no monograph)**	**Packaging and Storage/Labeling Statements (N/A if no monograph)**
Currently Official	No		N/A	N/A
Not Yet Official	No		N/A	N/A

Reviewer Assessment:

Deficiency	**No Deficiency**	
☐	☒	**Established name** is acceptable with regard to the USP monograph or the RLD's nonproprietary name.
☐	☒	RLD's non-proprietary **name is different from USP** established name.
☐	☒	**USP descriptor** is correctly used in the appropriate sections of the prescribing information.
USP RECOMMENDATIONS and/or DIFFERENCES IN TEST METHODS (QUALITY):		
☐	☒	**DISSOLUTION**: The applicant's dissolution statement is appropriate.

Deficiency	No Deficiency	
☐	☒	**ORGANIC IMPURITIES**: Drug product meets USP acceptance criteria for organic impurities.
☐	☒	**ASSAY**: Drug product meets USP acceptance criteria for assay.
Reviewer Comments: **Deficiency Comments:**		

4.5 MODEL CONTAINER LABELS (C8)

Model container/carton/blister labels (Source: NDA 021977 Annual Report-15, dated 4/20/22 **)**

5 ASSESSMENT OF ANDA LABELING AND LABELS (C8)

5.1 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS) (C8)

5.1.1 DRUG PRODUCT REVIEW (C8)

Insert screenshot of Labeling portion from drug product review if completed:
Drug Product Review complete

CYCLE 6 COMMENT:

Last completed drug product quality review was completed 6/11/14 (CR03) which had the following assessments for labeling:

A. Labeling & Package Insert

The description section, which includes chemical structure, chemical name, empirical formula, name of the inactive ingredients, and physical and chemical properties of drug substance, was reviewed. See the deficiency below for details.

The "how supplied" section is found satisfactory.

(b) (4)

The name of the manufacturer and address are the same as presented in the submission.

(b) (4)

B. Environmental Assessment Or Claim Of Categorical Exclusion

The firm has requested a categorical exclusion from the requirement of an Environmental Assessment Statement in accordance with 21 CFR 25.31(a) (Module 1.12.14).

The review of the Quality amendment in the 9/19/22 submission is still pending review at this time.

CYCLE 7 COMMENT:

The most recently completed drug product quality review (R04-IQ-CR), completed 12/2/22, has the following *additional* assessments for labeling including the 9/19/22 amendment:

Cover letter Notes dated 9/19/2022:

Labeling Updates

The labeling has been updated in accordance with the most recently approved labeling for the reference listed drug (RLD) VYVANSE® (lisdexamfetamine dimesylate) capsules (Rev. 01/2022), which was approved on February 25, 2022. Kindly note that our labeling has undergone corporate rebranding activities and the name of the company reflected on our labeling has also been changed from Roxane Laboratories to Hikma Pharmaceuticals USA Inc. as previously provided for in this application. The updated labeling documents and associated reference materials are provided in the following sections:

- Draft Container Labels (Section 1.14.1.1)
- Annotated Draft Labeling Text (Section 1.14.1.2)
- Draft Labeling Text (Insert) (Section 1.14.1.3)
- Annotated Comparison with Listed Drug (Section 1.14.3.1)
- Labeling Text for Reference Listed Drug (Section 1.14.3.3)

ANDA 202827 – Lisdexamfetamine Dimesylate Capsules, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg
Request for Final Approval
1.14.1.2 Annotated Draft Labeling Text **Page 1 of 1**

1.14.1.2 Annotated Draft Labeling Text

Side-by-Side Comparison of Proposed and RLD Bottle Labels

20 mg – Bottles of 30 – sbs-20mg-bottle-of-30-vs-rld
20 mg – Bottles of 100 – sbs-20mg-bottle-of-100-vs-rld

30 mg – Bottles of 30 – sbs-30mg-bottle-of-30-vs-rld
30 mg – Bottles of 100 – sbs-30mg-bottle-of-100-vs-rld

40 mg – Bottles of 30 – sbs-40mg-bottle-of-30-vs-rld
40 mg – Bottles of 100 – sbs-40mg-bottle-of-100-vs-rld

50 mg – Bottles of 30 – sbs-50mg-bottle-of-30-vs-rld
50 mg – Bottles of 100 – sbs-50mg-bottle-of-100-vs-rld

60 mg – Bottles of 30 – sbs-60mg-bottle-of-30-vs-rld
60 mg – Bottles of 100 – sbs-60mg-bottle-of-100-vs-rld

70 mg – Bottles of 30 – sbs-70mg-bottle-of-30-vs-rld
70 mg – Bottles of 100 – sbs-70mg-bottle-of-100-vs-rld

3 DOSAGE FORMS AND STRENGTHS

Lisdexamfetamine dimesylate capsules 20 mg: ivory body/ivory cap (imprinted with 54 990)

Lisdexamfetamine dimesylate capsules 30 mg: white body/orange cap (imprinted with 54 682)

Lisdexamfetamine dimesylate capsules 40 mg: white body/light green cap (imprinted with 54 098)

Lisdexamfetamine dimesylate capsules 50 mg: white body/blue cap (imprinted with 54 296)

Lisdexamfetamine dimesylate capsules 60 mg: blue body/blue cap (imprinted with 54 338)

Lisdexamfetamine dimesylate capsules 70 mg: orange body/blue cap (imprinted with 54 818)

Reviewer's Assessment (Current): Remains SATISFACTORY as per current submission dated 9/19/2022. No Change Reported in all pertaining sections to labeling; Labeling Review Team is currently issued In-Adequate Minor (On Hold).

II – CRL | List Of Deficiencies To Be Communicated:

- **Drug substance | Adequate**
  None

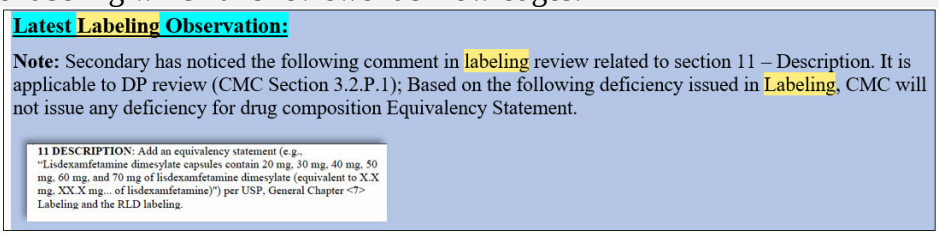
- **Drug product | Inadequate**
  None

(b) (4)

- **Labeling | Adequate**
  None

CYCLE 8 COMMENT:

The current DRAFT drug product quality review (R05a-IQ), uploaded 6/2/23, contains the following comment related to labeling which this reviewer acknowledges:



Latest Labeling Observation:

Note: Secondary has noticed the following comment in labeling review related to section 11 – Description. It is applicable to DP review (CMC Section 3.2.P.1); Based on the following deficiency issued in Labeling, CMC will not issue any deficiency for drug composition Equivalency Statement.

11 DESCRIPTION: Add an equivalency statement (e.g., "Lisdexamfetamine dimesylate capsules contain 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg of lisdexamfetamine dimesylate (equivalent to X.X mg, XX.X mg... of lisdexamfetamine)") per USP, General Chapter <7> Labeling and the RLD labeling.

As noted in the following **section 5.1.2**, the applicant satisfactorily added the equivalent values as requested.

5.1.2 DESCRIPTION (C8)

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling	*Information for VYVANSE capsules:* VYVANSE capsules contain 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg of lisdexamfetamine dimesylate (equivalent to 5.8 mg, 11.6 mg, 17.3 mg, 23.1 mg, 28.9 mg, 34.7 mg, and 40.5 mg of lisdexamfetamine). Inactive ingredients: microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The capsule shells contain gelatin, titanium dioxide, and one or more of the following: FD&C Red #3, FD&C Yellow #6, FD&C Blue #1, Black Iron Oxide, and Yellow Iron Oxide. *Information for VYVANSE chewable tablets:* VYVANSE chewable tablets contain 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, and 60 mg of lisdexamfetamine dimesylate (equivalent to 5.8 mg, 11.6 mg, 17.3 mg, 23.1 mg, 28.9 mg, and 34.7 mg of lisdexamfetamine). Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, guar gum, magnesium stearate, mannitol, microcrystalline cellulose, sucralose, artificial strawberry flavor.
Previous ANDA Labeling	(b) (4)

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
	(b) (4)
Current ANDA Labeling	Lisdexamfetamine dimesylate is a white to off-white powder that is soluble in water (792 mg/mL). Lisdexamfetamine dimesylate capsules contain 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg of lisdexamfetamine dimesylate (equivalent to 11.6 mg, 17.3 mg, 23.1 mg, 28.9 mg, 34.7 mg, and 40.5 mg of lisdexamfetamine) and the following inactive ingredients: ammonium hydroxide, calcium phosphate, gelatin, iron oxide black, isopropyl alcohol, magnesium stearate, microcrystalline cellulose, n-butyl alcohol, propylene glycol, shellac glaze, sodium starch glycolate, and titanium dioxide. In addition, the 20 mg capsule also contains yellow iron oxide. The 30 mg capsule also contains FD&C yellow #6. The 40 mg capsule also contains FD&C blue #1 and FD&C green #3. The 50 mg and 60 mg capsules also contain D&C red #28 and FD&C blue #1. The 70 mg capsule also contains D&C red #28, FD&C blue #1, and FD&C yellow #6. **CYCLE 8 COMMENT:** The applicant added equivalency values per C7 comment. Refer to **section 5.3** for detailed response.

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING (C8)

Table 8: Comparison of Model Labeling to ANDA Labeling	
Model Labeling	**16 HOW SUPPLIED/STORAGE AND HANDLING** **16.1 How Supplied** VYVANSE (lisdexamfetamine dimesylate) capsules: • VYVANSE capsules 10 mg: pink body/pink cap (imprinted with S489 and 10 mg), bottles of 100, NDC 59417-101-10 • VYVANSE capsules 20 mg: ivory body/ivory cap (imprinted with S489 and 20 mg), bottles of 100, NDC 59417-102-10 • VYVANSE capsules 30 mg: white body/orange cap (imprinted with S489 and 30 mg), bottles of 100, NDC 59417-103-10 • VYVANSE capsules 40 mg: white body/blue green cap (imprinted with S489 and 40 mg), bottles of 100, NDC 59417-104-10 • VYVANSE capsules 50 mg: white body/blue cap (imprinted with S489 and 50 mg), bottles of 100, NDC 59417-105-10 • VYVANSE capsules 60 mg: aqua blue body/aqua blue cap (imprinted with S489 and 60 mg), bottles of 100, NDC 59417-106-10 • VYVANSE capsules 70 mg: blue body/orange cap (imprinted with S489 and 70 mg), bottles of 100, NDC 59417-107-10 VYVANSE (lisdexamfetamine dimesylate) chewable tablets:

Table 8: Comparison of Model Labeling to ANDA Labeling	
	• VYVANSE chewable tablets 10 mg: White to off-white round shaped tablet debossed with '10' on one side and 'S489' on the other, bottles of 100, NDC 59417-115-01 • VYVANSE chewable tablets 20 mg: White to off-white hexagonal shaped tablet debossed with '20' on one side and 'S489' on the other, bottles of 100, NDC 59417-11601 • VYVANSE chewable tablets 30 mg: White to off-white arc triangular shaped tablet debossed with '30' on one side and 'S489' on the other, bottles of 100, NDC 59417-11701 • VYVANSE chewable tablets 40 mg: White to off-white capsule shaped tablet debossed with '40' on one side and 'S489' on the other, bottles of 100, NDC 59417-118-01 • VYVANSE chewable tablets 50 mg: White to off-white arc square shaped tablet debossed with '50' on one side and 'S489' on the other, bottles of 100, NDC 59417-11901 • VYVANSE chewable tablets 60 mg: White to off-white arc diamond shaped tablet debossed with '60' on one side and 'S489' on the other, bottles of 100, NDC 59417-12001 **16.2 Storage and Handling** Dispense in a tight, light-resistant container as defined in the USP. Store at room temperature, 20ºC to 25ºC (68ºF to 77ºF). Excursions permitted between 15ºC and 30ºC (59 to 86ºF) *[see USP Controlled Room Temperature]*. <u>Disposal</u> Comply with local laws and regulations on drug disposal of CNS stimulants. Dispose of remaining, unused, or expired VYVANSE by a medicine take-back program.
Previous ANDA Labeling	**16 HOW SUPPLIED/STORAGE AND HANDLING** **16.1 How Supplied** Lisdexamfetamine dimesylate capsules 20 mg: ivory body/ivory cap (imprinted with 54 990) Bottle of 30, NDC 0054-0370-13; Bottle of 100, NDC 0054-0370-25 Lisdexamfetamine dimesylate capsules 30 mg: white body/orange cap (imprinted with 54 682) Bottle of 30, NDC 0054-0371-13; Bottle of 100, NDC 0054-0371-25 Lisdexamfetamine dimesylate capsules 40 mg: white body/light green cap (imprinted with 54 098) Bottle of 30, NDC 0054-0372-13; Bottle of 100, NDC 0054-0372-25 Lisdexamfetamine dimesylate capsules 50 mg: white body/blue cap (imprinted with 54 296) Bottle of 30, NDC 0054-0373-13; Bottle of 100, NDC 0054-0373-25 Lisdexamfetamine dimesylate capsules 60 mg: blue body/blue cap (imprinted with 54 338) Bottle of 30, NDC 0054-0374-13; Bottle of 100, NDC 0054-0374-25 Lisdexamfetamine dimesylate capsules 70 mg: orange body/blue cap (imprinted with 54 818) Bottle of 30, NDC 0054-0375-13; Bottle of 100, NDC 0054-0375-25 **16.2 Storage and Handling** Dispense in a tight, light-resistant container as defined in the USP.

Table 8: Comparison of Model Labeling to ANDA Labeling	
	Store at 20° to 25°C (68° to 77°F). Excursions permitted between 15º to 30ºC (59 to 86ºF) [See USP Controlled Room Temperature]. *Disposal*: Comply with local laws and regulations on drug disposal of CNS stimulants. Dispose of remaining, unused, or expired lisdexamfetamine dimesylate capsules by a medicine take-back program. **CYCLE 7 COMMENT:** No changes noted.
Current ANDA Labeling	**16 HOW SUPPLIED/STORAGE AND HANDLING** **16.1 How Supplied** Lisdexamfetamine dimesylate capsules 20 mg: ivory body/ivory cap (imprinted with 54 990) Bottle of 30, NDC 0054-0370-13; Bottle of 100, NDC 0054-0370-25 Lisdexamfetamine dimesylate capsules 30 mg: white body/orange cap (imprinted with 54 682) Bottle of 30, NDC 0054-0371-13; Bottle of 100, NDC 0054-0371-25 Lisdexamfetamine dimesylate capsules 40 mg: white body/light green cap (imprinted with 54 098) Bottle of 30, NDC 0054-0372-13; Bottle of 100, NDC 0054-0372-25 Lisdexamfetamine dimesylate capsules 50 mg: white body/blue cap (imprinted with 54 296) Bottle of 30, NDC 0054-0373-13; Bottle of 100, NDC 0054-0373-25 Lisdexamfetamine dimesylate capsules 60 mg: blue body/blue cap (imprinted with 54 338) Bottle of 30, NDC 0054-0374-13; Bottle of 100, NDC 0054-0374-25 Lisdexamfetamine dimesylate capsules 70 mg: orange body/blue cap (imprinted with 54 818) Bottle of 30, NDC 0054-0375-13; Bottle of 100, NDC 0054-0375-25 **16.2 Storage and Handling** Dispense in a tight, light-resistant container as defined in the USP. Store at 20° to 25°C (68° to 77°F). Excursions permitted between 15º to 30ºC (59 to 86ºF) [See USP Controlled Room Temperature]. *Disposal:* Comply with local laws and regulations on drug disposal of CNS stimulants. Dispose of remaining, unused, or expired lisdexamfetamine dimesylate capsules by a medicine take-back program. **CYCLE 8 COMMENT:** No changes noted.

5.1.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER (C8)

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements	
Previous ANDA Labeling	
Name and Address on ANDA Prescribing Information	Distributed by: **Hikma Pharmaceuticals USA Inc.** Berkeley Heights, NJ 07922

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements	
	CYCLE 7 COMMENT: No changes noted.
Current ANDA Labeling	
Name and Address on ANDA Prescribing Information	Distributed by: **Hikma Pharmaceuticals USA Inc.** Berkeley Heights, NJ 07922 **CYCLE 8 COMMENT:** No changes noted.

5.2 CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS) (C8)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Container meets the **too small exemption** [21 CFR 201.10(i)]. Please enter Reviewer/Deficiency Comments if you select Deficiency.
		ESTABLISHED/PROPRIETARY NAME and STRENGTH:
☐	☒	**Tall Man** lettering complies with recommendations found on FDA webpage.
☐	☒	Established/proprietary **name and strength are the most prominent** information on the Principal Display Panel.
☐	☒	No **intervening text**(written, printed, or graphic matter) between established name and strength.
		THE FOLLOWING COMPONENTS ARE PROPERLY DISPLAYED:
☐	☒	**Net quantity** statement. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Dosage** statement.
☐	☒	**NDC number:** prominence, linear bar code, and its orientation.
☐	☒	**Expiration date and lot number** (or placeholder).
☐	☒	**Equivalency statement** (product strength).
☐	☒	**Medication Guide** Pharmacist instructions [21 CFR 208.24(d)].
☐	☒	Controlled Substance Symbol.
☐	☒	**Image of drug product** represents the true size, color, and imprint.
☐	☒	**Yellow #5** (tartrazine) warning statement is properly displayed.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Latex** warning statement is properly displayed [21 CFR 801.437.].
☐	☒	**Gluten** statement is appropriately stated.
		PRODUCT DIFFERENTIATION:
☐	☒	ANDA is the **same color** as the RLD labels as required (e.g. warfarin, levothyroxine, enoxaparin). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Multiple **strengths are differentiated** by use of different color or other acceptable means.
☐	☒	Labels of proposed product is differentiated from **related products**.
		STORAGE, DISPENSING, MANUFACTURER, and PACKAGING:
☐	☒	**Storage/dispensing** statement is consistent with the How Supplied section of the insert/RLD/USP. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Deficiency	No Deficiency	
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
☐	☒	Tamper evident (controlled substances) requirements are met.
☐	☒	Use of child-resistant closure (CRC) or non-CRC is appropriate. Describe **container closure**, cite source, and any issues in Reviewer Comments below.
OVERALL ASSESSMENT:		
☐	☒	Requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100). Please

Reviewer Comments:

CYCLE 6 COMMENTS:

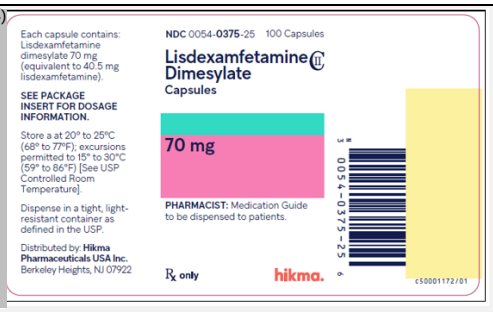
The container labels were satisfactory in Labeling Review #5 (C5) based on the 10/14/14 submission. The 9/19/22 amendment provides for revised container labels due to "corporate rebranding" and updated applicant holder.

Comparison of CONTAINER Labels (Representative samples shown)

(b) (4)

Currently Proposed

(b) (4)



Additional revisions to the corporate change and revised trade dress includes the inclusion of the equivalency statement which aligns with the RLD container labels. Revised container labels are satisfactory.

Updated container closure information -
Per 3.2.P.7 Quality, dated 9/19/22:

Packaging Configuration and Sizes

There are no changes being proposed to the packaging configurations or sizes as part of this Request for Final Approval. A summary of the proposed commercial packaging configurations for Lisdexamfetamine Dimesylate Capsules 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg (Bottles of 30 and 100 capsules) is provided in Table 3.

TABLE 3. PACKAGING CONFIGURATION AND SIZES

Bottles of 30 Capsules (20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg) [1] and Bottles of 100 Capsules (20 mg, 30 mg, 40 mg and 50 mg)	
Container/Closure	**Description**
(b) (4)	Bottle 90cc square wide mouth HDPE with neck ring
	(b) (4)
Bottles of 100 Capsules (60 and 70 mg)	
Container/Closure	**Description**
(b) (4)	Bottle 150cc square neck ring
	(b) (4)
	(b) (4)

Bottles of 30 and 100 are CRC and a tamper-evident heat induction seal is utilized in the packaging.

CYCLE 7 COMMENT:

The container labels were satisfactory in C6 based on the 9/19/22 submission. No new container labels were submitted in the 11/23/22 amendment for our review.

CYCLE 8 COMMENT:

The container labels were satisfactory in C6 based on the 9/19/22 submission. No new container labels were submitted in the 6/9/23 amendment for our review.

Deficiency Comments:

5.3 PRESCRIBING INFORMATION (C8)

Reviewer Assessment:

Deficiency	No Deficiency	
	HIGHLIGHTS:	
☐	☒	**Contact information** for applicant and FDA are listed correctly.
☐	☒	**Revision date** appears at the end of HIGHLIGHTS section (PLR) or end of prescribing information (non-PLR).
	DESCRIPTION/INACTIVE INGREDIENTS:	

Deficiency	No Deficiency	
☐	☒	Appropriate **warning/precaution** statements for inactive ingredients are present (21 CFR 201) Check only if applicable: ☐Sulfite (21 CFR 201.22) ☐Yellow #5 (Tartrazine) (21 CFR 201.20) ☐Phenylalanine/aspartame (21 CFR 201.21) ☐Latex (21 CFR 801.437).
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Gluten** statement is appropriately stated.
☐	☒	**Sterile** product statement [21 CFR 201.57(c)(12)(i)(D)].
☐	☒	**Dosage form, pharmacologic/therapeutic class, and route** of administration properly listed [21 CFR 201.57(c)(12)(i)(B)] and[21 CFR 201.57(c)(12)(i)(E)].
HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:		
☐	☒	All **submitted labels** and labeling are consistent with the HOW SUPPLIED section.
☐	☒	**Physical description** (e.g. scoring, color, imprint, capsule size, nozzle tip, cap color) of the finished product in the HOW SUPPLIED section are appropriately displayed.
☐	☒	**NDC** numbers are present.
☐	☒	Drug product is the **same color** as the RLD's drug product as required (e.g. warfarin, levothyroxine, enoxaparin).
☐	☒	**Storage or dispensing** statement is acceptable compared to the RLD/USP monograph. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**"Discard unused portion"** for single-dose products.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
REGULATORY/OVERALL ASSESSMENT:		
☐	☒	STIC requirements addressed appropriately.
☐	☒	Intent to join the **Antiretroviral Pregnancy Registry** (APR) upon full approval.
☐	☒	**Pregnancy registry** information is appropriately included/excluded as required for the RLD.
☐	☒	**Patent/exclusivity** carve out is acceptable. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Prescribing information meets **formatting requirements [**21 CFR 201.57 (PLR) or 21 CFR 201.80 (non-PLR)].
☐	☒	Prescribing Information is the same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

CYCLE 6 COMMENT:

Overall, the proposed PI and MG labeling follows the last approved RLD labeling. **However**, the applicant took liberties in their proposed PI labeling to replace key words (e.g., pediatric) with their own choice of words (e.g., children and adolescents) or to omit words (e.g., ADHD) which appear to be intentional in the RLD labeling. These differences may lead to misinterpretation and thus should be revised prior to approval. Refer to deficiency comments below.

The applicant omitted information related to the chewable tablets in the Quality sections of the PI labeling as well as additional sections, including but not limited to sections **2.2 General Instructions for Use, 12.3 Pharmacokinetics, and 17 PATIENT COUNSELING INFORMATION**. This is an acceptable omission.

CYCLE 7 COMMENT:

The applicant submitted point-by-point response to PI labeling deficiencies identified in C6 based on the 9/19/22 submission as detailed in the table below.

As noted in **section 5.1.2**, the proposed PI labeling is missing the (b) (4) statement which is included in the RLD labeling. The container labels accurately reflects the equivalency statements on the side panel. At this time, we will issue the deficiency comment below along with additional deficiencies identified in the proposed PI labeling.

Pregnancy Registry - The applicant retained the third party pregnancy registry information in accordance with the RLD. We will request that the applicant confirm acceptance of their data by the appropriate third party based on current DLR best practice as noted in Drug Facts (**section 4.1**) and internal Standard Comments document. Refer to comment below.

CYCLE 8 COMMENT:

The applicant submitted a point-by-point response to PI labeling deficiencies identified in C7 based on the 11/23/22 submission as detailed in the table below. The proposed PI labeling is satisfactory based on revisions made per C7 and minor editorial corrections and updated revision date.

Deficiency Comments:

Deficiency # 1 Created in C7 Prescribing Information	**11 DESCRIPTION**: Add an equivalency statement (e.g., "Lisdexamfetamine dimesylate capsules contain 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg of lisdexamfetamine dimesylate (equivalent to X.X mg, XX.X mg... of lisdexamfetamine)") per USP, General Chapter <7> Labeling and the RLD labeling.
Response / Assessment:	**Response:** In accordance with the Agency's request, the equivalency statement has been added to the DESCRIPTION section: "Lisdexamfetamine dimesylate capsules contain 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg of lisdexamfetamine dimesylate (equivalent to 11.6 mg, 17.3 mg, 23.1 mg, 28.9 mg, 34.7 mg, and 40.5 mg of lisdexamfetamine)" per USP, General Chapter <7> Labeling and the RLD labeling.
Deficiency # 2 Created in C7 Prescribing Information	Comment on the pregnancy registry information in your labeling. The labeling for the reference listed drug (RLD) contains third party pregnancy registry information in its labeling. Your proposed labeling may retain the information once you have verified with the third party that the data for your generic drug product will be accepted as part of their pregnancy registry. If it is determined that the data for your generic drug product will not be accepted by the third party, remove the pregnancy registry information in your labeling.
Response / Assessment:	**Response:** As requested by the Agency, Hikma has verified with the third party registry, via telephone, that the data for this generic drug product will be accepted as part of their pregnancy registry and therefore, the pregnancy registry information will remain in our proposed labeling.
Deficiency # 3 Created in C7 Prescribing Information	Highlights of Prescribing Information, Limitation statement: Revise both instances of the established name from "**LISDEXAMFETAMINE DIMESYLATE capsules**" to read, "**LISDEXAMFETAMINE DIMESYLATE CAPSULES**".

Response / Assessment:	**Response:** As requested by the Agency, both instances of the established name in the Highlights of Prescribing Information, Limitation statement have been revised to read, "LISDEXAMFETAMINE DIMESYLATE CAPSULES".
Deficiency # 4 Created in C7 Prescribing Information	**1 INDICATIONS AND USAGE**, Limitations of Use heading, 2nd bullet, 1st sentence: Revise the sentence from "Lisdexamfetamine dimesylate capsules are not indicated for weight loss" to read, "Lisdexamfetamine dimesylate capsules are not indicated or recommended for weight loss." in accordance with the RLD.
Response / Assessment:	**Response:** As requested by the Agency, the Limitations of Use section has been revised from "Lisdexamfetamine dimesylate capsules are not indicated for weight loss" to read, "Lisdexamfetamine dimesylate capsules are not indicated or recommended for weight loss." in accordance with the RLD.

5.4 MEDICATION GUIDE (C8)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Medication Guide is **up-to-date** with model labeling.
☐	☒	Medication Guide meets **content, format, and font size**.
☐	☒	**Phonetic spelling** of the established/proprietary name is present and correct.
☐	☒	Description of **child-resistant feature**(if also present in HOW SUPPLIED/STORAGE AND HANDLING).
☐	☒	**Revision date and approval statement** appear at the end of the Medication Guide correctly.
☐	☒	Applicant committed to provide a **sufficient number** of Medication Guides.
☐	☒	Applicant included the **1-800-FDA-1088** phone number.
☐	☒	Applicant included statement to print **electronic Medication Guide** if applicable.
☐	☒	Medication Guide is the same as the model labeling, except for allowable differences. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

CYCLE 6 COMMENT:

Proposed MG labeling follows the RLD model labeling and is satisfactory.

CYCLE 7 COMMENT:

The MG labeling was satisfactory in C6 based on the 9/19/22 submission. There are no updates to the RLD model labeling for the MG labeling and the proposed MG labeling remains satisfactory based on the 11/23/22 amendment.

CYCLE 8 COMMENT:

The MG labeling was satisfactory in C6 based on the 9/19/22 submission. There are no updates to the RLD model labeling for the MG labeling and the proposed MG labeling remains satisfactory based on the 6/9/23

amendment as only minor editorial corrections were made (e.g., capitalization when needed) and revision date was updated which are acceptable changes. **Deficiency Comments:**

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES (C8)

A labeling statement required verification from another division discipline. Check only if applicable.

Reviewer Assessment:

☐	Rubber
☐	Latex
☐	Gluten
☐	Alcohol (ethanol)
☐	Aluminum (small/large volume parenteral and pharmacy bulk package)
☐	Sulfite
☐	Phenylalanine (aspartame) - content calculation
☐	Yellow #5 (tartrazine)
☐	Ghost tablet/capsule (i.e. solid or semi-solid mass in stool)
☐	Other

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB): (For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue)
Reviewer Comments: **Deficiency Comments:**

Alison Park

Digitally signed by Alison Park
Date: 6/13/2023 01:20:55PM
GUID: 5063541100000db251c2d2cd0f7476af

Ellen Koo

Digitally signed by Ellen Koo
Date: 6/21/2023 02:39:08PM
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***** This document contains proprietary information that cannot be released to the public.***V.25**

Labeling Review

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	04/20/2023
ANDA Number(s)	202827
Review Number	7
Applicant Name	Hikma Pharmaceuticals USA Inc.
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Lisdexamfetamine Dimesylate Capsules, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg
Proposed Proprietary Name	None
Submission Received Date	November 23, 2022
Primary Labeling Reviewer	Alison Park
Secondary Labeling Reviewer	Refer to signature page

Review Conclusion

☐ Acceptable - No Comments
☐ Acceptable - Include Post Approval Comments
☒ Minor Deficiency* - Refer to Labeling Deficiencies and Comments for Letter to Applicant
☐ Major Deficiency** - Refer to Labeling Deficiencies and Comments for Letter to Applicant

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.

On Policy Alert List	☒ Yes	☐ No
Acceptable For Filing	☒ Yes	☐ No
Combined Insert/Outsert	☐ Yes	☒ No

TABLE OF CONTENTS

1 LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT
1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE
1.3 POST-APPROVAL REVISIONS

2 INSTRUCTIONS FOR ASSESSMENT
3 OVERALL ASSESSMENT OF MATERIALS REVIEWED
4 LABELING REVIEW INFORMATION

4.1 REGULATORY INFORMATION
4.2 MODEL PRESCRIBING INFORMATION
4.3 PATENTS AND EXCLUSIVITIES
4.4 UNITED STATES PHARMACOPEIA (USP)
4.5 MODEL CONTAINER LABELS

5 ASSESSMENT OF ANDA LABELING AND LABELS

5.1 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS)

5.1.1 DRUG PRODUCT REVIEW
5.1.2 DESCRIPTION
5.1.3 HOW SUPPLIED/STORAGE AND HANDLING
5.1.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER

5.2 CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS)

5.3 PRESCRIBING INFORMATION
5.4 MEDICATION GUIDE

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES

1 LABELING COMMENTS (C7)

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT (C7)

The following comments have been identified by the Division of Labeling Review (DLR) based on your submission(s) on November 23, 2022. Prior to final approval, the proposed labeling should be clear and precise (grammar, spelling, and formatting) for end users, and accurately reflect the Reference Listed Drug (RLD) information to comply with FDA policies, laws, regulations (i.e., 21 CFR 314.94(a)(8)), official compendia, and relevant guidance.

PRESCRIBING INFORMATION

a. Comment on the pregnancy registry information in your labeling. The labeling for the reference listed drug (RLD) contains third party pregnancy registry information in its labeling. Your proposed labeling may retain the information once you have verified with the third party that the data for your generic drug product will be accepted as part of their pregnancy registry. If it is determined that the data for your generic drug product will not be accepted by the third party, remove the pregnancy registry information in your labeling.
b. Highlights of Prescribing Information, Limitation statement: Revise both instances of the established name from "**LISDEXAMFETAMINE DIMESYLATE capsules**" to read, "**LISDEXAMFETAMINE DIMESYLATE CAPSULES**".
c. **1 INDICATIONS AND USAGE**, Limitations of Use heading, 2nd bullet, 1st sentence: Revise the sentence from "Lisdexamfetamine dimesylate capsules are not indicated for weight loss" to read, "Lisdexamfetamine dimesylate capsules are not indicated or recommended for weight loss." in accordance with the RLD.
d. **11 DESCRIPTION**: Add an equivalency statement (e.g., “Lisdexamfetamine dimesylate capsules contain 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg of lisdexamfetamine dimesylate (equivalent to X.X mg, XX.X mg... of lisdexamfetamine)") per USP, General Chapter <7> Labeling and the RLD labeling.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE (C7)

1.3 POST-APPROVAL REVISIONS (C7)

These comments will be addressed post approval (in the first labeling supplement review).

2 INSTRUCTIONS FOR ASSESSMENT (C7)

General Comments:

Select the "no deficiency" or "deficiency" radio button as appropriate for each row. If a "Deficiency Comments" appears, ensure it is appropriate for your situation, edit, or enter "Reviewer Comments" if necessary.

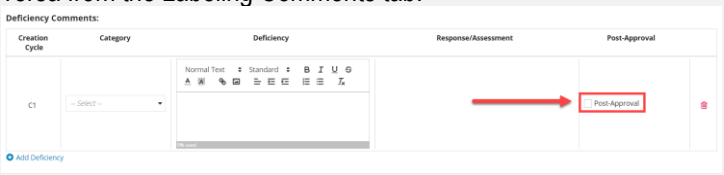
If there is no issue/concern, or if the question is not applicable. No "Deficiency Comments" will appear but reviewers can still enter "Reviewer Comments" if desired.

☐	☒	There is information in the Orange Book that the applicant needs to address.
☒	☐	Information in the Orange Book has **expired** and the applicant needs to revise labeling.

Reviewer Comments:
Enter free text in this section as necessary.

Deficiency Comments:

- Standardized comments/deficiencies are available for certain questions. For a complete list of standardized comments, reference the DLR Standardized Comments SharePoint.
- Reviewers can modify standardized comments/deficiencies for their situation.
- Deficiencies will have a review number, deficiency number, and roman numeral in the user interface. For first original reviews the review number and iteration numeral will align; however, older reviews may have review numbers and iteration numerals that differ due to some reviews being completed under past practices.
- Deficiency comments will populate by default to the Labeling Comments deficiency section unless you select the Post-Approval checkbox. Assessors also have the option to move all comments to the Post-Approval Revisions section or vice versa from the Labeling Comments tab.



3 OVERALL ASSESSMENT OF MATERIALS REVIEWED (C7)

Table 1: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Final	20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg - Bottles of 30 and 100 capsules	09/19/2022	Satisfactory
Blister	N/A	N/A		
Carton	N/A	N/A		

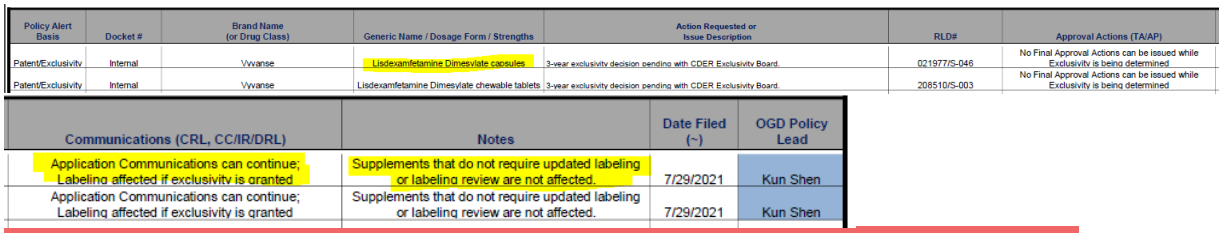
Table 2: Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	Revised November 2022	11/23/2022	Revise
Medication Guide	Draft	Revised November 2022	11/23/2022	Satisfactory

Table 2: Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Patient Information	N/A	N/A		
Instructions for Use	N/A	N/A		
SPL Data Elements				

4 LABELING REVIEW INFORMATION(C7)

4.1 REGULATORY INFORMATION (C7)

Yes	No	
☒	☐	Are there any applicable issues in **DLR's SharePoint Drug Facts** ? **CYCLE 7 COMMENT:** Posted 7/3/19 and updated 12/2/22 National Pregnancy Registry for Psychiatric Medications Brief Description Updated 12/2/2022: • Unless required as part of REMS, PR appears to be a third party's PR ◦ Add comment for Cycle 1 or if the PR is new in the NDA labeling ◦ If ANDA included the PR in labeling, we should comment for the ANDA applicant to reach out to third party and verify that the data for the generic product will be accepted as part of the PR (data might be collected for some generic products but not others). If it is verified that the data for the generic product will be accepted, the ANDA applicant can continue to include the PR in labeling. If data for the generic product will not be accepted, the ANDA applicant should remove the PR in labeling. ▪ Example comment to include in SCD: *The reference listed drug (RLD) for your drug product contains third party pregnancy registry information in its labeling. Please reach out to the third party to verify if the data for your generic drug product will be accepted as part of their pregnancy registry. If it is verified that the data for your generic drug product will be accepted by the third party, you can continue including the pregnancy registry information in your labeling. If it is determined that the data for your generic drug product will not be accepted by the third party, please remove the pregnancy registry information in your labeling.* ◦ If ANDA did not include PR in labeling, we should comment for the ANDA applicant to reach out to third party and determine if the data for the generic product will be accepted as part of the PR. If it is verified that the data for the generic product will be accepted, the ANDA applicant should include the PR in labeling. If data for the generic product will not be accepted, the ANDA applicant can continue to exclude the PR. ▪ Example comment to include in SCD: *The reference listed drug (RLD) for your drug product contains third party pregnancy registry information in its labeling. Please reach out to the third party to verify if the data for your generic drug product will be accepted as part of their pregnancy registry. If it is verified that the data for your generic drug product will be accepted by the third party, please include the pregnancy registry information in your labeling. If it is determined that the data for your generic drug product will not be accepted by the third party, you can continue excluding the pregnancy registry information in your labeling.*

Yes	No	
		There is a pregnancy registry established by the Massachusetts General Hospital and Havard Medical school for the class of psychiatric medications. There are three different groups under the pregnancy registry but the phone number for the PR is the same for all three. 1. The National Pregnancy Registry for Atypical Antipsychotics 2. The National Pregnancy Registry for Antidepressants 3. The National Pregnancy Registry for ADHD Medications. Per DPMH, this NDA holders are required to list this PR in their insert labeling. We will request all ANDAs for psychiatric medications to list this PR in their labeling to be the same as the RLD. We do NOT need to ask the firm to confirm that they are registred with this organization to participate in the PR. **Updated 4/14/2021: Added active ingredients for Atypical Antipsychotics, Antidepressants, and ADHD Medication. Please update as needed.** The RLD, Vyvanse, includes a pregnancy registry information in section **8.1 Pregnancy**. Refer to **section 5.3** for detailed assessment and deficiency comment if applicable.
☒	☐	Is the drug product listed in the Policy Alert Tracker on **OGD's SharePoint**?  | Policy Alert Basis	Docket #	Brand Name (or Drug Class)	Generic Name / Dosage Form / Strengths	Action Requested or Issue Description	RLD#	Approval Actions (TA/AP)	Communications (CRL, CC/IR/DRL)	Notes	Date Filed (~)	OGD Policy Lead
---	---	---	---	---	---	---	---	---	---	---
Patent/Exclusivity	Internal	Vyvanse	Lisdexamfetamine Dimesylate capsules	3-year exclusivity decision pending with CDER Exclusivity Board.	021977/S-046	No Final Approval Actions can be issued while Exclusivity is being determined	Application Communications can continue; Labeling affected if exclusivity is granted	Supplements that do not require updated labeling or labeling review are not affected.	7/29/2021	Kun Shen
Patent/Exclusivity	Internal	Vyvanse	Lisdexamfetamine Dimesylate chewable tablets	3-year exclusivity decision pending with CDER Exclusivity Board.	208510/S-003	No Final Approval Actions can be issued while Exclusivity is being determined	Application Communications can continue; Labeling affected if exclusivity is granted	Supplements that do not require updated labeling or labeling review are not affected.	7/29/2021	Kun Shen	 Primary discipline reviews may continue but NO final actions until final exclusivity determinations made.

4.2 MODEL PRESCRIBING INFORMATION (C7)

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling (Check the box used as the Model Labeling)

☒ MOST RECENTLY APPROVED NDA MODEL LABELING

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)

NDA#/Supplement# (S-000 if original): NDA 021977 / S-048 (Combined with NDA 208510/S-005, Vyvanse chewable tablets)

Supplement Approval Date: 02/25/2022

Proprietary Name: Vyvanse

Established Name: Lisdexamfetamine Dimesylate Capsules

Description of Supplement:

These supplemental new drug applications provide for revisions to the labeling for Vyvanse, Adderall XR and Mydayis consistent with the Agency's December 14, 2021, safety labeling change notification letter, notifying the Sponsor, under Section 505(o)(4) of the FDCA, of new safety information pertaining to the association between the use of amphetamines and intestinal ischemia, that the Agency believes should be included in the labeling for all amphetamines.

Link: https://analytics.fda.gov/workspace/hubble/external/object/v0/fda-communication?pk_communication=4943991_4538393_090140af80649ae3_NDA021977_3411801

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling (Check the box used as the Model Labeling)
☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**
☒ **OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out):** (b) (4)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	ANDA is **up-to-date** with the RLD/Model labeling.

Reviewer Comments:

CYCLE 6 COMMENT:

Tentative Approval was granted on 6/23/2014.

A transfer of ANDA ownership was completed between Roxane Laboratories to West-Ward (2016) and then to Hikma (2019).

A gratuitous labeling amendment was submitted on 10/14/14 (reviewed under Labeling Review #5 (C5)) with the following minor deficiencies identified.

Labeling Deficiencies determined on September 28, 2015 based on your submission dated October 14, 2014:

1. GENERAL COMMENTS

   State how you will address the I-703 (Moderate to severe binge eating disorder (BED)) exclusivity and, if necessary, revise your labeling accordingly.

2. PRESCRIBING INFORMATION

   a. Revise your labeling to be in accordance with the most recently approved reference listed drug (RLD) labeling, Vyvanse® NDA 021977/S-039, approved April 17, 2015.

   b. HIGHLIGHTS OF PRESCRIBING INFORMATION

      i. **Limitation** statement: Revise both instances of the established name (which includes the dosage form) to use upper case letters as such:

         These highlights do not include all the information needed to use LISDEXAMFETAMINE DIMESYLATE CAPSULES safely and effectively. See full prescribing information for LISDEXAMFETAMINE DIMESYLATE CAPSULES.

      ii. **Title** section: Revise to use lower case for the dosage form as such:

         LISDEXAMFETAMINE DIMESYLATE capsules, for oral use, CII

   c. FULL PRESCRIBING INFORMATION

      8.1 Pregnancy subsection: Add the subheading "(b) (4)" We refer you to 21 CFR 201.57(c)(9)(i)(A).

3. MEDICATION GUIDE

   We refer you to PRESCRIBING INFORMATION comment 2.a.

However, it appears that the deficiency comments above were not issued to the applicant based on the 10/14/14 submission based on the lack of acknowledgement by the applicant in subsequent amendments.

Nevertheless, the 9/19/22 "minor amendment final approval requested" submission provides for revised container, prescribing information (PI) and Medication Guide (MG) labeling which supersedes any previously identified deficiencies.

Per 9/19/22 cover letter:

> In accordance with the Agency's Guidance for Industry ANDA Submissions – Amendments and Requests for Final Approval to Tentatively Approved ANDAs (September 2020), when an application has been granted Tentative Approval (TA) Status 3 or More Years Before the Earliest Lawful Approval Date, the Agency recommends an ANDA applicant to consider the changes and updates made to the application and submit the Request for Final Approval with enough time to allow the Agency to assess these changes that have been made to the application. Therefore, Hikma is herein submitting our Request for Final Approval approximately 12 months before the date on which we seek final approval (August 24, 2023).
>
> A summary of the changes that have been made to the application since receipt of Tentative Approval (June 23, 2014) is summarized below and further detailed, as applicable, in the respective module documents.
>
> **Labeling Updates**
>
> The labeling has been updated in accordance with the most recently approved labeling for the reference listed drug (RLD) VYVANSE® (lisdexamfetamine dimesylate) capsules (Rev. 01/2022), which was approved on February 25, 2022. Kindly note that our labeling has undergone corporate rebranding activities and the name of the company reflected on our labeling has also been changed from Roxane Laboratories to Hikma Pharmaceuticals USA Inc. as previously provided for in this application. The updated labeling documents and associated reference materials are provided in the following sections:
>
> - Draft Container Labels (Section 1.14.1.1)
> - Annotated Draft Labeling Text (Section 1.14.1.2)
> - Draft Labeling Text (Insert) (Section 1.14.1.3)
> - Annotated Comparison with Listed Drug (Section 1.14.3.1)
> - Labeling Text for Reference Listed Drug (Section 1.14.3.3)

Refer to **sections 5.2, 5.3, and 5.4** for detailed assessments.

CYCLE 7 COMMENT:

The applicant submitted a point-by-point response to prescribing information (PI) labeling deficiencies identified in Labeling Review #6 (C6) based on the 9/19/22 submission.

Per 11/23/22 amendment cover letter:

> Hikma Pharmaceuticals USA Inc. (Hikma) wishes to amend ANDA 202827 for Lisdexamfetamine Dimesylate Capsules, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg in response to receiving the Discipline Response Letter (DRL) dated November 18, 2022. Hikma is submitting our complete responses to the Agency's November 18, 2022 DRL inquiries in the attached Appendix.

The RLD model labeling remains the same in this review cycle as in C6.

Refer to **sections 5.3 and 5.4** for detailed assessment of the PI and MG labeling.

Deficiency Comments:

4.3 PATENTS AND EXCLUSIVITIES (C7)

The Orange Book was searched on 04/20/2023

Table 4 provides Orange Book patents for the Model Labeling (NDA 021977) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 4: Impact of Model Labeling Patents on ANDA Labeling							
Strengths	**Patent Number**	**Patent Expiration**	**Patent Use Code**	**Patent Use Code Definition**	**Patent Certification**	**Date of Patent Cert Submission**	**Labeling Impact**
20 mg, 30 mg, 50 mg, 60 mg, 70 mg	7105486	02/24/2023	U-727	FOR THE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)	IV	08/20/2012	Expired
20 mg, 40 mg, 60 mg	7105486	02/24/2023	U-842	INDICATED FOR THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)	IV	08/20/2012	Expired
20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7105486*PED	08/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7223735	02/24/2023			IV	08/20/2012	Expired
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7223735*PED	08/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7655630	02/24/2023			IV	08/20/2012	Expired
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7655630*PED	08/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7659253	02/24/2023	U-727	FOR THE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)	IV	08/20/2012	Expired
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7659253*PED	08/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7659254	02/24/2023	U-1034	TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN ADULTS	IV	08/20/2012	Expired

Table 4: Impact of Model Labeling Patents on ANDA Labeling							
Strengths	**Patent Number**	**Patent Expiration**	**Patent Use Code**	**Patent Use Code Definition**	**Patent Certification**	**Date of Patent Cert Submission**	**Labeling Impact**
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7659254*PED	08/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7662787	02/24/2023			IV	08/20/2012	Expired
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7662787*PED	08/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7662788	02/24/2023	U-727	FOR THE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)	IV	08/20/2012	Expired
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7662788*PED	08/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7671030	02/24/2023	U-727	FOR THE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)	IV	08/20/2012	Expired
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7671030*PED	08/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7671031	02/24/2023	U-727	FOR THE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)	IV	08/20/2012	Expired
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7671031*PED	08/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50	7674774	02/24/2023	U-842	INDICATED FOR THE TREATMENT OF ATTENTION-	IV	08/20/2012	Expired

Table 4: Impact of Model Labeling Patents on ANDA Labeling							
Strengths	**Patent Number**	**Patent Expiration**	**Patent Use Code**	**Patent Use Code Definition**	**Patent Certification**	**Date of Patent Cert Submission**	**Labeling Impact**
mg, 60 mg, 70 mg				DEFICIT/HYPERACTIVITY DISORDER (ADHD)			
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7674774*PED	08/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7678770	02/24/2023	U-842	INDICATED FOR THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)	IV	08/20/2012	Expired
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7678770*PED	08/24/2023			IV	08/20/2012	None
10 mg	7678771	02/24/2023			IV	08/20/2012	Expired
20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7678771	02/24/2023	U-842	INDICATED FOR THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)	IV	08/20/2012	Expired
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7678771*PED	08/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7687466	02/24/2023			IV	08/20/2012	Expired
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7687466*PED	08/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7687467	02/24/2023	U-842	INDICATED FOR THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)	IV	08/20/2012	Expired
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7687467*PED	08/24/2023			IV	08/20/2012	None

Table 4: Impact of Model Labeling Patents on ANDA Labeling							
Strengths	**Patent Number**	**Patent Expiration**	**Patent Use Code**	**Patent Use Code Definition**	**Patent Certification**	**Date of Patent Cert Submission**	**Labeling Impact**
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7700561	02/24/2023			IV	08/20/2012	Expired
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7700561*PED	08/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7713936	02/24/2023	U-727	FOR THE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)	IV	08/20/2012	Expired
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7713936*PED	08/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7718619	02/24/2023	U-842	INDICATED FOR THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)	IV	08/20/2012	Expired
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7718619*PED	08/24/2023			IV	08/20/2012	None
20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7723305	02/24/2023	U-842	INDICATED FOR THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)	IV	08/20/2012	Expired
20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7723305*PED	08/24/2023			IV	08/20/2012	None

Table 5 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling						
Strengths	**Exclusivity Code**	**Exclusivity Expiration**	**Exclusivity Code Definition**	**Exclusivity Statement**	**Date of Exclusivity Submission**	**Labeling Impact**
	N/A					

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	There is information in the Orange Book that the applicant needs to address.
☐	☒	Information in the Orange Book has **expired** and the applicant needs to revise labeling.

Reviewer Comments:

CYCLE 7 COMMENT:

No newly listed patents and no currently listed exclusivities. Note that expired patents above are retained in the table as they are still listed in the Orange Book at this time.

Deficiency Comments:

4.4 UNITED STATES PHARMACOPEIA (USP) (C7)

The USP was searched on 04/20/2023

Table 6: USP				
	YES or NO	**Date**	**Monograph Title (N/A if no monograph)**	**Packaging and Storage/Labeling Statements (N/A if no monograph)**
Currently Official	No		N/A	N/A
Not Yet Official	No		N/A	N/A

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	**Established name** is acceptable with regard to the USP monograph or the RLD's nonproprietary name.
☐	☒	RLD's non-proprietary **name is different from USP** established name.
☐	☒	**USP descriptor** is correctly used in the appropriate sections of the prescribing information.
		USP RECOMMENDATIONS and/or DIFFERENCES IN TEST METHODS (QUALITY):
☐	☒	**DISSOLUTION**: The applicant's dissolution statement is appropriate.
☐	☒	**ORGANIC IMPURITIES**: Drug product meets USP acceptance criteria for organic impurities.
☐	☒	**ASSAY**: Drug product meets USP acceptance criteria for assay.

Reviewer Comments:

Deficiency Comments:

4.5 MODEL CONTAINER LABELS (C7)

Model container/carton/blister labels (Source: NDA 021977 Annual Report-15, dated 4/20/22 **)**

5 ASSESSMENT OF ANDA LABELING AND LABELS (C7)

5.1 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS) (C7)

5.1.1 DRUG PRODUCT REVIEW (C7)

Insert screenshot of Labeling portion from drug product review if completed:
Drug Product Review complete

CYCLE 6 COMMENT:

Last completed drug product quality review was completed 6/11/14 (CR03) which had the following assessments for labeling:

A. Labeling & Package Insert

The description section, which includes chemical structure, chemical name, empirical formula, name of the inactive ingredients, and physical and chemical properties of drug substance, was reviewed. See the deficiency below for details.

The "how supplied" section is found satisfactory.

(b) (4)

(b) (4)

The name of the manufacturer and address are the same as presented in the submission.

(b) (4)

B. Environmental Assessment Or Claim Of Categorical Exclusion

The firm has requested a categorical exclusion from the requirement of an Environmental Assessment Statement in accordance with 21 CFR 25.31(a) (Module 1.12.14).

The review of the Quality amendment in the 9/19/22 submission is still pending review at this time.

CYCLE 7 COMMENT:

The most recently completed drug product quality review (R04-IQ-CR), completed 12/2/22, has the following *additional* assessments for labeling including the 9/19/22 amendment:

Cover letter Notes dated 9/19/2022:

Labeling Updates

The labeling has been updated in accordance with the most recently approved labeling for the reference listed drug (RLD) VYVANSE® (lisdexamfetamine dimesylate) capsules (Rev. 01/2022), which was approved on February 25, 2022. Kindly note that our labeling has undergone corporate rebranding activities and the name of the company reflected on our labeling has also been changed from Roxane Laboratories to Hikma Pharmaceuticals USA Inc. as previously provided for in this application. The updated labeling documents and associated reference materials are provided in the following sections:

- Draft Container Labels (Section 1.14.1.1)
- Annotated Draft Labeling Text (Section 1.14.1.2)
- Draft Labeling Text (Insert) (Section 1.14.1.3)
- Annotated Comparison with Listed Drug (Section 1.14.3.1)
- Labeling Text for Reference Listed Drug (Section 1.14.3.3)

ANDA 202827 – Lisdexamfetamine Dimesylate Capsules, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg
Request for Final Approval
1.14.1.2 Annotated Draft Labeling Text **Page 1 of 1**

1.14.1.2 Annotated Draft Labeling Text

Side-by-Side Comparison of Proposed and RLD Bottle Labels

20 mg – Bottles of 30 – sbs-20mg-bottle-of-30-vs-rld
20 mg – Bottles of 100 – sbs-20mg-bottle-of-100-vs-rld

30 mg – Bottles of 30 – sbs-30mg-bottle-of-30-vs-rld
30 mg – Bottles of 100 – sbs-30mg-bottle-of-100-vs-rld

40 mg – Bottles of 30 – sbs-40mg-bottle-of-30-vs-rld
40 mg – Bottles of 100 – sbs-40mg-bottle-of-100-vs-rld

50 mg – Bottles of 30 – sbs-50mg-bottle-of-30-vs-rld
50 mg – Bottles of 100 – sbs-50mg-bottle-of-100-vs-rld

60 mg – Bottles of 30 – sbs-60mg-bottle-of-30-vs-rld
60 mg – Bottles of 100 – sbs-60mg-bottle-of-100-vs-rld

70 mg – Bottles of 30 – sbs-70mg-bottle-of-30-vs-rld
70 mg – Bottles of 100 – sbs-70mg-bottle-of-100-vs-rld

3 DOSAGE FORMS AND STRENGTHS

Lisdexamfetamine dimesylate capsules 20 mg: ivory body/ivory cap (imprinted with 54 990)

Lisdexamfetamine dimesylate capsules 30 mg: white body/orange cap (imprinted with 54 682)

Lisdexamfetamine dimesylate capsules 40 mg: white body/light green cap (imprinted with 54 098)

Lisdexamfetamine dimesylate capsules 50 mg: white body/blue cap (imprinted with 54 296)

Lisdexamfetamine dimesylate capsules 60 mg: blue body/blue cap (imprinted with 54 338)

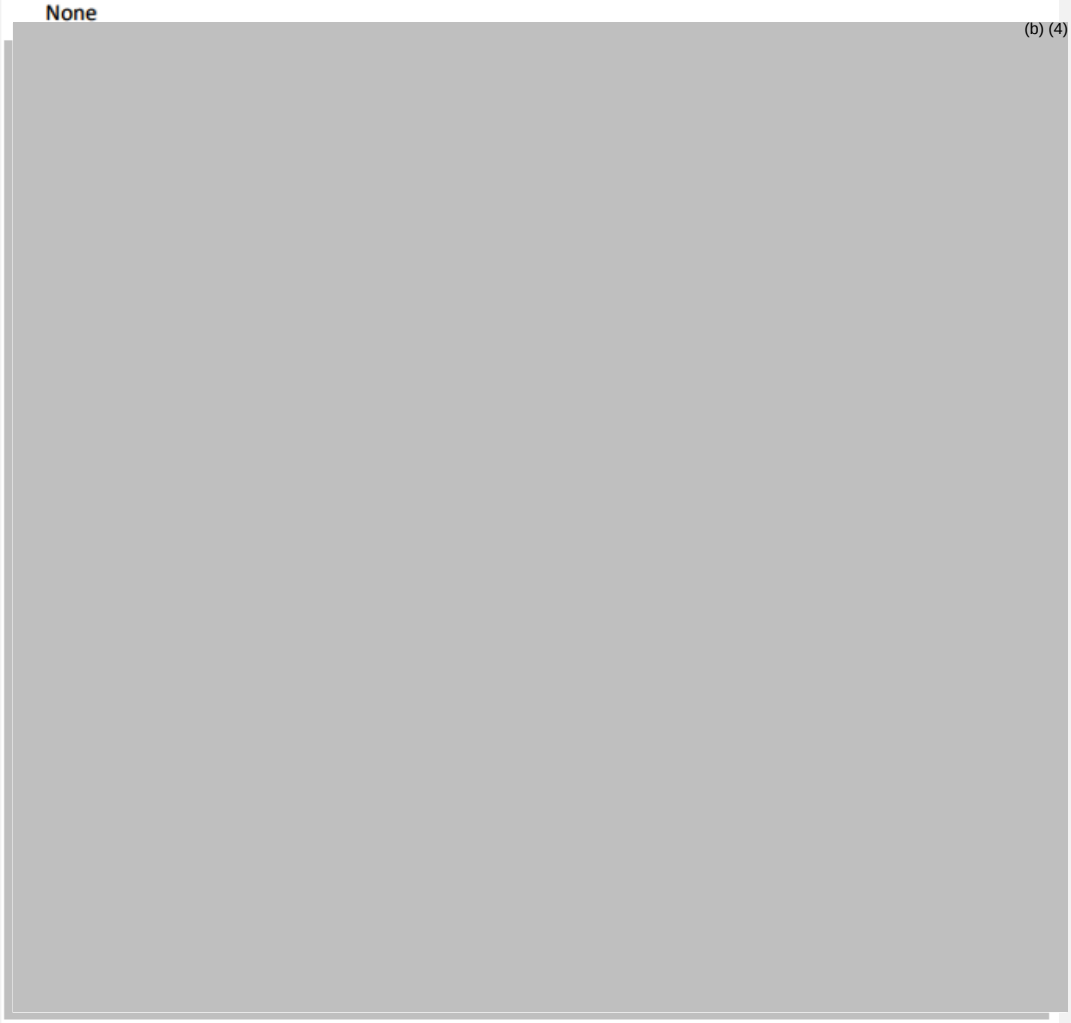
Lisdexamfetamine dimesylate capsules 70 mg: orange body/blue cap (imprinted with 54 818)

Reviewer's Assessment (Current): Remains SATISFACTORY as per current submission dated 9/19/2022. No Change Reported in all pertaining sections to labeling; Labeling Review Team is currently issued In-Adequate Minor (On Hold).

II – CRL | List Of Deficiencies To Be Communicated:

- **Drug substance | Adequate**
  None
- **Drug product | Inadequate**
  None

(b) (4)



- **Labeling | Adequate**
  None

5.1.2 DESCRIPTION (C7)

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling	*Information for VYVANSE capsules:* VYVANSE capsules contain 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg of lisdexamfetamine dimesylate (equivalent to 5.8 mg, 11.6 mg, 17.3 mg, 23.1 mg, 28.9 mg, 34.7 mg, and 40.5 mg of lisdexamfetamine). Inactive ingredients: microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The capsule shells contain gelatin, titanium dioxide, and one or more of the following: FD&C Red #3, FD&C Yellow #6, FD&C Blue #1, Black Iron Oxide, and Yellow Iron Oxide. *Information for VYVANSE chewable tablets:*

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
	VYVANSE chewable tablets contain 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, and 60 mg of lisdexamfetamine dimesylate (equivalent to 5.8 mg, 11.6 mg, 17.3 mg, 23.1 mg, 28.9 mg, and 34.7 mg of lisdexamfetamine). Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, guar gum, magnesium stearate, mannitol, microcrystalline cellulose, sucralose, artificial strawberry flavor.
Previous ANDA Labeling	(b) (4)
Current ANDA Labeling	Lisdexamfetamine dimesylate is a white to off-white powder that is soluble in water (792 mg/mL). Lisdexamfetamine dimesylate capsules contain 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg of lisdexamfetamine dimesylate and the following inactive ingredients: ammonium hydroxide, calcium phosphate, gelatin, iron oxide black, isopropyl alcohol, magnesium stearate, microcrystalline cellulose, n-butyl alcohol, propylene glycol, shellac glaze, sodium starch glycolate, and titanium dioxide. In addition, the 20 mg capsule also contains yellow iron oxide. The 30 mg capsule also contains FD&C yellow #6. The 40 mg capsule also contains FD&C blue #1 and FD&C green #3. The 50 mg and 60 mg capsules also contain D&C red #28 and FD&C blue #1. The 70 mg capsule also contains D&C red #28, FD&C blue #1, and FD&C yellow #6. **CYCLE 7 COMMENT:** No changes to the inactive ingredients. However, in the **Cycle 6** comment above, the missing equivalency values were identified and deficiency comment was intended to be captured in **section 5.3**. However, the deficiency comment was not included with the other PI labeling deficiencies identified. Thus, it will be issued in this review cycle. Refer to **section 5.3** for comment.

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING (C7)

Table 8: Comparison of Model Labeling to ANDA Labeling	
Model Labeling	**16 HOW SUPPLIED/STORAGE AND HANDLING**

Table 8: Comparison of Model Labeling to ANDA Labeling	
	16.1 How Supplied VYVANSE (lisdexamfetamine dimesylate) capsules: • VYVANSE capsules 10 mg: pink body/pink cap (imprinted with S489 and 10 mg), bottles of 100, NDC 59417-101-10 • VYVANSE capsules 20 mg: ivory body/ivory cap (imprinted with S489 and 20 mg), bottles of 100, NDC 59417-102-10 • VYVANSE capsules 30 mg: white body/orange cap (imprinted with S489 and 30 mg), bottles of 100, NDC 59417-103-10 • VYVANSE capsules 40 mg: white body/blue green cap (imprinted with S489 and 40 mg), bottles of 100, NDC 59417-104-10 • VYVANSE capsules 50 mg: white body/blue cap (imprinted with S489 and 50 mg), bottles of 100, NDC 59417-105-10 • VYVANSE capsules 60 mg: aqua blue body/aqua blue cap (imprinted with S489 and 60 mg), bottles of 100, NDC 59417-106-10 • VYVANSE capsules 70 mg: blue body/orange cap (imprinted with S489 and 70 mg), bottles of 100, NDC 59417-107-10 VYVANSE (lisdexamfetamine dimesylate) chewable tablets: • VYVANSE chewable tablets 10 mg: White to off-white round shaped tablet debossed with ‘10’ on one side and ‘S489’ on the other, bottles of 100, NDC 59417-115-01 • VYVANSE chewable tablets 20 mg: White to off-white hexagonal shaped tablet debossed with ‘20’ on one side and ‘S489’ on the other, bottles of 100, NDC 59417-11601 • VYVANSE chewable tablets 30 mg: White to off-white arc triangular shaped tablet debossed with ‘30’ on one side and ‘S489’ on the other, bottles of 100, NDC 59417-11701 • VYVANSE chewable tablets 40 mg: White to off-white capsule shaped tablet debossed with ‘40’ on one side and ‘S489’ on the other, bottles of 100, NDC 59417-118-01 • VYVANSE chewable tablets 50 mg: White to off-white arc square shaped tablet debossed with ‘50’ on one side and ‘S489’ on the other, bottles of 100, NDC 59417-11901 • VYVANSE chewable tablets 60 mg: White to off-white arc diamond shaped tablet debossed with ‘60’ on one side and ‘S489’ on the other, bottles of 100, NDC 59417-12001 **16.2 Storage and Handling** Dispense in a tight, light-resistant container as defined in the USP. Store at room temperature, 20ºC to 25ºC (68ºF to 77ºF). Excursions permitted between 15ºC and 30ºC (59 to 86ºF) *[see USP Controlled Room Temperature]*. Disposal

Table 8: Comparison of Model Labeling to ANDA Labeling	
	Comply with local laws and regulations on drug disposal of CNS stimulants. Dispose of remaining, unused, or expired VYVANSE by a medicine take-back program.
Previous ANDA Labeling	**16 HOW SUPPLIED/STORAGE AND HANDLING** **16.1 How Supplied** Lisdexamfetamine dimesylate capsules 20 mg: ivory body/ivory cap (imprinted with 54 990) Bottle of 30, NDC 0054-0370-13; Bottle of 100, NDC 0054-0370-25 Lisdexamfetamine dimesylate capsules 30 mg: white body/orange cap (imprinted with 54 682) Bottle of 30, NDC 0054-0371-13; Bottle of 100, NDC 0054-0371-25 Lisdexamfetamine dimesylate capsules 40 mg: white body/light green cap (imprinted with 54 098) Bottle of 30, NDC 0054-0372-13; Bottle of 100, NDC 0054-0372-25 Lisdexamfetamine dimesylate capsules 50 mg: white body/blue cap (imprinted with 54 296) Bottle of 30, NDC 0054-0373-13; Bottle of 100, NDC 0054-0373-25 Lisdexamfetamine dimesylate capsules 60 mg: blue body/blue cap (imprinted with 54 338) Bottle of 30, NDC 0054-0374-13; Bottle of 100, NDC 0054-0374-25 Lisdexamfetamine dimesylate capsules 70 mg: orange body/blue cap (imprinted with 54 818) Bottle of 30, NDC 0054-0375-13; Bottle of 100, NDC 0054-0375-25 **16.2 Storage and Handling** Dispense in a tight, light-resistant container as defined in the USP. Store at 20° to 25°C (68° to 77°F). Excursions permitted between 15º to 30ºC (59 to 86ºF) [See USP Controlled Room Temperature]. *Disposal*: Comply with local laws and regulations on drug disposal of CNS stimulants. Dispose of remaining, unused, or expired lisdexamfetamine dimesylate capsules by a medicine take-back program. **CYCLE 6 COMMENT:** Addition of storage temperature excursions is acceptable from a labeling perspective.
Current ANDA Labeling	**16 HOW SUPPLIED/STORAGE AND HANDLING** **16.1 How Supplied** Lisdexamfetamine dimesylate capsules 20 mg: ivory body/ivory cap (imprinted with 54 990) Bottle of 30, NDC 0054-0370-13; Bottle of 100, NDC 0054-0370-25 Lisdexamfetamine dimesylate capsules 30 mg: white body/orange cap (imprinted with 54 682) Bottle of 30, NDC 0054-0371-13; Bottle of 100, NDC 0054-0371-25 Lisdexamfetamine dimesylate capsules 40 mg: white body/light green cap (imprinted with 54 098) Bottle of 30, NDC 0054-0372-13; Bottle of 100, NDC 0054-0372-25 Lisdexamfetamine dimesylate capsules 50 mg: white body/blue cap (imprinted with 54 296) Bottle of 30, NDC 0054-0373-13; Bottle of 100, NDC 0054-0373-25 Lisdexamfetamine dimesylate capsules 60 mg: blue body/blue cap (imprinted with 54 338) Bottle of 30, NDC 0054-0374-13; Bottle of 100, NDC 0054-0374-25 Lisdexamfetamine dimesylate capsules 70 mg: orange body/blue cap (imprinted with 54 818) Bottle of 30, NDC 0054-0375-13; Bottle of 100, NDC 0054-0375-25

Table 8: Comparison of Model Labeling to ANDA Labeling	
	16.2 Storage and Handling Dispense in a tight, light-resistant container as defined in the USP. Store at 20° to 25°C (68° to 77°F). Excursions permitted between 15º to 30ºC (59 to 86ºF) [See USP Controlled Room Temperature]. *Disposal*: Comply with local laws and regulations on drug disposal of CNS stimulants. Dispose of remaining, unused, or expired lisdexamfetamine dimesylate capsules by a medicine take-back program. **CYCLE 7 COMMENT:** No changes noted.

5.1.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER (C7)

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements	
Previous ANDA Labeling	
Name and Address on ANDA Prescribing Information	Distributed by: **Hikma Pharmaceuticals USA Inc.** Berkeley Heights, NJ 07922 **CYCLE 6 COMMENT:** Revised distributor information which coincides with transfer of ownership.
Current ANDA Labeling	
Name and Address on ANDA Prescribing Information	Distributed by: **Hikma Pharmaceuticals USA Inc.** Berkeley Heights, NJ 07922 **CYCLE 7 COMMENT:** No changes noted.

5.2 CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS) (C7)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Container meets the **too small exemption** [21 CFR 201.10(i)]. Please enter Reviewer/Deficiency Comments if you select Deficiency.
ESTABLISHED/PROPRIETARY NAME and STRENGTH:		
☐	☒	**Tall Man** lettering complies with recommendations found on FDA webpage.
☐	☒	Established/proprietary **name and strength are the most prominent** information on the Principal Display Panel.
☐	☒	No **intervening text**(written, printed, or graphic matter) between established name and strength.

Deficiency	No Deficiency	
	THE FOLLOWING COMPONENTS ARE PROPERLY DISPLAYED:	
☐	☒	**Net quantity** statement. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Dosage** statement.
☐	☒	**NDC number:** prominence, linear bar code, and its orientation.
☐	☒	**Expiration date and lot number** (or placeholder).
☐	☒	**Equivalency statement** (product strength).
☐	☒	**Medication Guide** Pharmacist instructions [21 CFR 208.24(d)].
☐	☒	Controlled Substance Symbol.
☐	☒	**Image of drug product** represents the true size, color, and imprint.
☐	☒	**Yellow #5** (tartrazine) warning statement is properly displayed.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Latex** warning statement is properly displayed [21 CFR 801.437.].
	PRODUCT DIFFERENTIATION:	
☐	☒	ANDA is the **same color** as the RLD labels as required (e.g. warfarin, levothyroxine, enoxaparin). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Multiple **strengths are differentiated** by use of different color or other acceptable means.
☐	☒	Labels of proposed product is differentiated from **related products**.
	STORAGE, DISPENSING, MANUFACTURER, and PACKAGING:	
☐	☒	**Storage/dispensing** statement is consistent with the How Supplied section of the insert/RLD/USP. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
☐	☒	Tamper evident (controlled substances) requirements are met.
☐	☒	Use of child-resistant closure (CRC) or non-CRC is appropriate. Describe **container closure**, cite source, and any issues in Reviewer Comments below. Please enter Reviewer/Deficiency Comments if you select Deficiency.
	OVERALL ASSESSMENT:	
☐	☒	Requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

CYCLE 6 COMMENTS:

The container labels were satisfactory in Labeling Review #5 (C5) based on the 10/14/14 submission. The 9/19/22 amendment provides for revised container labels due to "corporate rebranding" and updated applicant holder.

Comparison of CONTAINER Labels (Representative samples shown)	
(b) (4)	**Currently Proposed**

Additional revisions to the corporate change and revised trade dress includes the inclusion of the equivalency statement which aligns with the RLD container labels. Revised container labels are satisfactory.

Updated container closure information -

Per 3.2.P.7 Quality, dated 9/19/22:

Packaging Configuration and Sizes

There are no changes being proposed to the packaging configurations or sizes as part of this Request for Final Approval. A summary of the proposed commercial packaging configurations for Lisdexamfetamine Dimesylate Capsules 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg (Bottles of 30 and 100 capsules) is provided in Table 3.

TABLE 3. PACKAGING CONFIGURATION AND SIZES

Bottles of 30 Capsules (20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg) [1] and Bottles of 100 Capsules (20 mg, 30 mg, 40 mg and 50 mg)	
Container/Closure	Description
(b) (4)	Bottle 90cc square wide mouth HDPE with neck ring
	(b) (4)
Bottles of 100 Capsules (60 and 70 mg)	
Container/Closure	Description
(b) (4)	Bottle 150cc square neck ring
	(b) (4)
	(b) (4)

Bottles of 30 and 100 are CRC and a tamper-evident heat induction seal is utilized in the packaging.

CYCLE 7 COMMENT:

The container labels were satisfactory in C6 based on the 9/19/22 submission. No new container labels were submitted in the 11/23/22 amendment for our review.

Deficiency Comments:

5.3 PRESCRIBING INFORMATION (C7)

Reviewer Assessment:

Deficiency	No Deficiency	
	HIGHLIGHTS:	
☐	☒	**Contact information** for applicant and FDA are listed correctly.
☐	☒	**Revision date** appears at end of HIGHLIGHTS section.
	DESCRIPTION/INACTIVE INGREDIENTS:	
☐	☒	Appropriate **warning/precaution** statements for inactive ingredients are present (21 CFR 201) Check only if applicable: ☐Sulfite (21 CFR 201.22) ☐Yellow #5 (Tartrazine) (21 CFR 201.20) ☐Phenylalanine/aspartame (21 CFR 201.21) ☐Latex (21 CFR 801.437). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Gluten** statement is appropriately stated. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Sterile** product statement [21 CFR 201.57(c)(12)(D)].
☐	☒	**Dosage form and route** of administration properly listed [21 CFR 201.57(c)(12)(B)].
	HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:	
☐	☒	All **submitted labels** and labeling are consistent with the HOW SUPPLIED section.
☐	☒	**Physical description** (e.g. scoring, color, imprint, capsule size, nozzle tip, cap color) of the finished product in the HOW SUPPLIED section are appropriately displayed.
☐	☒	**NDC** numbers are present.
☐	☒	Drug product is the **same color** as the RLD's drug product as required (e.g. warfarin, levothyroxine, enoxaparin).

Deficiency	No Deficiency	
☐	☒	**Storage or dispensing** statement is acceptable compared to the RLD/USP monograph. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**"Discard unused portion"** for single-dose products.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:		
☐	☒	STIC requirements addressed appropriately.
☐	☒	Intent to join the **Antiretroviral Pregnancy Registry** (APR) upon full approval.
☒	☐	**Pregnancy registry** information is appropriately included/excluded as required for the RLD. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Patent/exclusivity** carve out is acceptable. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☒	☐	Prescribing Information is the same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

CYCLE 6 COMMENT:

Overall, the proposed PI and MG labeling follows the last approved RLD labeling. **However**, the applicant took liberties in their proposed PI labeling to replace key words (e.g., pediatric) with their own choice of words (e.g., children and adolescents) or to omit words (e.g., ADHD) which appear to be intentional in the RLD labeling. These differences may lead to misinterpretation and thus should be revised prior to approval. Refer to deficiency comments below.

The applicant omitted information related to the chewable tablets in the Quality sections of the PI labeling as well as additional sections, including but not limited to sections **2.2 General Instructions for Use, 12.3 Pharmacokinetics, and 17 PATIENT COUNSELING INFORMATION**. This is an acceptable omission.

CYCLE 7 COMMENT:

The applicant submitted point-by-point response to PI labeling deficiencies identified in C6 based on the 9/19/22 submission as detailed in the table below.

As noted in **section 5.1.2**, the proposed PI labeling is missing the salt equivalency statement which is included in the RLD labeling. The container labels accurately reflects the equivalency statements on the side panel. At this time, we will issue the deficiency comment below along with additional deficiencies identified in the proposed PI labeling.

Pregnancy Registry - The applicant retained the third party pregnancy registry information in accordance with the RLD. We will request that the applicant confirm acceptance of their data by the appropriate third party based on current DLR best practice as noted in Drug Facts (**section 4.1**) and internal Standard Comments document. Refer to comment below.

Deficiency Comments:

Deficiency # 1 Created in C6 Prescribing Information	CONTENTS*: Delete [redacted] (b) (4) " from the end of the table of contents (below "**17 PATIENT COUNSELING INFORMATION**").

Response / Assessment:	Response Hikma acknowledges the Agency's request and has revised CONTENTS* to delete "MEDICATION GUIDE" from the end of the table of contents.
Deficiency # 2 Created in C6 Prescribing Information Response / Assessment:	**2.1 Pre-treatment Screening**, 1st sentence: Replace "children, adolescents, and adults" with "patients" and add "including lisdexamfetamine dimesylate capsules," after "CNS stimulants," in accordance with the RLD. Response As requested by the Agency, 2.1 Pre-treatment Screening is revised to replace "children, adolescents, and adults" with "patients" and to add "including lisdexamfetamine dimesylate capsules," after "CNS stimulants," in accordance with the RLD.
Deficiency # 3 Created in C6 Prescribing Information Response / Assessment:	**2.2 General Instructions for Use**: Retain the heading "*Information for lisdexamfetamine dimesylate capsules:*" in accordance with the RLD. Response In 2.2 General Instructions for Use, added the heading "Information for lisdexamfetamine dimesylate capsules:" in accordance with the RLD.
Deficiency # 4 Created in C6 Prescribing Information Response / Assessment:	**2.5** subsection heading: Add "in" for clarity as such: **2.5 Dosage in Patients with Renal Impairment.** Response As requested by the Agency, under 2.5 subsection heading, Hikma added "in" for clarity in accordance with RLD.
Deficiency # 5 Created in C6 Prescribing Information Response / Assessment:	**5.2 Serious Cardiovascular Reactions**, 2nd sentence: Replace "children and adolescents" with "pediatric patients" in accordance with the RLD. Response As requested by the Agency, "children and adolescents" have been replaced with "pediatric patients" in 5.2 Serious Cardiovascular Reactions, 2nd sentence in accordance with the RLD.
Deficiency # 6 Created in C6 Prescribing Information Response / Assessment:	**6.1 Clinical Trials Experience**, 2nd heading: Add "ADHD" in the heading as such: *Adverse Reactions Associated with Discontinuation of Treatment in ADHD Clinical Trials:* Response Hikma acknowledges the Agency's request and has revised 6.1 Clinical Trials Experience, 2nd heading to added "ADHD" in the heading.
Deficiency # 7 Created in C6 Prescribing Information	**Table 1** title: Revise in accordance with the RLD as such: **Table 1 Adverse Reactions Reported by 2% or More of Pediatric Patients Ages 6 to 12 Years with ADHD Taking Lisdexamfetamine Dimesylate and Greater than or Equal to Twice the Incidence in Patients Taking Placebo in a 4-Week Clinical Trial (Study 1)**

Response / Assessment:	Response As requested by the Agency, the title for Table 1 was revised to “Table 1 Adverse Reactions Reported by 2% or More of Pediatric Patients Ages 6 to 12 Years with ADHD Taking Lisdexamfetamine Dimesylate and Greater than or Equal to Twice the Incidence in Patients Taking Placebo in a 4-Week Clinical Trial (Study 1)” in accordance with the RLD.
Deficiency # 8 Created in C6 Prescribing Information Response / Assessment:	**Table 1**, Insomnia row: Revise (b) (4)%" to "22%" in accordance with the RLD. Response Hikma acknowledges the Agency’s request and has revised Table 1, Insomnia row from (b) (4)%” to “22%” in accordance with the RLD.
Deficiency # 9 Created in C6 Prescribing Information Response / Assessment:	**Table 2** title: Revise in accordance with the RLD as such: **Table 2 Adverse Reactions Reported by 2% or More of Pediatric Patients Ages 13 to 17 Years with ADHD Taking Lisdexamfetamine Dimesylate and Greater than or Equal to Twice the Incidence in Patients Taking Placebo in a 4-Week Clinical Trial (Study 4)** Response As requested by the Agency, the title for Table 2 was revised “Table 2 Adverse Reactions Reported by 2% or More of Pediatric Patients Ages 13 to 17 Years with ADHD Taking Lisdexamfetamine Dimesylate and Greater than or Equal to Twice the Incidence in Patients Taking Placebo in a 4-Week Clinical Trial (Study 4)” in accordance with the RLD.
Deficiency # 10 Created in C6 Prescribing Information Response / Assessment:	**Table 3** title: Add "with ADHD" in accordance with the RLD. Response Hikma acknowledges the Agency’s request and has revised the title in Table 3 to add “with ADHD” in accordance with the RLD.
Deficiency # 11 Created in C6 Prescribing Information Response / Assessment:	**8.5 Geriatric Use**, 2nd sentence: Revise beginning of the sentence to read, "Other reported clinical experience and pharmacokinetic data *[see Clinical Pharmacology (12.3)]* have not identified..." in accordance with the RLD. Response As requested by the Agency, 8.5 Geriatric Use, 2nd sentence has been revised to read “Other reported clinical experience and pharmacokinetic data [see Clinical Pharmacology (12.3)] have not identified...” in accordance with the RLD.
Deficiency # 12 Created in C6 Prescribing Information Response / Assessment:	**Figure 4** title: Replace "Children" with "Pediatric Patients" in accordance with the RLD. Response

(b) (4)

5.4 MEDICATION GUIDE (C7)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Medication Guide is **up-to-date** with model labeling.
☐	☒	Medication Guide meets **content, format, and font size**.
☐	☒	**Phonetic spelling** of the established/proprietary name is present and correct.
☐	☒	Description of **child-resistant feature**(if also present in HOW SUPPLIED/STORAGE AND HANDLING).
☐	☒	**Revision date and approval statement** appear at the end of the Medication Guide correctly.
☐	☒	Applicant committed to provide a **sufficient number** of Medication Guides.
☐	☒	Applicant included the **1-800-FDA-1088** phone number.
☐	☒	Medication Guide is the same as the model labeling, except for allowable differences. Please enter Reviewer/Deficiency Comments if you select Deficiency.
Reviewer Comments:		

CYCLE 6 COMMENT:

Proposed MG labeling follows the RLD model labeling and is satisfactory.

CYCLE 7 COMMENT:

The MG labeling was satisfactory in C6 based on the 9/19/22 submission. There are no updates to the RLD model labeling for the MG labeling and the proposed MG labeling remains satisfactory based on the 11/23/22 amendment.

Deficiency Comments:

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES (C7)

A labeling statement required verification from another division discipline. Check only if applicable.

Reviewer Assessment:

☐	Rubber
☐	Latex
☐	Gluten
☐	Alcohol (ethanol)
☐	Aluminum (small/large volume parenteral and pharmacy bulk package)
☐	Sulfite
☐	Phenylalanine (aspartame) - content calculation
☐	Yellow #5 (tartrazine)
☐	Ghost tablet/capsule (i.e. solid or semi-solid mass in stool)
☐	Other

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB): (For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue)

Reviewer Comments:

Deficiency Comments:

Alison Park

Digitally signed by Alison Park
Date: 4/20/2023 06:44:52PM
GUID: 5063541100000db251c2d2cd0f7476af

Ellen Koo

Digitally signed by Ellen Koo
Date: 4/27/2023 02:38:21PM
GUID: 508da73d0002b687dfbf9b3859d80789

***** This document contains proprietary information that cannot be released to the public.***V.25**

Labeling Review

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	10/17/2022
ANDA Number(s)	202827
Review Number	6
Applicant Name	Hikma Pharmaceuticals USA Inc.
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Lisdexamfetamine Dimesylate Capsules, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg
Proposed Proprietary Name	None
Submission Received Date	September 19, 2022
Primary Labeling Reviewer	Alison Park
Secondary Labeling Reviewer	Refer to signature page

Review Conclusion

☐ Acceptable - No Comments
☐ Acceptable - Include Post Approval Comments
☒ Minor Deficiency* - Refer to Labeling Deficiencies and Comments for Letter to Applicant
☐ Major Deficiency** - Refer to Labeling Deficiencies and Comments for Letter to Applicant

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.

On Policy Alert List	☒ Yes	☐ No
Acceptable For Filing	☒ Yes	☐ No
Combined Insert/Outsert	☐ Yes	☒ No

TABLE OF CONTENTS

1 LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT
1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE
1.3 POST-APPROVAL REVISIONS

2 INSTRUCTIONS FOR ASSESSMENT
3 OVERALL ASSESSMENT OF MATERIALS REVIEWED
4 LABELING REVIEW INFORMATION

4.1 REGULATORY INFORMATION
4.2 MODEL PRESCRIBING INFORMATION
4.3 PATENTS AND EXCLUSIVITIES
4.4 UNITED STATES PHARMACOPEIA (USP)
4.5 MODEL CONTAINER LABELS

5 ASSESSMENT OF ANDA LABELING AND LABELS

5.1 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS)

5.1.1 DRUG PRODUCT REVIEW
5.1.2 DESCRIPTION
5.1.3 HOW SUPPLIED/STORAGE AND HANDLING
5.1.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER

5.2 CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS)

5.3 PRESCRIBING INFORMATION
5.4 MEDICATION GUIDE

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES

1 LABELING COMMENTS (C6)

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT (C6)

PRESCRIBING INFORMATION

a. CONTENTS*: Delete "(b) (4)" from the end of the table of contents (below "**17 PATIENT COUNSELING INFORMATION**").
b. **2.1 Pre-treatment Screening**, 1st sentence: Replace "children, adolescents, and adults" with "patients" and add "including lisdexamfetamine dimesylate capsules," after "CNS stimulants," in accordance with the RLD.
c. **2.2 General Instructions for Use**: Retain the heading "*Information for lisdexamfetamine dimesylate capsules:*" in accordance with the RLD.
d. **2.5** subsection heading: Add "in" for clarity as such:
   2.5 Dosage in Patients with Renal Impairment.
e. **5.2 Serious Cardiovascular Reactions**, 2nd sentence: Replace "children and adolescents" with "pediatric patients" in accordance with the RLD.
f. **6.1 Clinical Trials Experience**, 2nd heading: Add "ADHD" in the heading as such:
   Adverse Reactions Associated with Discontinuation of Treatment in ADHD Clinical Trials:
g. **Table 1** title: Revise in accordance with the RLD as such:
   Table 1 Adverse Reactions Reported by 2% or More of Pediatric Patients Ages 6 to 12 Years with ADHD Taking Lisdexamfetamine Dimesylate and Greater than or Equal to Twice the Incidence in Patients Taking Placebo in a 4-Week Clinical Trial (Study 1)
h. **Table 1**, Insomnia row: Revise (b) (4)%" to "22%" in accordance with the RLD.
i. **Table 2** title: Revise in accordance with the RLD as such:
   Table 2 Adverse Reactions Reported by 2% or More of Pediatric Patients Ages 13 to 17 Years with ADHD Taking Lisdexamfetamine Dimesylate and Greater than or Equal to Twice the Incidence in Patients Taking Placebo in a 4-Week Clinical Trial (Study 4)
j. **Table 3** title: Add "with ADHD" in accordance with the RLD.
k. **8.5 Geriatric Use**, 2nd sentence: Revise beginning of the sentence to read, "Other reported clinical experience and pharmacokinetic data *[see Clinical Pharmacology (12.3)]* have not identified..." in accordance with the RLD.
l. **Figure 4** title: Replace "Children" with "Pediatric Patients" in accordance with the RLD.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE (C6)

1.3 POST-APPROVAL REVISIONS (C6)

These comments will be addressed post approval (in the first labeling supplement review).

2 INSTRUCTIONS FOR ASSESSMENT (C6)

General Comments:

Select the "no deficiency" or "deficiency" radio button as appropriate for each row. If a "Deficiency Comments" appears, ensure it is appropriate for your situation, edit, or enter "Reviewer Comments" if necessary.

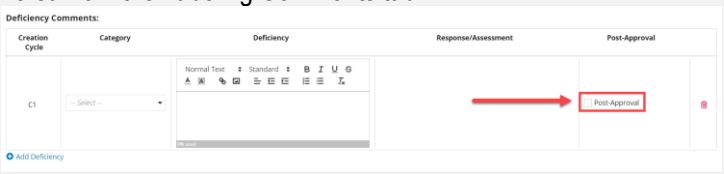
If there is no issue/concern, or if the question is not applicable. No "Deficiency Comments" will appear but reviewers can still enter "Reviewer Comments" if desired.

☐	☒	There is information in the Orange Book that the applicant needs to address.
☒	☐	Information in the Orange Book has **expired** and the applicant needs to revise labeling.

Reviewer Comments:
Enter free text in this section as necessary.

Deficiency Comments:

- Standardized comments/deficiencies are available for certain questions. For a complete list of standardized comments, reference the DLR Standardized Comments SharePoint.
- Reviewers can modify standardized comments/deficiencies for their situation.
- Deficiencies will have a review number, deficiency number, and roman numeral in the user interface. For first original reviews the review number and iteration numeral will align; however, older reviews may have review numbers and iteration numerals that differ due to some reviews being completed under past practices.
- Deficiency comments will populate by default to the Labeling Comments deficiency section unless you select the Post-Approval checkbox. Assessors also have the option to move all comments to the Post-Approval Revisions section or vice versa from the Labeling Comments tab.



3 OVERALL ASSESSMENT OF MATERIALS REVIEWED (C6)

Table 1: Review Summary of Container Label and Carton Labeling

	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation
Container	Final	20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg - Bottles of 30 and 100 capsules	09/19/2022	Satisfactory
Blister	N/A	N/A		

Table 1: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Carton	N/A	N/A		

Table 2: Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	Revised August 2022	09/19/2022	Revise
Medication Guide	Draft	Revised August 2022	09/19/2022	Satisfactory
Patient Information	N/A	N/A		
Instructions for Use	N/A	N/A		
SPL Data Elements				

4 LABELING REVIEW INFORMATION(C6)

4.1 REGULATORY INFORMATION (C6)

Yes	No	
☐	☒	Are there any applicable issues in **DLR's SharePoint Drug Facts** ?
☒	☐	Is the drug product listed in the Policy Alert Tracker on **OGD's SharePoint**?

Policy Alert Basis	Docket #	Brand Name (or Drug Class)	Generic Name / Dosage Form / Strengths	Action Requested or Issue Description	RLD#	Approval Actions (TA/AP)
Patent/Exclusivity	Internal	Vyvanse	Lisdexamfetamine Dimesylate capsules	3-year exclusivity decision pending with CDER Exclusivity Board.	021977/S-046	No Final Approval Actions can be issued while Exclusivity is being determined
Patent/Exclusivity	Internal	Vyvanse	Lisdexamfetamine Dimesylate chewable tablets	3-year exclusivity decision pending with CDER Exclusivity Board.	208510/S-003	No Final Approval Actions can be issued while Exclusivity is being determined

Communications (CRL, CC/IR/DRL)	Notes	Date Filed (~)	OGD Policy Lead
Application Communications can continue; Labeling affected if exclusivity is granted	Supplements that do not require updated labeling or labeling review are not affected.	7/29/2021	Kun Shen
Application Communications can continue; Labeling affected if exclusivity is granted	Supplements that do not require updated labeling or labeling review are not affected.	7/29/2021	Kun Shen

Primary discipline reviews may continue but NO final actions until final exclusivity determinations made.

4.2 MODEL PRESCRIBING INFORMATION (C6)

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling (Check the box used as the Model Labeling)
☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)

NDA#/Supplement# (S-000 if original): NDA021977 / S-048 (Combined with NDA 208510/S-005, Vyvanse chewable tablets)

Supplement Approval Date: 02/25/2022

Proprietary Name: Vyvanse

Established Name: Lisdexamfetamine Dimesylate Capsules

Description of Supplement:

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling (Check the box used as the Model Labeling)
These supplemental new drug applications provide for revisions to the labeling for Vyvanse, Adderall XR and Mydayis consistent with the Agency's December 14, 2021, safety labeling change notification letter, notifying the Sponsor, under Section 505(o)(4) of the FDCA, of new safety information pertaining to the association between the use of amphetamines and intestinal ischemia, that the Agency believes should be included in the labeling for all amphetamines. **Link:** https://analytics.fda.gov/workspace/hubble/external/object/v0/fda-communication?pk_communication=4943991_4538393_090140af80649ae3_NDA021977_3411801
☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**
☒ (b) (4)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	ANDA is **up-to-date** with the RLD/Model labeling.

Reviewer Comments:

Tentative Approval was granted on 6/23/2014.

A transfer of ANDA ownership was completed between Roxane Laboratories to West-Ward (2016) and then to Hikma (2019).

A gratuitous labeling amendment was submitted on 10/14/14 (reviewed under Labeling Review #5 (C5)) with the following minor deficiencies identified.

Labeling Deficiencies determined on September 28, 2015 based on your submission dated October 14, 2014:

1. GENERAL COMMENTS

   State how you will address the I-703 (Moderate to severe binge eating disorder (BED)) exclusivity and, if necessary, revise your labeling accordingly.

2. PRESCRIBING INFORMATION

   a. Revise your labeling to be in accordance with the most recently approved reference listed drug (RLD) labeling, Vyvanse® NDA 021977/S-039, approved April 17, 2015.

   b. HIGHLIGHTS OF PRESCRIBING INFORMATION

      i. **Limitation** statement: Revise both instances of the established name (which includes the dosage form) to use upper case letters as such:

         These highlights do not include all the information needed to use LISDEXAMFETAMINE DIMESYLATE CAPSULES safely and effectively. See full prescribing information for LISDEXAMFETAMINE DIMESYLATE CAPSULES.

      ii. **Title** section: Revise to use lower case for the dosage form as such:

         LISDEXAMFETAMINE DIMESYLATE capsules, for oral use, CII

   c. FULL PRESCRIBING INFORMATION

      8.1 Pregnancy subsection: Add the subheading (b) (4) We refer you to 21 CFR 201.57(c)(9)(i)(A).

3. MEDICATION GUIDE

   We refer you to PRESCRIBING INFORMATION comment 2.a.

However, it appears that the deficiency comments above were not issued to the applicant based on the 10/14/14 submission based on the lack of acknowledgement by the applicant in subsequent amendments.

Nevertheless, the 9/19/22 "minor amendment final approval requested" submission provides for revised container, prescribing information (PI) and Medication Guide (MG) labeling which supersedes any previously identified deficiencies.

Per 9/19/22 cover letter:

In accordance with the Agency's Guidance for Industry ANDA Submissions – Amendments and Requests for Final Approval to Tentatively Approved ANDAs (September 2020), when an application has been granted Tentative Approval (TA) Status 3 or More Years Before the Earliest Lawful Approval Date, the Agency recommends an ANDA applicant to consider the changes and updates made to the application and submit the Request for Final Approval with enough time to allow the Agency to assess these changes that have been made to the application. Therefore, Hikma is herein submitting our Request for Final Approval approximately 12 months before the date on which we seek final approval (August 24, 2023).

A summary of the changes that have been made to the application since receipt of Tentative Approval (June 23, 2014) is summarized below and further detailed, as applicable, in the respective module documents.

Labeling Updates

The labeling has been updated in accordance with the most recently approved labeling for the reference listed drug (RLD) VYVANSE® (lisdexamfetamine dimesylate) capsules (Rev. 01/2022), which was approved on February 25, 2022. Kindly note that our labeling has undergone corporate rebranding activities and the name of the company reflected on our labeling has also been changed from Roxane Laboratories to Hikma Pharmaceuticals USA Inc. as previously provided for in this application. The updated labeling documents and associated reference materials are provided in the following sections:

- Draft Container Labels (Section 1.14.1.1)
- Annotated Draft Labeling Text (Section 1.14.1.2)
- Draft Labeling Text (Insert) (Section 1.14.1.3)
- Annotated Comparison with Listed Drug (Section 1.14.3.1)
- Labeling Text for Reference Listed Drug (Section 1.14.3.3)

Refer to **sections 5.2, 5.3, and 5.4** for detailed assessments.

Deficiency Comments:

4.3 PATENTS AND EXCLUSIVITIES (C6)

The Orange Book was searched on 10/17/2022

Table 4 provides Orange Book patents for the Model Labeling (NDA021977) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 4: Impact of Model Labeling Patents on ANDA Labeling

Strengths	Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
20 mg, 30 mg, 50 mg, 60 mg, 70 mg	7105486	02/24/2023	U-727	FOR THE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)	IV	08/20/2012	None
20 mg, 40 mg, 60 mg	7105486	02/24/2023	U-842	INDICATED FOR THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)	IV	08/20/2012	None
20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7105486*PED	08/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50	7223735	02/24/2023			IV	08/20/2012	None

Table 4: Impact of Model Labeling Patents on ANDA Labeling							
Strengths	**Patent Number**	**Patent Expiration**	**Patent Use Code**	**Patent Use Code Definition**	**Patent Certification**	**Date of Patent Cert Submission**	**Labeling Impact**
mg, 60 mg, 70 mg							
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7223735*PED	08/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7655630	02/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7655630*PED	08/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7659253	02/24/2023	U-727	FOR THE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)	IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7659253*PED	08/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7659254	02/24/2023	U-1034	TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN ADULTS	IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7659254*PED	08/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7662787	02/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7662787*PED	08/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7662788	02/24/2023	U-727	FOR THE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)	IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7662788*PED	08/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg,	7671030	02/24/2023	U-727	FOR THE TREATMENT OF ATTENTION DEFICIT	IV	08/20/2012	None

Table 4: Impact of Model Labeling Patents on ANDA Labeling							
Strengths	**Patent Number**	**Patent Expiration**	**Patent Use Code**	**Patent Use Code Definition**	**Patent Certification**	**Date of Patent Cert Submission**	**Labeling Impact**
40 mg, 50 mg, 60 mg, 70 mg				HYPERACTIVITY DISORDER (ADHD)			
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7671030*PED	08/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7671031	02/24/2023	U-727	FOR THE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)	IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7671031*PED	08/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7674774	02/24/2023	U-842	INDICATED FOR THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)	IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7674774*PED	08/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7678770	02/24/2023	U-842	INDICATED FOR THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)	IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7678770*PED	08/24/2023			IV	08/20/2012	None
10 mg	7678771	02/24/2023			IV	08/20/2012	None
20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7678771	02/24/2023	U-842	INDICATED FOR THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)	IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7678771*PED	08/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7687466	02/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7687466*PED	08/24/2023			IV	08/20/2012	None

Table 4: Impact of Model Labeling Patents on ANDA Labeling							
Strengths	**Patent Number**	**Patent Expiration**	**Patent Use Code**	**Patent Use Code Definition**	**Patent Certification**	**Date of Patent Cert Submission**	**Labeling Impact**
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7687467	02/24/2023	U-842	INDICATED FOR THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)	IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7687467*PED	08/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7700561	02/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7700561*PED	08/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7713936	02/24/2023	U-727	FOR THE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)	IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7713936*PED	08/24/2023			IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7718619	02/24/2023	U-842	INDICATED FOR THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)	IV	08/20/2012	None
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7718619*PED	08/24/2023			IV	08/20/2012	None
20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7723305	02/24/2023	U-842	INDICATED FOR THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)	IV	08/20/2012	None
20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg	7723305*PED	08/24/2023			IV	08/20/2012	None

Table 5 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling						
Strengths	**Exclusivity Code**	**Exclusivity Expiration**	**Exclusivity Code Definition**	**Exclusivity Statement**	**Date of Exclusivity Submission**	**Labeling Impact**
	N/A					

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	There is information in the Orange Book that the applicant needs to address.
☐	☒	Information in the Orange Book has **expired** and the applicant needs to revise labeling.
Reviewer Comments: **Deficiency Comments:**		

4.4 UNITED STATES PHARMACOPEIA (USP) (C6)

The USP was searched on 10/17/2022

Table 6: USP				
	YES or NO	**Date**	**Monograph Title (N/A if no monograph)**	**Packaging and Storage/Labeling Statements (N/A if no monograph)**
Currently Official	No		N/A	N/A
Not Yet Official	No		N/A	N/A

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	**Established name** is acceptable with regard to the USP monograph or the RLD's nonproprietary name.
☐	☒	RLD's non-proprietary **name is different from USP** established name.
☐	☒	**USP descriptor** is correctly used in the appropriate sections of the prescribing information.
USP RECOMMENDATIONS and/or DIFFERENCES IN TEST METHODS (QUALITY):		
☐	☒	**DISSOLUTION**: The applicant's dissolution statement is appropriate.
☐	☒	**ORGANIC IMPURITIES**: Drug product meets USP acceptance criteria for organic impurities.
☐	☒	**ASSAY**: Drug product meets USP acceptance criteria for assay.
Reviewer Comments: **Deficiency Comments:**		

4.5 MODEL CONTAINER LABELS (C6)

Model container/carton/blister labels (Source: NDA 021977 Annual Report-15, dated 4/20/22 **)**

5 ASSESSMENT OF ANDA LABELING AND LABELS (C6)

5.1 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS) (C6)

5.1.1 DRUG PRODUCT REVIEW (C6)

Insert screenshot of Labeling portion from drug product review if completed:
Drug Product Review pending

Last completed drug product quality review was completed 6/11/14 (CR03) which had the following assessments for labeling:

A. Labeling & Package Insert

The description section, which includes chemical structure, chemical name, empirical formula, name of the inactive ingredients, and physical and chemical properties of drug substance, was reviewed. See the deficiency below for details.

The "how supplied" section is found satisfactory.

(b) (4)
(b) (4)

The name of the manufacturer and address are the same as presented in the submission.

(b) (4)

B. Environmental Assessment Or Claim Of Categorical Exclusion

The firm has requested a categorical exclusion from the requirement of an Environmental Assessment Statement in accordance with 21 CFR 25.31(a) (Module 1.12.14).

The review of the Quality amendment in the 9/19/22 submission is still pending review at this time.

5.1.2 DESCRIPTION (C6)

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling	*Information for VYVANSE capsules:* VYVANSE capsules contain 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg of lisdexamfetamine dimesylate (equivalent to 5.8 mg, 11.6 mg, 17.3 mg, 23.1 mg, 28.9 mg, 34.7 mg, and 40.5 mg of lisdexamfetamine). Inactive ingredients: microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The capsule shells contain gelatin, titanium dioxide, and one or more of the following: FD&C Red #3, FD&C Yellow #6, FD&C Blue #1, Black Iron Oxide, and Yellow Iron Oxide. *Information for VYVANSE chewable tablets:* VYVANSE chewable tablets contain 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, and 60 mg of lisdexamfetamine dimesylate (equivalent to 5.8 mg, 11.6 mg, 17.3 mg, 23.1 mg, 28.9 mg, and 34.7 mg of lisdexamfetamine). Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, guar gum, magnesium stearate, mannitol, microcrystalline cellulose, sucralose, artificial strawberry flavor.
Previous ANDA Labeling	Lisdexamfetamine dimesylate is a white to off-white powder that is soluble in water (792 mg/mL). Lisdexamfetamine dimesylate capsules contain 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg of lisdexamfetamine dimesylate and the following inactive ingredients: ammonium hydroxide, calcium phosphate, gelatin, iron oxide black, isopropyl alcohol, magnesium stearate, microcrystalline cellulose, n-butyl alcohol, propylene glycol, shellac glaze, sodium starch glycolate, and titanium dioxide. In addition, the 20 mg capsule also contains yellow iron oxide. The 30 mg capsule also contains FD&C yellow #6. The 40 mg

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
	capsule also contains FD&C blue #1 and FD&C green #3. The 50 mg and 60 mg capsules also contain D&C red #28 and FD&C blue #1. The 70 mg capsule also contains D&C red #28, FD&C blue #1, and FD&C yellow #6.
Current ANDA Labeling	Lisdexamfetamine dimesylate is a white to off-white powder that is soluble in water (792 mg/mL). Lisdexamfetamine dimesylate capsules contain 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg of lisdexamfetamine dimesylate and the following inactive ingredients: ammonium hydroxide, calcium phosphate, gelatin, iron oxide black, isopropyl alcohol, magnesium stearate, microcrystalline cellulose, n-butyl alcohol, propylene glycol, shellac glaze, sodium starch glycolate, and titanium dioxide. In addition, the 20 mg capsule also contains yellow iron oxide. The 30 mg capsule also contains FD&C yellow #6. The 40 mg capsule also contains FD&C blue #1 and FD&C green #3. The 50 mg and 60 mg capsules also contain D&C red #28 and FD&C blue #1. The 70 mg capsule also contains D&C red #28, FD&C blue #1, and FD&C yellow #6. **CYCLE 6 COMMENT:** No changes to the inactive ingredients. However, the applicant must add the equivalency statement and quantities for the base drug in accordance to the most recently approved RLD labeling. Refer to deficiency comment in **section 5.3**.

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING (C6)

Table 8: Comparison of Model Labeling to ANDA Labeling	
Model Labeling	**16 HOW SUPPLIED/STORAGE AND HANDLING** **16.1 How Supplied** VYVANSE (lisdexamfetamine dimesylate) capsules: • VYVANSE capsules 10 mg: pink body/pink cap (imprinted with S489 and 10 mg), bottles of 100, NDC 59417-101-10 • VYVANSE capsules 20 mg: ivory body/ivory cap (imprinted with S489 and 20 mg), bottles of 100, NDC 59417-102-10 • VYVANSE capsules 30 mg: white body/orange cap (imprinted with S489 and 30 mg), bottles of 100, NDC 59417-103-10 • VYVANSE capsules 40 mg: white body/blue green cap (imprinted with S489 and 40 mg), bottles of 100, NDC 59417-104-10 • VYVANSE capsules 50 mg: white body/blue cap (imprinted with S489 and 50 mg), bottles of 100, NDC 59417-105-10 • VYVANSE capsules 60 mg: aqua blue body/aqua blue cap (imprinted with S489 and 60 mg), bottles of 100, NDC 59417-106-10 • VYVANSE capsules 70 mg: blue body/orange cap (imprinted with S489 and 70 mg), bottles of 100, NDC 59417-107-10 VYVANSE (lisdexamfetamine dimesylate) chewable tablets:

Table 8: Comparison of Model Labeling to ANDA Labeling	
	• VYVANSE chewable tablets 10 mg: White to off-white round shaped tablet debossed with '10' on one side and 'S489' on the other, bottles of 100, NDC 59417-115-01 • VYVANSE chewable tablets 20 mg: White to off-white hexagonal shaped tablet debossed with '20' on one side and 'S489' on the other, bottles of 100, NDC 59417-11601 • VYVANSE chewable tablets 30 mg: White to off-white arc triangular shaped tablet debossed with '30' on one side and 'S489' on the other, bottles of 100, NDC 59417-11701 • VYVANSE chewable tablets 40 mg: White to off-white capsule shaped tablet debossed with '40' on one side and 'S489' on the other, bottles of 100, NDC 59417-118-01 • VYVANSE chewable tablets 50 mg: White to off-white arc square shaped tablet debossed with '50' on one side and 'S489' on the other, bottles of 100, NDC 59417-11901 • VYVANSE chewable tablets 60 mg: White to off-white arc diamond shaped tablet debossed with '60' on one side and 'S489' on the other, bottles of 100, NDC 59417-12001 **16.2 Storage and Handling** Dispense in a tight, light-resistant container as defined in the USP. Store at room temperature, 20ºC to 25ºC (68ºF to 77ºF). Excursions permitted between 15ºC and 30ºC (59 to 86ºF) *[see USP Controlled Room Temperature]*. <u>Disposal</u> Comply with local laws and regulations on drug disposal of CNS stimulants. Dispose of remaining, unused, or expired VYVANSE by a medicine take-back program.
Previous ANDA Labeling	**16 HOW SUPPLIED/STORAGE AND HANDLING** **16.1 How Supplied** Lisdexamfetamine dimesylate capsules 20 mg: ivory body/ivory cap (imprinted with 54 990) Bottle of 30, NDC 0054-0370-13; Bottle of 100, NDC 0054-0370-25 Lisdexamfetamine dimesylate capsules 30 mg: white body/orange cap (imprinted with 54 682) Bottle of 30, NDC 0054-0371-13; Bottle of 100, NDC 0054-0371-25 Lisdexamfetamine dimesylate capsules 40 mg: white body/light green cap (imprinted with 54 098) Bottle of 30, NDC 0054-0372-13; Bottle of 100, NDC 0054-0372-25 Lisdexamfetamine dimesylate capsules 50 mg: white body/blue cap (imprinted with 54 296) Bottle of 30, NDC 0054-0373-13; Bottle of 100, NDC 0054-0373-25 Lisdexamfetamine dimesylate capsules 60 mg: blue body/blue cap (imprinted with 54 338) Bottle of 30, NDC 0054-0374-13; Bottle of 100, NDC 0054-0374-25 Lisdexamfetamine dimesylate capsules 70 mg: orange body/blue cap (imprinted with 54 818) Bottle of 30, NDC 0054-0375-13; Bottle of 100, NDC 0054-0375-25 **16.2 Storage and Handling** Dispense in a tight, light-resistant container as defined in the USP.

Table 8: Comparison of Model Labeling to ANDA Labeling	
	Store at 20° to 25°C (68° to 77°F). Excursions permitted between 15º to 30ºC (59 to 86ºF) [See USP Controlled Room Temperature]. Disposal: Comply with local laws and regulations on drug disposal of CNS stimulants. Dispose of remaining, unused, or expired lisdexamfetamine dimesylate capsules by a medicine take-back program.
Current ANDA Labeling	**16 HOW SUPPLIED/STORAGE AND HANDLING** **16.1 How Supplied** Lisdexamfetamine dimesylate capsules 20 mg: ivory body/ivory cap (imprinted with 54 990) Bottle of 30, NDC 0054-0370-13; Bottle of 100, NDC 0054-0370-25 Lisdexamfetamine dimesylate capsules 30 mg: white body/orange cap (imprinted with 54 682) Bottle of 30, NDC 0054-0371-13; Bottle of 100, NDC 0054-0371-25 Lisdexamfetamine dimesylate capsules 40 mg: white body/light green cap (imprinted with 54 098) Bottle of 30, NDC 0054-0372-13; Bottle of 100, NDC 0054-0372-25 Lisdexamfetamine dimesylate capsules 50 mg: white body/blue cap (imprinted with 54 296) Bottle of 30, NDC 0054-0373-13; Bottle of 100, NDC 0054-0373-25 Lisdexamfetamine dimesylate capsules 60 mg: blue body/blue cap (imprinted with 54 338) Bottle of 30, NDC 0054-0374-13; Bottle of 100, NDC 0054-0374-25 Lisdexamfetamine dimesylate capsules 70 mg: orange body/blue cap (imprinted with 54 818) Bottle of 30, NDC 0054-0375-13; Bottle of 100, NDC 0054-0375-25 **16.2 Storage and Handling** Dispense in a tight, light-resistant container as defined in the USP. Store at 20° to 25°C (68° to 77°F). Excursions permitted between 15º to 30ºC (59 to 86ºF) [See USP Controlled Room Temperature]. *Disposal*: Comply with local laws and regulations on drug disposal of CNS stimulants. Dispose of remaining, unused, or expired lisdexamfetamine dimesylate capsules by a medicine take-back program. **CYCLE 6 COMMENT:** Addition of storage temperature excursions is acceptable from a labeling perspective.

5.1.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER (C6)

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements	
Previous ANDA Labeling	
Name and Address on ANDA Prescribing Information	Roxane Laboratories, Inc. Columbus, Ohio 43216
Current ANDA Labeling	

Name and Address on ANDA Prescribing Information	Distributed by: **Hikma Pharmaceuticals USA Inc.** Berkeley Heights, NJ 07922 Revised distributor information which coincides with transfer of ownership.

5.2 CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS) (C6)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Container meets the **too small exemption** [21 CFR 201.10(i)]. Please enter Reviewer/Deficiency Comments if you select Deficiency.
	ESTABLISHED/PROPRIETARY NAME and STRENGTH:	
☐	☒	**Tall Man** lettering complies with recommendations found on FDA webpage.
☐	☒	Established/proprietary **name and strength are the most prominent** information on the Principal Display Panel.
☐	☒	No **intervening text**(written, printed, or graphic matter) between established name and strength.
	THE FOLLOWING COMPONENTS ARE PROPERLY DISPLAYED:	
☐	☒	**Net quantity** statement. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Dosage** statement.
☐	☒	**NDC number:** prominence, linear bar code, and its orientation.
☐	☒	**Expiration date and lot number** (or placeholder).
☐	☒	**Equivalency statement** (product strength).
☐	☒	**Medication Guide** Pharmacist instructions [21 CFR 208.24(d)].
☐	☒	Controlled Substance Symbol.
☐	☒	**Image of drug product** represents the true size, color, and imprint.
☐	☒	**Yellow #5** (tartrazine) warning statement is properly displayed.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Latex** warning statement is properly displayed [21 CFR 801.437.].
	PRODUCT DIFFERENTIATION:	
☐	☒	ANDA is the **same color** as the RLD labels as required (e.g. warfarin, levothyroxine, enoxaparin). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Multiple **strengths are differentiated** by use of different color or other acceptable means.
☐	☒	Labels of proposed product is differentiated from **related products**.
	STORAGE, DISPENSING, MANUFACTURER, and PACKAGING:	
☐	☒	**Storage/dispensing** statement is consistent with the How Supplied section of the insert/RLD/USP. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
☐	☒	Tamper evident (controlled substances) requirements are met.
☐	☒	Use of child-resistant closure (CRC) or non-CRC is appropriate. Describe **container closure**, cite source, and any issues in Reviewer Comments below. Please enter Reviewer/Deficiency Comments if you select Deficiency.
	OVERALL ASSESSMENT:	

Deficiency	No Deficiency	
☐	☒	Requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100). Please

Reviewer Comments:

CYCLE 6 COMMENTS:

The container labels were satisfactory in Labeling Review #5 (C5) based on the 10/14/14 submission. The 9/19/22 amendment provides for revised container labels due to "corporate rebranding" and updated applicant holder.

Comparison of CONTAINER Labels (Representative samples shown)

(b) (4)

Currently Proposed

Additional revisions to the corporate change and revised trade dress includes the inclusion of the equivalency statement which aligns with the RLD container labels. Revised container labels are satisfactory.

Updated container closure information -
Per 3.2.P.7 Quality, dated 9/19/22:

Packaging Configuration and Sizes

There are no changes being proposed to the packaging configurations or sizes as part of this Request for Final Approval. A summary of the proposed commercial packaging configurations for Lisdexamfetamine Dimesylate Capsules 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg (Bottles of 30 and 100 capsules) is provided in Table 3.

TABLE 3. PACKAGING CONFIGURATION AND SIZES

Bottles of 30 Capsules (20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg) [1] and Bottles of 100 Capsules (20 mg, 30 mg, 40 mg and 50 mg)	
Container/Closure	**Description**
(b) (4)	Bottle 90cc square wide mouth HDPE with neck ring (b) (4)
Bottles of 100 Capsules (60 and 70 mg)	
Container/Closure	**Description**
(b) (4)	Bottle 150cc square neck ring (b) (4)

(b) (4)

Bottles of 30 and 100 are CRC and a tamper-evident heat induction seal is utilized in the packaging.

Deficiency Comments:

5.3 PRESCRIBING INFORMATION (C6)

Reviewer Assessment:

Deficiency	No Deficiency	
	HIGHLIGHTS:	
☐	☒	**Contact information** for applicant and FDA are listed correctly.
☐	☒	**Revision date** appears at end of HIGHLIGHTS section.
	DESCRIPTION/INACTIVE INGREDIENTS:	
☐	☒	Appropriate **warning/precaution** statements for inactive ingredients are present (21 CFR 201) Check only if applicable: ☐Sulfite (21 CFR 201.22) ☐Yellow #5 (Tartrazine) (21 CFR 201.20) ☐Phenylalanine/aspartame (21 CFR 201.21) ☐Latex (21 CFR 801.437). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Gluten** statement is appropriately stated. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Sterile** product statement [21 CFR 201.57(c)(12)(D)].
☐	☒	**Dosage form and route** of administration properly listed [21 CFR 201.57(c)(12)(B)].
	HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:	
☐	☒	All **submitted labels** and labeling are consistent with the HOW SUPPLIED section.
☐	☒	**Physical description** (e.g. scoring, color, imprint, capsule size, nozzle tip, cap color) of the finished product in the HOW SUPPLIED section are appropriately displayed.
☐	☒	**NDC** numbers are present.
☐	☒	Drug product is the **same color** as the RLD's drug product as required (e.g. warfarin, levothyroxine, enoxaparin).

Deficiency	No Deficiency	
☐	☒	**Storage or dispensing** statement is acceptable compared to the RLD/USP monograph. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**"Discard unused portion"** for single-dose products.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:		
☐	☒	STIC requirements addressed appropriately.
☐	☒	Intent to join the **Antiretroviral Pregnancy Registry** (APR) upon full approval.
☐	☒	**Pregnancy registry** information is appropriately included/excluded as required for the RLD. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Patent/exclusivity** carve out is acceptable. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☒	☐	Prescribing Information is the same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

Overall, the proposed PI and MG labeling follows the last approved RLD labeling. **However**, the applicant took liberties in their proposed PI labeling to replace key words (e.g., pediatric) with their own choice of words (e.g., children and adolescents) or to omit words (e.g., ADHD) which appear to be intentional in the RLD labeling. These differences may lead to misinterpretation and thus should be revised prior to approval. Refer to deficiency comments below.

The applicant omitted information related to the chewable tablets in the Quality sections of the PI labeling as well as additional sections, including but not limited to sections **2.2 General Instructions for Use, 12.3 Pharmacokinetics, and 17 PATIENT COUNSELING INFORMATION**. This is an acceptable omission.

Deficiency Comments:

Deficiency # 1 Created in C6 Prescribing Information Response / Assessment:	CONTENTS*: Delete [redacted] (b) (4) from the end of the table of contents (below "**17 PATIENT COUNSELING INFORMATION**").
Deficiency # 2 Created in C6 Prescribing Information Response / Assessment:	**2.1 Pre-treatment Screening**, 1st sentence: Replace "children, adolescents, and adults" with "patients" and add "including lisdexamfetamine dimesylate capsules," after "CNS stimulants," in accordance with the RLD.
Deficiency # 3 Created in C6 Prescribing Information Response / Assessment:	**2.2 General Instructions for Use**: Retain the heading "*Information for lisdexamfetamine dimesylate capsules:*" in accordance with the RLD.
Deficiency # 4 Created in C6	**2.5** subsection heading: Add "in" for clarity as such: **2.5 Dosage in Patients with Renal Impairment.**

Prescribing Information Response / Assessment:	
Deficiency # 5 Created in C6 Prescribing Information Response / Assessment:	**5.2 Serious Cardiovascular Reactions**, 2nd sentence: Replace "children and adolescents" with "pediatric patients" in accordance with the RLD.
Deficiency # 6 Created in C6 Prescribing Information Response / Assessment:	**6.1 Clinical Trials Experience**, 2nd heading: Add "ADHD" in the heading as such: *Adverse Reactions Associated with Discontinuation of Treatment in ADHD Clinical Trials:*
Deficiency # 7 Created in C6 Prescribing Information Response / Assessment:	**Table 1** title: Revise in accordance with the RLD as such: **Table 1 Adverse Reactions Reported by 2% or More of Pediatric Patients Ages 6 to 12 Years with ADHD Taking Lisdexamfetamine Dimesylate and Greater than or Equal to Twice the Incidence in Patients Taking Placebo in a 4-Week Clinical Trial (Study 1)**
Deficiency # 8 Created in C6 Prescribing Information Response / Assessment:	**Table 1**, Insomnia row: Revise (b) (4)%" to "22%" in accordance with the RLD.
Deficiency # 9 Created in C6 Prescribing Information Response / Assessment:	**Table 2** title: Revise in accordance with the RLD as such: **Table 2 Adverse Reactions Reported by 2% or More of Pediatric Patients Ages 13 to 17 Years with ADHD Taking Lisdexamfetamine Dimesylate and Greater than or Equal to Twice the Incidence in Patients Taking Placebo in a 4-Week Clinical Trial (Study 4)**
Deficiency # 10 Created in C6 Prescribing Information Response / Assessment:	**Table 3** title: Add "with ADHD" in accordance with the RLD.
Deficiency # 11 Created in C6 Prescribing Information	**8.5 Geriatric Use**, 2nd sentence: Revise beginning of the sentence to read, "Other reported clinical experience and pharmacokinetic data *[see Clinical Pharmacology (12.3)]* have not identified..." in accordance with the RLD.

5.4 MEDICATION GUIDE (C6)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Medication Guide is **up-to-date** with model labeling.
☐	☒	Medication Guide meets **content, format, and font size**.
☐	☒	**Phonetic spelling** of the established/proprietary name is present and correct.
☐	☒	Description of **child-resistant feature**(if also present in HOW SUPPLIED/STORAGE AND HANDLING).
☐	☒	**Revision date and approval statement** appear at the end of the Medication Guide correctly.
☐	☒	Applicant committed to provide a **sufficient number** of Medication Guides.
☐	☒	Applicant included the **1-800-FDA-1088** phone number.
☐	☒	Medication Guide is the same as the model labeling, except for allowable differences. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:
Proposed MG labeling follows the RLD model labeling and is satisfactory.

Deficiency Comments:

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES (C6)

A labeling statement required verification from another division discipline. Check only if applicable.

Reviewer Assessment:

☐	Rubber
☐	Latex
☐	Gluten
☐	Alcohol (ethanol)
☐	Aluminum (small/large volume parenteral and pharmacy bulk package)
☐	Sulfite
☐	Phenylalanine (aspartame) - content calculation
☐	Yellow #5 (tartrazine)
☐	Ghost tablet/capsule (i.e. solid or semi-solid mass in stool)
☐	Other

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB): (For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue)

Reviewer Comments:

Deficiency Comments:

Alison Park

Digitally signed by Alison Park
Date: 10/19/2022 03:42:25PM
GUID: 5063541100000db251c2d2cd0f7476af

Ellen Koo

Digitally signed by Ellen Koo
Date: 11/02/2022 11:08:14AM
GUID: 508da73d0002b687dfbf9b3859d80789

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	09/28/2015
ANDA Number(s)	202827
Review Number	5
Applicant Name	Roxane Laboratories, Inc.
Established Name & Strength(s)	Lisdexamfetamine Dimesylate Capsules, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg
Proposed Proprietary Name	None
Submission Received Date	10/14/2014 (amendment)
Labeling Reviewer	Alison Park, Pharm.D.
Labeling Team Leader	Lisa Kwok, Pharm.D.

Review Conclusion

☐ ACCEPTABLE – No Comments.

☐ ACCEPTABLE – Include Post Approval Comments

☒ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for the Letter to Applicant.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily Correctable Deficiency if all other OGD reviews are acceptable. Otherwise, the labeling minor deficiencies will be included in the Complete Response (CR) letter to the applicant.

☐ On Policy Alert List

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on September 28, 2015 based on your submission dated October 14, 2014:

1. GENERAL COMMENTS

   State how you will address the I-703 (Moderate to severe binge eating disorder (BED)) exclusivity and, if necessary, revise your labeling accordingly.

2. PRESCRIBING INFORMATION

   a. Revise your labeling to be in accordance with the most recently approved reference listed drug (RLD) labeling, Vyvanse® NDA 021977/S-039, approved April 17, 2015.

   b. HIGHLIGHTS OF PRESCRIBING INFORMATION

      i. **Limitation** statement: Revise both instances of the established name (which includes the dosage form) to use upper case letters as such:

         These highlights do not include all the information needed to use LISDEXAMFETAMINE DIMESYLATE CAPSULES safely and effectively. See full prescribing information for LISDEXAMFETAMINE DIMESYLATE CAPSULES.

      ii. **Title** section: Revise to use lower case for the dosage form as such:

         LISDEXAMFETAMINE DIMESYLATE capsules, for oral use, CII

   c. FULL PRESCRIBING INFORMATION

      8.1 Pregnancy subsection: Add the subheading [redacted] (b) (4) We refer you to 21 CFR 201.57(c)(9)(i)(A).

3. MEDICATION GUIDE

   We refer you to PRESCRIBING INFORMATION comment 2.a.

Submit your revised labeling electronically in final print format.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained.

Prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

N/A

1.3 POST APPROVAL REVISIONS

These comments will NOT be sent to the applicants at this time.
These comments will be addressed post approval (in the first labeling supplement review).

None.

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s) [e.g. "The below comments are from the labeling review C3 based on the submission dated 7/4/15."].

LABELING HISTORY

- **02/23/2011:** Original ANDA 202827 received by FDA.
- **07/30/2012:** Labeling Review #1 completed with general, container, prescribing information (PI), and medication guide (MG) deficiencies identified.
- **07/30/2012:** Easily Correctable Deficiency (ECD) comments for Labeling Review #1 faxed to the applicant.
- **08/14/2012:** Labeling amendment submitted.
- **11/26/2012:** Labeling Review #2 completed with PI and SPL deficiencies identified. Container labels were found Acceptable.
- **01/07/2013:** Complete Response (CR) #1 issued for product quality (major) and labeling deficiencies.
- **02/06/2013:** Resubmission after CR #1 received by FDA with revised container, PI, MG, and SPL submissions.
- **06/25/2013:** Labeling Review #3 completed with PI and MG deficiencies identified.
- **10/24/2013:** CR #2 issued for product quality (minor) and labeling deficiencies.
- **02/13/2014:** Resubmission after CR #2 received by FDA with revised PI, MG, and SPL submissions.
- **02/25/2014:** Labeling Review #4 completed with container, PI, MG, and SPL found acceptable (Approval Summary #1). However, the following post approval revisions were identified which have not yet been communicated to the applicant. (Note comments that are no longer applicable have been indicated with a ~~strikethrough~~.)
    - From Labeling Review #4:

      REVISIONS NEEDED POST APPROVAL? *Yes*

      INSERT

      ~~a. **Highlights of Prescribing Information**, Title section: We encourage you to revise the presentation of the drug name to appear in all capital letters. The title should appear as such:~~

      ~~**LISDEXAMFETAMINE dimesylate capsules, for oral use CII**~~

      b. **8.1 Pregnancy** subsection: Please add the subheading "Teratogenic effects." We refer you to 21 CFR 201.57(c)(9)(i)(A).

      ~~MEDICATION GUIDE~~

      ~~**MEDICATION GUIDE** heading, immediately following the established name: Please include the phonetic spelling of the established name in accordance with 21 CFR 208.20(b)(1)~~.

- **06/23/2014:** Tentative Approval (TA) received for the 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg strengths.
- **10/14/2014:** Gratuitous labeling amendment received with revised container, PI, MG, and SPL labeling submissions.
    - From cover letter:

      We wish to amend ANDA 202827 for Lisdexamfetamine Dimesylate Capsules, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg in response to the updated RLD labeling approved by the FDA on 7/ 18/2014. We are also submitting updated bottle labels with a revised storage statement.

This amendment is the subject of this review.

Reviewer Comments:

As noted above, the last labeling review (#4) was an Approval Summary review with no revisions requested except for post approval comments, which were not yet communicated to the applicant. As such, there are no deficiencies for the applicant to address. This 10/14/2014 gratuitous labeling amendment is to revise PI and MG labeling to be in accordance with an update to the reference listed drug (RLD) on 07/18/2014. Note that since this 10/14/2014 amendment, the RLD has updated labeling three (3) additional times. The applicant also submitted revised container labels with this 10/14/2014 amendment.

Refer to **section 2.1** for assessment of the revised container labels, to **section 3.2** for assessment of the revised PI and MG, and to **section 7/Table 9** for assessment of the SPL data elements.

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?
YES

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Comparison of CONTAINER Labels (Representative samples shown)
(b) (4)

(b) (4)

The applicant revised the temperature storage statement to include "[See USP Controlled Room Temperature.]"

No other revisions are noted.

We find the revised labels acceptable.

Reviewer Comments: Acceptable.

As noted above, the applicant made revisions to the controlled room temperature storage statement on the side panel to the preferred format.

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments:

None

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's Repository files? NO If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review
Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? NO If Yes, please explain.

3.2 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)
☒ **MOST RECENTLY APPROVED NDA MODEL LABELING** *(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA model labeling information.)* **NDA# /Supplement# (S-000 if original):** 021977/S-039 **Supplement Approval Date:** 04/17/2015 **Proprietary Name:** Vyvanse® **Established Name:** lisdexamfetamine dimesylate capsules **Description of Supplement:** This supplemental new drug application provides for the addition of "rhabdomyolysis" to the Adverse Reactions-Postmarketing Experience section consistent with the Agency's February 2, 2015 letter, which notified the sponsor, under Section 505(o)(4) of the FDCA, of new safety information that the Agency believes should be included in the labeling for Vyvanse (lisdexamfetamine dimesylate). This information pertains to the association between the use of stimulants used to treat Attention Deficit Hyperactivity Disorder (ADHD) and rhabdomyolysis.
☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING** **ANDA#/Supplement# (S-000 if original):** N/A **Supplement Approval Date:** N/A **Proprietary Name:** N/A **Established Name:** N/A **Description of Supplement:** N/A
☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** N/A
☐ **OTHER (Describe):** N/A

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **NO**

Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old)? **YES, but see additional comments below.**
Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

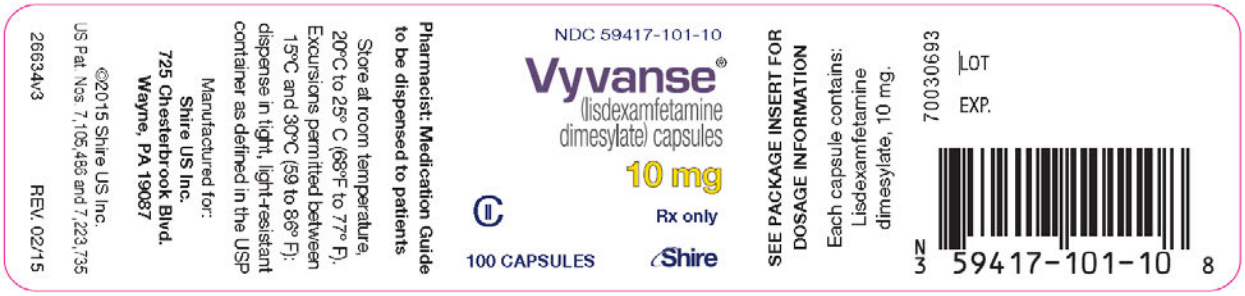
Reviewer Comments: Not acceptable.

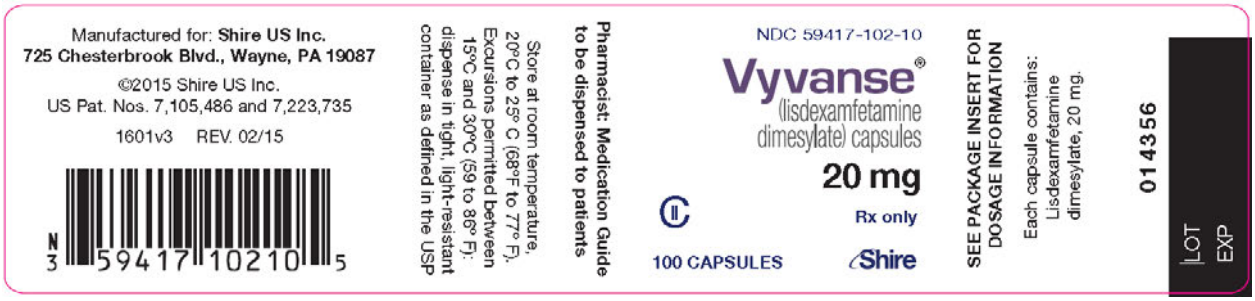
- The proposed PI and MG labeling is not the same as the most recently approved RLD model labeling, Vyvanse NDA 021977/S-039, approved 04/17/2015.
- The 10/14/2014 labeling submission uses the RLD, approved 07/18/2014, as the model. However, the RLD has updated the labeling an additional three (3) times since this amendment (S-033/approved 11/14/2014, S-036 and S-037/approved 01/30/2015, and S-039/approved 04/17/2015).
- Moreover, the S-037 (approved 01/30/2015) revision is an efficacy supplement which provides for data supporting the safety and effectiveness of Vyvanse for the treatment of moderate to severe Binge Eating Disorder (BED). Note that the applicant received 3 year Waxman-Hatch exclusivity (I-703) for this supplement. Refer to **section 3.5** for additional information.
- We will request that the applicant update their labeling (PI and MG) to be in accordance with the most recently approved RLD labeling (S-039 approved 04/17/2015). Additionally, the applicant must address the new I-703 exclusivity and revise their labeling accordingly (carve out or no impact). Refer to **section 1.1** for detailed comment to the applicant.
- Additionally at this time, we will request formatting revisions for the HIGHLIGHTS Limitation

  review #4 into the deficiency comments at this time. Refer to **section 1.1** for detailed comment to the

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: DARRTS NDA 021977 Annual Report-8, dated 04/23/2015]





NDC 59417-103-10

Vyvanse®
(lisdexamfetamine dimesylate) capsules
30 mg
Rx only
100 CAPSULES
Shire

Pharmacist: Medication Guide to be dispensed to patients

Store at room temperature, 20°C to 25° C (68°F to 77° F). Excursions permitted between 15°C and 30°C (59 to 86° F); dispense in tight, light-resistant container as defined in the USP

Manufactured for:
Shire US Inc.
725 Chesterbrook Blvd.
Wayne, PA 19087

US Pat. Nos. 7,105,486 and 7,223,735

1629v3 REV. 02/15

SEE PACKAGE INSERT FOR DOSAGE INFORMATION

Each capsule contains: Lisdexamfetamine dimesylate, 30 mg.

70030695
LOT
EXP.

N 3 59417-10310 2

NDC 59417-104-10

Vyvanse®
(lisdexamfetamine dimesylate) capsules
40 mg
Rx only
100 CAPSULES
Shire

Pharmacist: Medication Guide to be dispensed to patients

Store at room temperature, 20°C to 25° C (68°F to 77° F). Excursions permitted between 15°C and 30°C (59 to 86° F); dispense in tight, light-resistant container as defined in the USP

Manufactured for:
Shire US Inc.
725 Chesterbrook Blvd.
Wayne, PA 19087

US Pat. Nos. 7,105,486 and 7,223,735

1630v3 REV. 02/15

SEE PACKAGE INSERT FOR DOSAGE INFORMATION

Each capsule contains: Lisdexamfetamine dimesylate, 40 mg.

70030696
LOT
EXP.

N 3 59417-10410 9

NDC 59417-105-10

Vyvanse®
(lisdexamfetamine dimesylate) capsules
50 mg
Rx only
100 CAPSULES
Shire

Pharmacist: Medication Guide to be dispensed to patients

Store at room temperature, 20°C to 25° C (68°F to 77° F). Excursions permitted between 15°C and 30°C (59 to 86° F); dispense in tight, light-resistant container as defined in the USP

Manufactured for:
Shire US Inc.
725 Chesterbrook Blvd.
Wayne, PA 19087

US Pat. Nos. 7,105,486 and 7,223,735

1631v5 REV. 02/15

SEE PACKAGE INSERT FOR DOSAGE INFORMATION

Each capsule contains: Lisdexamfetamine dimesylate, 50 mg.

70030697
LOT
EXP.

N 3 59417-10510 6

NDC 59417-106-10

Vyvanse®
(lisdexamfetamine dimesylate) capsules
60 mg
Rx only
100 CAPSULES
Shire

Pharmacist: Medication Guide to be dispensed to patients

Store at room temperature, 20°C to 25° C (68°F to 77° F). Excursions permitted between 15°C and 30°C (59 to 86° F); dispense in tight, light-resistant container as defined in the USP

Manufactured for:
Shire US Inc.
725 Chesterbrook Blvd.
Wayne, PA 19087

US Pat. Nos. 7,105,486 and 7,223,735

1632v3 REV. 02/15

SEE PACKAGE INSERT FOR DOSAGE INFORMATION

Each capsule contains: Lisdexamfetamine dimesylate, 60 mg.

70030698
LOT
EXP.

N 3 59417-10610 3

NDC 59417-107-10

Vyvanse®
(lisdexamfetamine dimesylate) capsules
70 mg
Rx only
100 CAPSULES
Shire

Pharmacist: Medication Guide to be dispensed to patients

Store at room temperature, 20°C to 25° C (68°F to 77° F). Excursions permitted between 15°C and 30°C (59 to 86° F); dispense in tight, light-resistant container as defined in the USP

Manufactured for:
Shire US Inc.
725 Chesterbrook Blvd.
Wayne, PA 19087

US Pat. Nos. 7,105,486 and 7,223,735

1633v3 REV. 02/15

SEE PACKAGE INSERT FOR DOSAGE INFORMATION

Each capsule contains: Lisdexamfetamine dimesylate, 70 mg.

70030699
LOT
EXP.

N 3 59417-10710 0

3.4 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph.

	Date Searched	Monograph? YES or NO	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
USP 38	9/28/2015	NO	N/A	N/A
PF 41(5)	9/28/2015	NO	N/A	N/A

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 9/28/2015.
Table 3 provides Orange Book patents for the Model Labeling and ANDA patent certifications.
(For applications that have no patents, N/A is entered in the patent number column)

Table 8: Impact of Model Labeling Patents on ANDA Labeling

Patent Number*	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
7105486	Feb 24, 2023	U - 842[1]	INDICATED FOR THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)	IV	*08/20/2012 amended*	None
		U - 727[2]	FOR THE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)			
7223735[3]						
7655630[3]						
7659253[3]		U - 727	FOR THE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)			
7659254[3]		U - 1034	TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN ADULTS			
7662787[3]						
7662788[3]		U - 727	FOR THE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)			
7671030[3]						
7671031[3]						
7674774[3]		U - 842	INDICATED FOR THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)			
7678770[3]						
7678771[3]						
7687466[3]						
7687467[3]		U - 842	INDICATED FOR THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)			
7700561[3]						
7713936[3]		U - 727	FOR THE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)			
7718619[3]		U - 842	INDICATED FOR THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)			
7723305						

[1] U - 842 – 20 mg, 40 mg, 60 mg only
[2] U - 727 – 20 mg, 30 mg, 50 mg, 60 mg, 70 mg only
[3] These patents apply to the 10 mg strength also. Note that this subject ANDA 202827 is not proposing the 10 mg strength.
Blue highlight notes a change since the last labeling review.

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments:

Updates have been made to some patent expiration dates and use codes in the Orange Book since the last review. The patent and exclusivity data, which vary by strength, is shown below and is current as of the date of this review (9/28/15).

For the 20 mg and 60 mg strengths:

Patent and Exclusivity Search Results from query on Appl No 021977 Product 004 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N021977	004	7105486	Feb 24, 2023			U - 842	
N021977	004	7105486	Feb 24, 2023			U - 727	
N021977	004	7223735	Feb 24, 2023		Y		
N021977	004	7655630	Feb 24, 2023	Y			
N021977	004	7659253	Feb 24, 2023	Y	Y	U - 727	
N021977	004	7659254	Feb 24, 2023			U - 1034	
N021977	004	7662787	Feb 24, 2023	Y			
N021977	004	7662788	Feb 24, 2023			U - 727	
N021977	004	7671030	Feb 24, 2023		Y	U - 727	
N021977	004	7671031	Feb 24, 2023			U - 727	
N021977	004	7674774	Feb 24, 2023		Y	U - 842	
N021977	004	7678770	Feb 24, 2023			U - 842	
N021977	004	7678771	Feb 24, 2023		Y	U - 842	
N021977	004	7687466	Feb 24, 2023		Y		
N021977	004	7687467	Feb 24, 2023		Y	U - 842	
N021977	004	7700561	Feb 24, 2023		Y		
N021977	004	7713936	Feb 24, 2023			U - 727	
N021977	004	7718619	Feb 24, 2023		Y	U - 842	
N021977	004	7723305	Feb 24, 2023		Y	U - 842	

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
N021977	004	I - 703	Jan 30, 2018
N021977	004	I - 645	Jan 31, 2015

For the 40 mg strength:

Patent and Exclusivity Search Results from query on Appl No 021977 Product 005 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N021977	005	7105486	Feb 24, 2023			U - 842	
N021977	005	7223735	Feb 24, 2023		Y		
N021977	005	7655630	Feb 24, 2023	Y			
N021977	005	7659253	Feb 24, 2023	Y	Y	U - 727	
N021977	005	7659254	Feb 24, 2023			U - 1034	
N021977	005	7662787	Feb 24, 2023	Y			
N021977	005	7662788	Feb 24, 2023			U - 727	
N021977	005	7671030	Feb 24, 2023		Y	U - 727	
N021977	005	7671031	Feb 24, 2023			U - 727	
N021977	005	7674774	Feb 24, 2023		Y	U - 842	
N021977	005	7678770	Feb 24, 2023			U - 842	
N021977	005	7678771	Feb 24, 2023		Y	U - 842	
N021977	005	7687466	Feb 24, 2023		Y		
N021977	005	7687467	Feb 24, 2023		Y	U - 842	
N021977	005	7700561	Feb 24, 2023		Y		
N021977	005	7713936	Feb 24, 2023			U - 727	
N021977	005	7718619	Feb 24, 2023		Y	U - 842	
N021977	005	7723305	Feb 24, 2023		Y	U - 842	

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
N021977	005	I - 703	Jan 30, 2018
N021977	005	I - 645	Jan 31, 2015

For the 30 mg, 50 mg, and 70 mg strengths:

Patent and Exclusivity Search Results from query on Appl No 021977 Product 003 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N021977	003	7105486	Feb 24, 2023			U - 727	
N021977	003	7223735	Feb 24, 2023		Y		
N021977	003	7655630	Feb 24, 2023	Y			
N021977	003	7659253	Feb 24, 2023	Y	Y	U - 727	
N021977	003	7659254	Feb 24, 2023			U - 1034	
N021977	003	7662787	Feb 24, 2023	Y			
N021977	003	7662788	Feb 24, 2023			U - 727	
N021977	003	7671030	Feb 24, 2023		Y	U - 727	
N021977	003	7671031	Feb 24, 2023			U - 727	
N021977	003	7674774	Feb 24, 2023		Y	U - 842	
N021977	003	7678770	Feb 24, 2023			U - 842	
N021977	003	7678771	Feb 24, 2023		Y	U - 842	
N021977	003	7687466	Feb 24, 2023		Y		
N021977	003	7687467	Feb 24, 2023		Y	U - 842	
N021977	003	7700561	Feb 24, 2023		Y		
N021977	003	7713936	Feb 24, 2023			U - 727	
N021977	003	7718619	Feb 24, 2023		Y	U - 842	
N021977	003	7723305	Feb 24, 2023		Y	U - 842	

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
N021977	003	I - 703	Jan 30, 2018
N021977	003	I - 645	Jan 31, 2015

For the 10 mg strength:

Patent and Exclusivity Search Results from query on Appl No 021977 Product 007 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N021977	007	7223735	Feb 24, 2023		Y		
N021977	007	7655630	Feb 24, 2023	Y			
N021977	007	7659253	Feb 24, 2023	Y	Y	U - 727	
N021977	007	7659254	Feb 24, 2023			U - 1034	
N021977	007	7662787	Feb 24, 2023	Y			
N021977	007	7662788	Feb 24, 2023			U - 727	
N021977	007	7671030	Feb 24, 2023		Y	U - 727	
N021977	007	7671031	Feb 24, 2023			U - 727	
N021977	007	7674774	Feb 24, 2023		Y	U - 842	
N021977	007	7678770	Feb 24, 2023			U - 842	
N021977	007	7678771	Feb 24, 2023		Y		
N021977	007	7687466	Feb 24, 2023		Y		
N021977	007	7687467	Feb 24, 2023		Y	U - 842	
N021977	007	7700561	Feb 24, 2023		Y		
N021977	007	7713936	Feb 24, 2023			U - 727	
N021977	007	7718619	Feb 24, 2023		Y	U - 842	

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
N021977	007	I - 703	Jan 30, 2018
N021977	007	I - 645	Jan 31, 2015

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	**Exclusivity Expiration**	**Exclusivity Code Definition**	**Exclusivity Statement**	**Date of Exclusivity Submission**	**Labeling Impact**
I - 645	**Jan 31, 2015 (expired)**	MAINTENANCE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN ADULTS	Roxane Laboratories, Inc. states that the labeling for the drug product for which it is seeking approval does not include the indication that is covered by this exclusivity.	*08/20/2012 amended*	None
I - 703	**Jan 30, 2018**	MODERATE TO SEVERE BINGE EATING DISORDER (BED)	Must certify.		

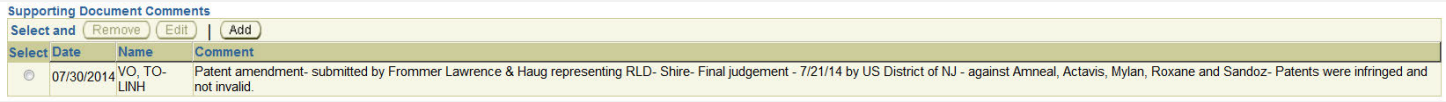
Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **To be determined (TBD)**

Reviewer Comments:

The applicant has yet to address the newly listed I-703 exclusivity. We will request that the applicant state how they will address this exclusivity (i.e., carve out or wait till expiry). Refer to **section 1.1** for comment to the applicant.

NOTE: The last patent amendment was received on 07/24/2014 (paper document only) which included a judgment for the patent holder as noted below:


Supporting Document Comments

Select and Remove Edit | Add

Select	Date	Name	Comment
	07/30/2014	VO, TO-LINH	Patent amendment- submitted by Frommer Lawrence & Haug representing RLD- Shire- Final judgement - 7/21/14 by US District of NJ - against Amneal, Actavis, Mylan, Roxane and Sandoz- Patents were infringed and not invalid.

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**
Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **NO**
Are there changes to the manufacturer/distributor/packer statements? **NO**
If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review (completed 02/25/14)	**Currently Proposed**	**Assessment**
(b) (4)	Lisdexamfetamine dimesylate capsules contain 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg of lisdexamfetamine dimesylate and the following inactive ingredients: ammonium hydroxide, calcium phosphate, gelatin, iron oxide black, isopropyl alcohol, magnesium stearate, microcrystalline cellulose, n-butyl alcohol, propylene glycol, shellac glaze, sodium starch glycolate, and titanium dioxide. In addition, the 20 mg capsule also contains yellow iron oxide. The 30 mg capsule also contains FD&C yellow #6. The 40 mg capsule also contains FD&C blue #1 and FD&C green #3. The 50 mg and 60 mg capsules also contain D&C red #28 and FD&C blue #1. The 70 mg capsule also contains D&C red #28, FD&C blue #1, and FD&C yellow #6.	**Correction of typographical error.** **NO other change.** **Acceptable.**

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
(b) (4)	**Currently Proposed**	**Assessment**
	16 HOW SUPPLIED/STORAGE AND HANDLING **16.1 How Supplied** Lisdexamfetamine dimesylate capsules 20 mg: ivory body/ivory cap (imprinted with 54 990) Bottle of 30, NDC 0054-0370-13; Bottle of 100, NDC 0054-0370-25 Lisdexamfetamine dimesylate capsules 30 mg: white body/orange cap (imprinted with 54 682) Bottle of 30, NDC 0054-0371-13; Bottle of 100, NDC 0054-0371-25 Lisdexamfetamine dimesylate capsules 40 mg: white body/light green cap (imprinted with 54 098) Bottle of 30, NDC 0054-0372-13; Bottle of 100, NDC 0054-0372-25 Lisdexamfetamine dimesylate capsules 50 mg: white body/blue cap (imprinted with 54 296) Bottle of 30, NDC 0054-0373-13; Bottle of 100, NDC 0054-0373-25 Lisdexamfetamine dimesylate capsules 60 mg: blue body/blue cap (imprinted with 54 338) Bottle of 30, NDC 0054-0374-13; Bottle of 100, NDC 0054-0374-25 Lisdexamfetamine dimesylate capsules 70 mg: orange body/blue cap (imprinted with 54 818) Bottle of 30, NDC 0054-0375-13; Bottle of 100, NDC 0054-0375-25 **16.2 Storage and Handling** Dispense in a tight, light-resistant container as defined in the USP. Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.] *Disposal*: Comply with local laws and regulations on drug disposal of CNS stimulants. Dispose of remaining, unused, or expired lisdexamfetamine dimesylate capsules by a medicine take-back program.	**Revision to temperature storage statement.** **NO other change.** **Acceptable.**

Table 7: Manufacturer/Distributor/Packer Statements		
	(b) (4)	Assessment
1		Revision date changed as expected. NO other change. Acceptable.

5. COMMENTS FOR CHEMISTRY REVIEWER

Describe issue(s) sent to and/or received from the chemistry (also known as drug product quality) reviewer:

Reviewer Comments:
None.

6. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline reviewer(s):

Reviewer Comments:
None.

7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item "Final, Draft, or "NA". If you enter "NA" under the second column, you do NOT need to enter "NA" for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Final	20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg - Bottles of 30 and 100.	10/14/2014	Satisfactory
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information (7 pt font size)	Final	Revised July 2014	10/14/2014	Revise
Medication Guide (not stand-alone, 10 pt font size)	Final	Revised July 2014		Revise
SPL Data Elements		Revised: 7/2014		Satisfactory

Office of Generic Drugs

REVIEW OF PROFESSIONAL LABELING (Labeling Review #4)

APPROVAL SUMMARY #1

ANDA Number:	202827
Date of Submission:	February 13, 2014 (resubmission, SD 15)
Applicant:	Roxane Laboratories, Inc.
Established Name and Strength:	Lisdexamfetamine Dimesylate Capsules, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg
Proposed Proprietary Name:	None

Labeling Comments below are considered:

☐ Minor Deficiency *

* Please note that the RPM may change the status from Minor Deficiency to Easily Correctable Deficiency if other disciplines are acceptable.

☒ No Comments **(**Labeling Approval Summary or Tentative Approval Summary)

RPM Note - Labeling comments to be sent to the firm start below:

The Labeling Review Branch has no further questions/comments at this time based on your labeling submission dated February 13, 2014.

Please continue to monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book and the NF-USP online for recent updates, and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17.

Note RPM - Labeling comments end here

REVISIONS NEEDED POST APPROVAL? *Yes*

INSERT

a. **Highlights of Prescribing Information**, Title section: We encourage you to revise the presentation of the drug name to appear in all capital letters. The title should appear as such:

LISDEXAMFETAMINE dimesylate capsules, for oral use CII

b. **8.1 Pregnancy** subsection: Please add the subheading [redacted] (b) (4) We refer you to 21 CFR 201.57(c)(9)(i)(A).

MEDICATION GUIDE

MEDICATION GUIDE heading, immediately following the established name: Please include the phonetic spelling of the established name in accordance with 21 CFR 208.20(b)(1).

NOTES/QUESTIONS TO THE CHEMIST/BIO REVIEWER/MICRO REVIEWER: None

Review Summary

Labeling Submitted	Date submitted	Final or Draft	Recommendation
CONTAINER – 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg Bottles of 30 and 100.	August 14, 2012	Final	Acceptable (in 11/26/12 Labeling Review)
INSERT – w/3 attached, perforated MG 6 pt font size (insert) 10 pt font size (MG)	February 13, 2014	Final	Acceptable†
MEDICATION GUIDE – not stand-alone	February 13, 2014	Final	Acceptable†
SPL	February 13, 2014	N/A	Acceptable
†Post-approval revisions			

From 2/13/14 cover letter:

In response to the above mentioned Complete Response letter, we have revised the labeling to be in accord with the most recent Vyvanse® labeling.

REMS required?	**(OTC do NOT require)**	☐ Yes	☒ No
MedGuides and/or PPIs (505-1(e))		☒ Yes	☐ No
Communication plan (505-1(e))		☐ Yes	☒ No
Elements to assure safe use (ETASU) (505-1(f)(3))		☐ Yes	☒ No
Implementation system if certain ETASU (505-1(f)(4))		☐ Yes	☒ No
Timetable for assessment (505-1(d))		☐ Yes	☒ No
ANDA REMS acceptable?		☐ Yes	☐ No ☒ N/A

FOR THE RECORD: (Portions taken from previous reviews)

1. **MODEL LABELING** (Checked Drugs@FDA on February 18, 2014)

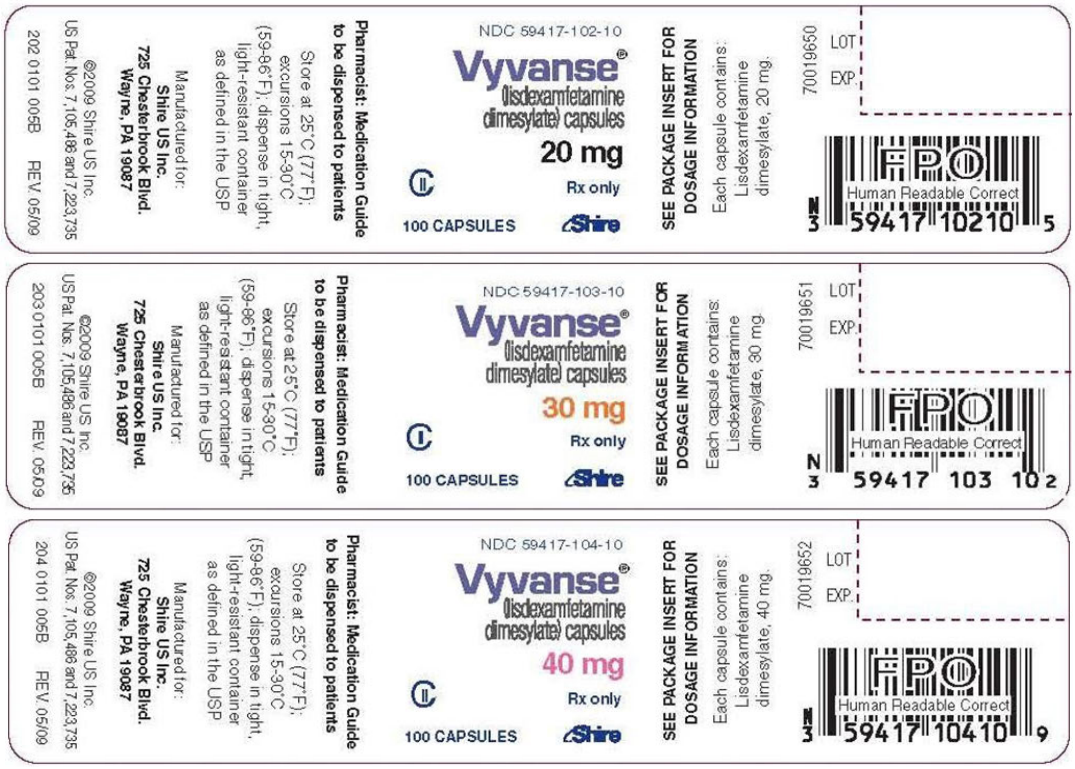
   The reference listed drug (RLD) is Vyvanse® (lisdexamfetamine dimesylate capsules), NDA 021977/S-030, approved December 6, 2013 (owner, Shire Development, Inc.).

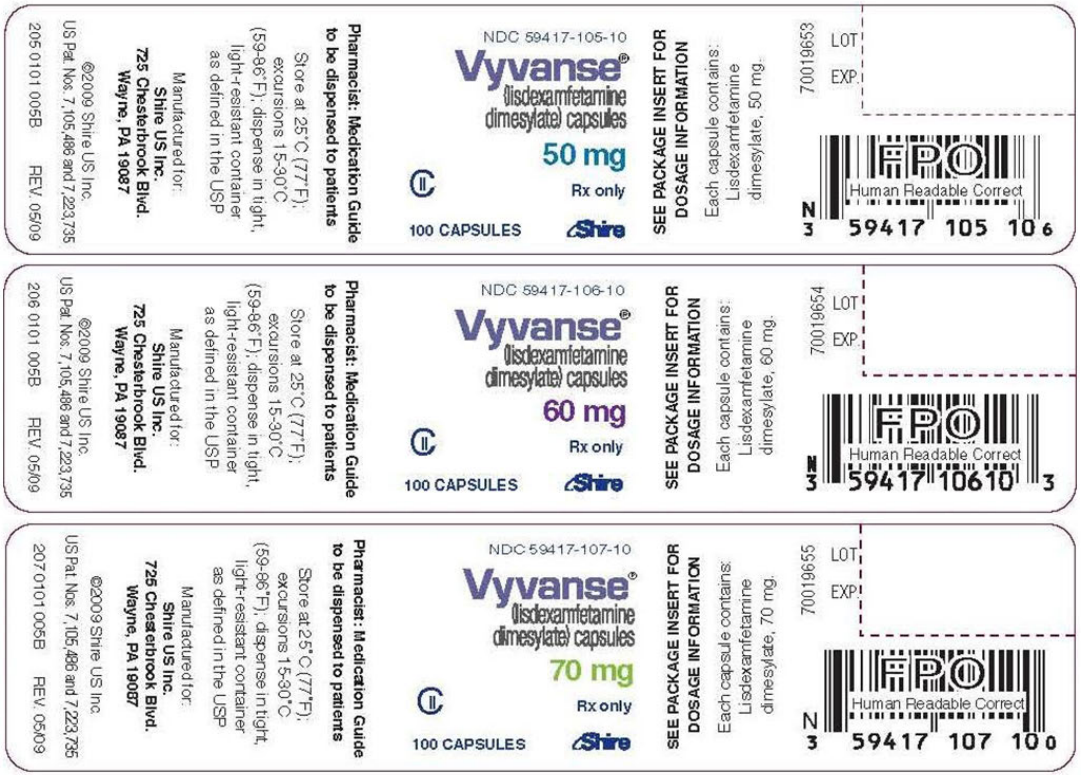
   - **S-030, approved 12/6/13**: This "Prior Approval" supplemental new drug application proposes the addition of "libido changes, and frequent or prolonged erections" to the Adverse Reactions-Postmarketing Experience section of labeling.

   Additional information:

   - **S-031, submitted 12/19/13**: This *pending* CBE proposes the following change: Addition of "bruxism" to Section 6.2, Postmarketing Experience.
   - **S-032, submitted 1/22/14**: This *pending* Prior Approval Supplement (PAS) proposes the following change(s): Update Dosage and Administration and Clinical Pharmacology sections in the FPI based on data from two clinical pharmacology studies.
   - **MedWatch** (Checked on February 18, 2014): Recent posting addressed in RLD NDA 021977/S-030, approved 12/6/13.

   - Container Labels for RLD NDA 021977 from DailyMed (Checked on February 18, 2014):





2. **USP 36** (Checked on February 18, 2014): Drug product is not compendial.

   PF 40(1) (Checked on February 18, 2014): No documents found.

3. **PATENT AND EXCLUSIVITY** (Checked Orange Book on February 18, 2014)

   Patent Data – NDA 021977

No	Expiration	Use Code	How filed	Labeling Impact
7105486	Jun 29, 2023	U - 727	IV	None
7223735	Jun 29, 2023		IV	None
7655630	Feb 24, 2023		IV	None
7659253	Feb 24, 2023	U - 727	IV	None
7659254	Feb 24, 2023	U - 1034	IV	None
7662787	Feb 24, 2023		IV	None
7662788	Feb 24, 2023	U - 727	IV	None
7671030	Feb 24, 2023	U - 727	IV	None
7671031	Feb 28, 2023	U - 727	IV	None
7674774	Mar 18, 2023	U - 842	IV	None
7678770	Mar 25, 2023	U - 842	IV	None
7678771	Mar 25, 2023	U - 842	IV	None
7687466	Feb 24, 2023		IV	None
7687467	Apr 8, 2023	U - 842	IV	None
7700561	Jun 29, 2023		IV	None
7713936	Feb 24, 2023	U - 727	IV	None
7718619	Feb 24, 2023	U - 842	IV	None
7723305	Feb 24, 2023	U - 842	IV	None

U - 727	FOR THE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)
U - 1034	TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN ADULTS
U - 842	INDICATED FOR THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)

Exclusivity Data– NDA 021977

Code	Reference	Expiration	Labeling impact
I - 645	MAINTENANCE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN ADULTS	Jan 31, 2015	Carve out
NPP	NEW PATIENT POPULATION	Nov 10, 2013	N/A-expired

For 20 mg, 40 mg, and 60 mg strengths:

Patent and Exclusivity Search Results from query on Appl No 021977 Product 004 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N021977	004	7105486	Jun 29, 2023			U - 842	
N021977	004	7223735	Jun 29, 2023		Y		
N021977	004	7655630	Feb 24, 2023	Y			
N021977	004	7659253	Feb 24, 2023	Y	Y	U - 727	
N021977	004	7659254	Feb 24, 2023			U - 1034	
N021977	004	7662787	Feb 24, 2023	Y			
N021977	004	7662788	Feb 24, 2023			U - 727	
N021977	004	7671030	Feb 24, 2023		Y	U - 727	
N021977	004	7671031	Feb 28, 2023			U - 727	
N021977	004	7674774	Mar 18, 2023		Y	U - 842	
N021977	004	7678770	Mar 25, 2023			U - 842	
N021977	004	7678771	Mar 25, 2023		Y	U - 842	
N021977	004	7687466	Feb 24, 2023		Y		
N021977	004	7687467	Apr 8, 2023		Y	U - 842	
N021977	004	7700561	Jun 29, 2023		Y		
N021977	004	7713936	Feb 24, 2023			U - 727	
N021977	004	7718619	Feb 24, 2023		Y	U - 842	
N021977	004	7723305	Feb 24, 2023		Y	U - 842	

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
N021977	004	I - 645	Jan 31, 2015
N021977	004	NPP	Nov 10, 2013

For 30 mg, 50 mg, and 70 mg strengths:

Patent and Exclusivity Search Results from query on Appl No 021977 Product 003 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N021977	003	7105486	Jun 29, 2023			U - 727	
N021977	003	7223735	Jun 29, 2023		Y		
N021977	003	7655630	Feb 24, 2023	Y			
N021977	003	7659253	Feb 24, 2023	Y	Y	U - 727	
N021977	003	7659254	Feb 24, 2023			U - 1034	
N021977	003	7662787	Feb 24, 2023	Y			
N021977	003	7662788	Feb 24, 2023			U - 727	
N021977	003	7671030	Feb 24, 2023		Y	U - 727	
N021977	003	7671031	Feb 28, 2023			U - 727	
N021977	003	7674774	Mar 18, 2023		Y	U - 842	
N021977	003	7678770	Mar 25, 2023			U - 842	
N021977	003	7678771	Mar 25, 2023		Y	U - 842	
N021977	003	7687466	Feb 24, 2023		Y		
N021977	003	7687467	Apr 8, 2023		Y	U - 842	
N021977	003	7700561	Jun 29, 2023		Y		
N021977	003	7713936	Feb 24, 2023			U - 727	
N021977	003	7718619	Feb 24, 2023		Y	U - 842	
N021977	003	7723305	Feb 24, 2023		Y	U - 842	

Exclusivity Data

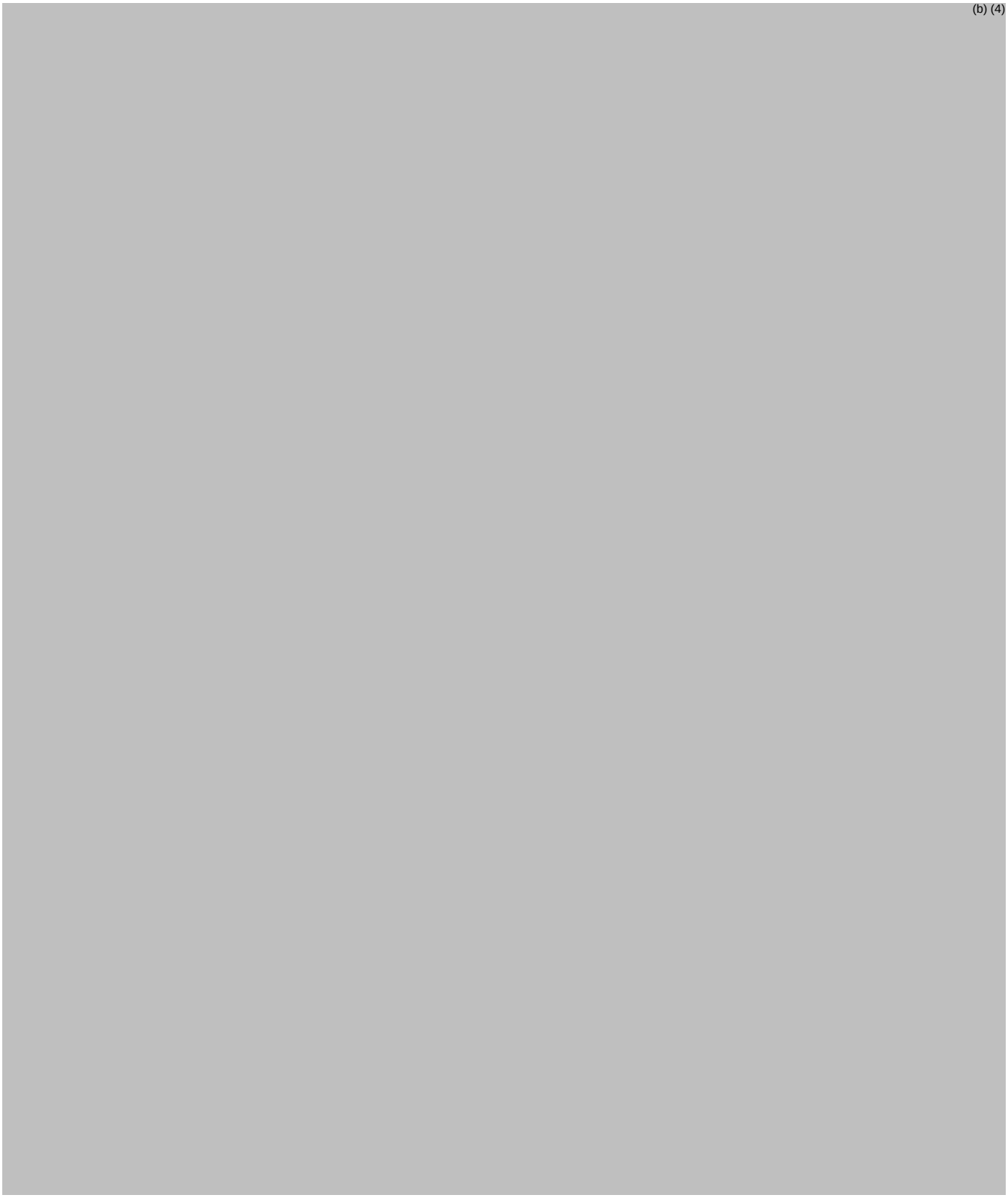
Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
N021977	003	I - 645	Jan 31, 2015
N021977	003	NPP	Nov 10, 2013

4. **INACTIVE INGREDIENTS (From 10/18/13 Quality review)**

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition.

From insert labeling: Lisdexamfetamine dimesylate capsules contain 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg of lisdexamfetamine dimesylate and the following inactive ingredients: ammonium hydroxide, calcium phosphate, gelatin, iron oxide black, isopropyl alcohol, magnesium stearate, microcrystalline cellulose, n-butyl alcohol, propylene glycol, shellac glaze, sodium starch glycolate, and titanium dioxide.

In addition, the 20 mg capsule also contains yellow iron oxide. The 30 mg capsule also contains FD&C yellow #6. The 40 mg capsule also contains FD&C blue #1 and FD&C green #3. The 50 mg and 60 mg capsules also contains D&C red #28 and FD&C blue #1. The 70 mg capsule also contains D&C red #28, FD&C blue #1, and FD&C yellow #6.


(b) (4)

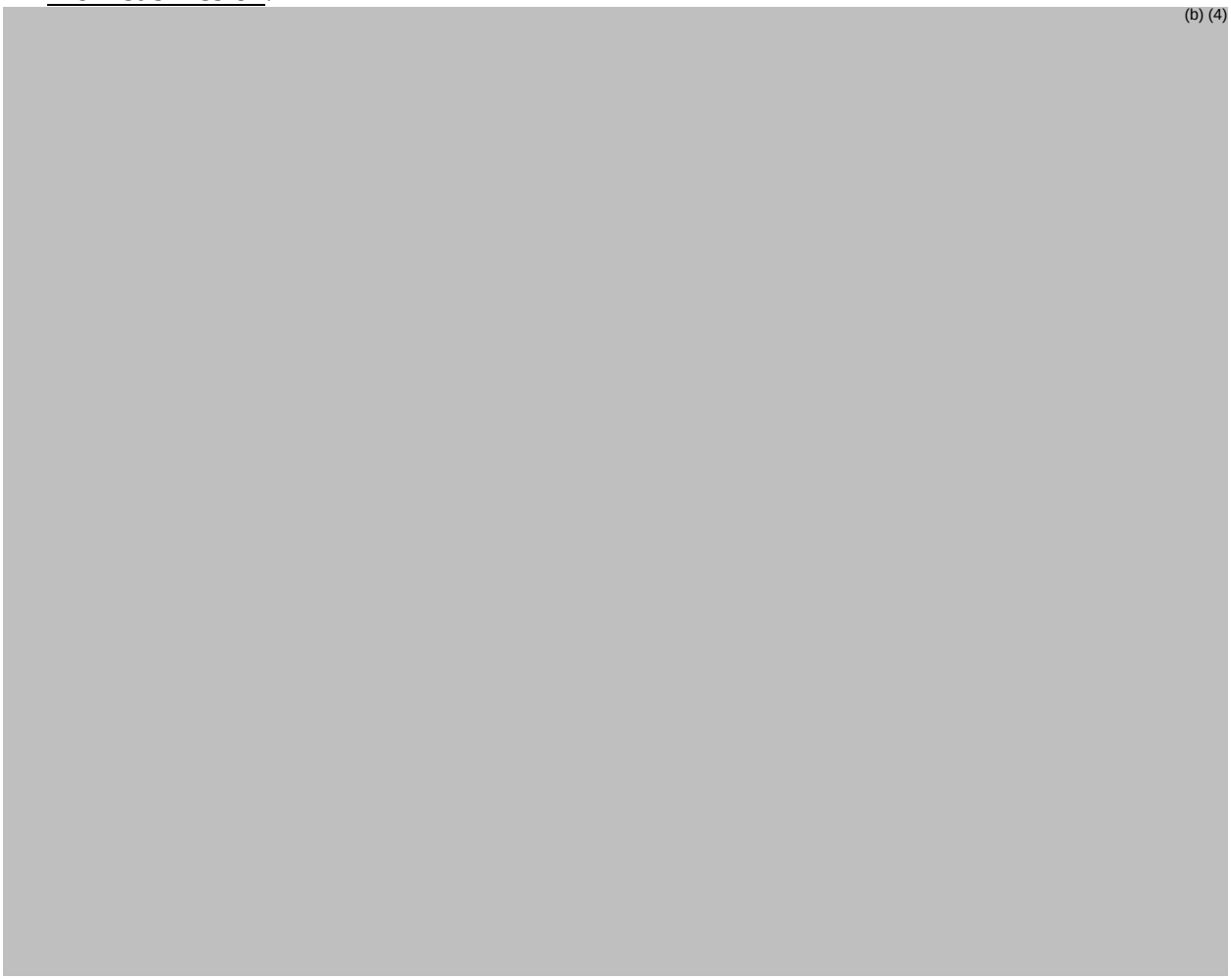
5. **MANUFACTURING FACILITY (From 10/18/13 Quality review)**

6. **FINISHED PRODUCT DESCRIPTION**

RLD: Vyvanse capsules 20 mg: ivory body/ivory cap (imprinted with S489 and 20 mg), bottles of 100, NDC 59417102-10
Vyvanse capsules 30 mg: white body/orange cap (imprinted with S489 and 30 mg), bottles of 100, NDC 59417103-10
Vyvanse capsules 40 mg: white body/blue green cap (imprinted with S489 and 40 mg), bottles of 100, NDC 59417-104-10
Vyvanse capsules 50 mg: white body/blue cap (imprinted with S489 and 50 mg), bottles of 100, NDC 59417105-10
Vyvanse capsules 60 mg: aqua blue body/aqua blue cap (imprinted with S489 and 60 mg), bottles of 100, NDC 59417-106-10
Vyvanse capsules 70 mg: blue body/orange cap (imprinted with S489 and 70 mg), bottles of 100, NDC 59417107-10

ANDA: Lisdexamfetamine dimesylate capsules 20 mg: ivory body/ivory cap (imprinted with 54 990) Bottle of 30, NDC 0054-0370-13; Bottle of 100, NDC 0054-0370-25
Lisdexamfetamine dimesylate capsules 30 mg: white body/orange cap (imprinted with 54 682) Bottle of 30, NDC 0054-0371-13; Bottle of 100, NDC 0054-0371-25
Lisdexamfetamine dimesylate capsules 40 mg: white body/light green cap (imprinted with 54 098) Bottle of 30, NDC 0054-0372-13; Bottle of 100, NDC 0054-0372-25
Lisdexamfetamine dimesylate capsules 50 mg: white body/blue cap (imprinted with 54 296) Bottle of 30, NDC 0054-0373-13; Bottle of 100, NDC 0054-0373-25
Lisdexamfetamine dimesylate capsules 60 mg: blue body/blue cap (imprinted with 54 338) Bottle of 30, NDC 0054-0374-13; Bottle of 100, NDC 0054-0374-25
Lisdexamfetamine dimesylate capsules 70 mg: orange body/blue cap (imprinted with 54 818) Bottle of 30, NDC 0054-0375-13; Bottle of 100, NDC 0054-0375-25

From submission:



7. **STORAGE STATEMENT AND DISPENSING RECOMMENDATIONS**

RLD: Dispense in a tight, light-resistant container as defined in the USP.

Store at 25º C (77º F). Excursions permitted to 15-30º C (59-86º F) *[see USP Controlled Room Temperature]*.

Disposal

Comply with local laws and regulations on drug disposal of CNS stimulants. Dispose of remaining, unused, or expired Vyvanse by a medicine take-back program.

ANDA: Dispense in a tight, light-resistant container as defined in the USP.

Store at 25°C (77°F). Excursions permitted to 15° to 30°C (59° to 86°F). *[See USP Controlled Room Temperature.]*

Disposal: Comply with local laws and regulations on drug disposal of CNS stimulants. Dispose of remaining, unused, or expired lisdexamfetamine dimesylate capsules by a medicine take-back program.

Stability (From 10/18/13 Quality review):

(b) (4)

8. **PRODUCT LINE**

RLD: 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg
Bottles of 100.

ANDA: 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg
Bottles of 30 and 100.

9. **CONTAINER/CLOSURE (From 10/18/13 Quality review)**

Bottles of 30 Capsules (20, 30, 40, 50, 60 and 70 mg)
and Bottles of 100 Capsules (20, 30, 40 and 50 mg)

(b) (4)

- Tamper-evident feature: printed induction seal

10. **MEDICATION GUIDES**

- 3 copies of Medication Guide attached to the end of the professional insert/outsert.

11. **RELATED APPLICATIONS:** None

12. **SPL DATA ELEMENTS**

- Data Elements acceptable in February 13, 2014 submission.
- See FTR #14 for capsule size comparison.

13. **CITIZENS PETITION/PROPRIETARY NAME/CONSULTS:** None

14. **CAPSULE SIZE COMPARISON WITH RLD**

From 10/18/13 Quality review:

Parameters*	Reference Product [Vyvanse, 20 mg]	[ANDA product, 20 mg]
Type	Hard gelatin capsules	Hard gelatin capsules
Description	Ivory body/ivory cap, imprinted with NRP104 or S489 and 20mg	(b) (4)
Target Weight/Fill Volume	125 mg	80 mg
Dimensions/Size	Size 3 capsule	Size 4 capsule
Container/Closure Design	HDPE bottles (60 cc) of 100 capsules, CRC.	HDPE containers (90cc) of 30 or 100 capsules, CRC.
Excipients (not in RLD) which require label warning		NA

Parameters*	Reference Product [Vyvanse, 30 mg]	[ANDA product, 30 mg]
Type	Hard gelatin capsules	Hard gelatin capsules
Description	white body/orange cap, imprinted with NRP104 or S489 and 30mg	(b) (4)
Target Weight/Fill Volume	187.5 mg	120 mg
Dimensions/Size	Size 3 capsule	Size 4 capsule
Container/Closure Design	HDPE bottles (60 cc) of 100 capsules, CRC.	HDPE containers (90cc) of 30 or 100 capsules, CRC.
Excipients (not in RLD) which require label warning		NA

Parameters*	Reference Product [Vyvanse, 40 mg]	[ANDA product, 40 mg]
Type	Hard gelatin capsules	Hard gelatin capsules
Description	white body/blue green cap, imprinted with NRP104 or S489 and 40mg	(b) (4)
Target Weight/Fill Volume	160 mg	160 mg
Dimensions/Size	Size 3 capsule	Size 3 capsule
Container/Closure Design	HDPE bottles (60 cc) of 100 capsules, CRC.	HDPE containers (90cc) of 30 or 100 capsules, CRC.
Excipients (not in RLD) which require label warning		NA

Parameters*	Reference Product [Vyvanse, 50 mg]	[ANDA product, 50 mg]
Type	Hard gelatin capsules	Hard gelatin capsules
Description	white body/blue cap, imprinted with NRP104 or S489 and 50mg	(b) (4)
Target Weight/Fill Volume	125 mg	200 mg
Dimensions/Size	Size 3 capsule	Size 3 capsule
Container/Closure Design	HDPE bottles (60 cc) of 100 capsules, CRC.	HDPE containers (90cc) of 30 or 100 capsules, CRC.
Excipients (not in RLD) which require label warning		NA

Parameters*	Reference Product [Vyvanse, 60 mg]	[ANDA product, 60 mg]
Type	Hard gelatin capsules	Hard gelatin capsules
Description	Aqua blue body/aqua blue cap, imprinted with NRP104 or S489 and 60mg	(b) (4)
Target Weight/Fill Volume	150 mg	240 mg
Dimensions/Size	Size 3 capsule	Size 2 capsule
Container/Closure Design	HDPE bottles (60 cc) of 100 capsules, CRC.	90 cc HDPE containers of 30 capsules, or 150cc HDPE containers of 100 capsules. CRC.
Excipients (not in RLD) which require label warning		NA

Parameters*	Reference Product [Vyvanse, 70 mg]	[ANDA product, 70 mg]
Type	Hard gelatin capsules	Hard gelatin capsules
Description	blue body/orange cap, imprinted with NRP104 or S489 and 70mg	(b) (4)
Target Weight/Fill Volume	175 mg	280 mg
Dimensions/Size	Size 3 capsule	Size 2 capsule
Container/Closure Design	HDPE bottles (60 cc) of 100 capsules, CRC.	90 cc HDPE containers of 30 capsules, or 150cc HDPE containers of 100 capsules. CRC.
Excipients (not in RLD) which require label warning		NA

15. **ADDITIONAL INFORMATION**

From 10/18/13 Quality review:

Deficiency:

The RLD labeling indicates that 'the capsule may be opened and the entire contents dissolved in a glass of water'. Please provide data to demonstrate that your proposed generic performs similarly to the RLD when dissolved in a glass of water for alternative administration as discussed in the RLD labeling.

Response: ACCEPTABLE

The firm conducted a study in which capsules of each strength were dissolved in 240mL water and analyzed for Assay value. The data from both generic and brand products were generated and compared. The results demonstrated the generic product performs similarly with the RLD.

Labeling comments from 10/18/13 Quality review:

A. Labeling & Package Insert

The description section, which includes chemical structure, chemical name, empirical formula, name of the inactive ingredients, and physical and chemical properties of drug substance, was reviewed. See the deficiency below for details.

The "how supplied" section is found satisfactory.

The storage statement, "Store at 25°C (77°F). Excursions permitted to 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature.]" is consistent with the long term stability storage condition used in the pre- and post-approval stability protocols.

The name of the manufacturer and address are the same as presented in the submission.

Date of Review: February 19, 2014

Primary Reviewer: Alison Park

Team Leader: Koung Lee

LRev_Orig_4_AP1

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALISON J PARK
02/20/2014

KOUNG U LEE
02/25/2014

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	202827
Date of Submission:	February 6, 2013 (Resubmission)
Applicant's Name:	Roxane Laboratories, Inc.
Established Name and Strength:	Lisdexamfetamine Dimesylate Capsules, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg
Proposed Proprietary Name:	None

Labeling Comments below are considered:

☐ NOT easily correctable (applicant cannot respond within 10 business days)

☒ Easily correctable (respond within 10 business days)

☐ No Comments **(**Labeling Approval Summary or Tentative Approval Summary)

RPM Note - Labeling comments to be sent to the firm start below:

Labeling Deficiencies determined on June 20, 2013 based on your submission dated February 6, 2013:

1. GENERAL COMMENT

   To assist in our review, we request that labeling be submitted in MS Word format. We note that the February 6, 2013 insert labeling submission in MS Word format did not match the February 6, 2013 FPL submission.

2. PRESCRIBING INFORMATION/PHYSICIAN INSERT

   Please revise your labeling in accordance to the most recently approved reference listed drug (RLD) labeling (NDA 021977/S-028, approved June 14, 2013). We refer you to the Drugs@FDA website for the RLD labeling.

3. MEDICATION GUIDE

   We refer you to PRESCRIBING INFORMATION/PHYSICIAN INSERT comment.

4. SPL

   The SPL provided does not contain the most recently approved language as found in the RLD labeling. Please revise.

Submit your revised labeling electronically in final print format.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained.

Prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the Electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

Note RPM - Labeling comments end here

REMS required? ☐ Yes ☒ No

MedGuides and/or PPIs (505-1(e))	☒ Yes	☐ No
Communication plan (505-1(e))	☐ Yes	☒ No
Elements to assure safe use (ETASU) (505-1(f)(3))	☐ Yes	☒ No
Implementation system if certain ETASU (505-1(f)(4))	☐ Yes	☒ No
Timetable for assessment (505-1(d))	☐ Yes	☒ No

ANDA REMS acceptable?
☐ Yes ☐ No ☒ N/A

	Date submitted	Final or Draft	Recommendation
CONTAINER **Bottles of 30 and 100.**	August 14, 2012	Final	Acceptable in November 26, 2012 Labeling Review
INSERT **6 point**	February 6, 2013	Final	Not Acceptable
MEDICATION GUIDE **10 point**	February 6, 2013	Final	Not Acceptable
SPL	February 6, 2013	N/A	Not Acceptable.

NOTES/QUESTIONS TO THE CHEMIST/BIO REVIEWER/MICRO REVIEWER:

None

FOR THE RECORD:

1. **MODEL LABELING** (Checked Drugs@FDA on June 19, 2013)

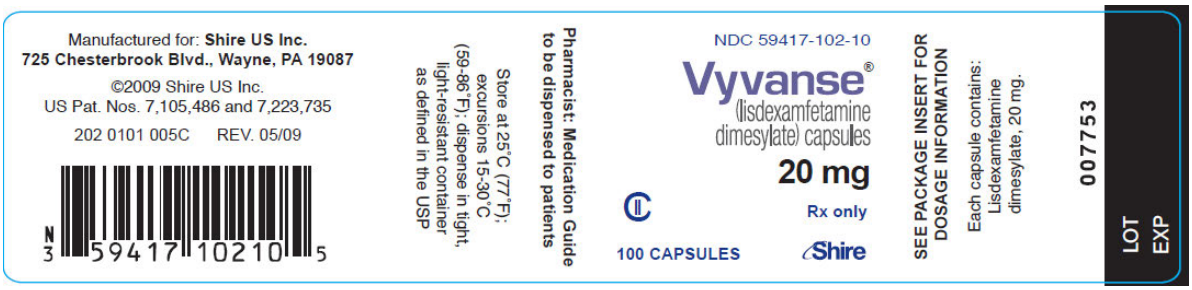
   - RLD is NDA 021977/S-028, approved June 14, 2013, Vyvanse® (owner Shire Development, Inc.).

Additional Information:

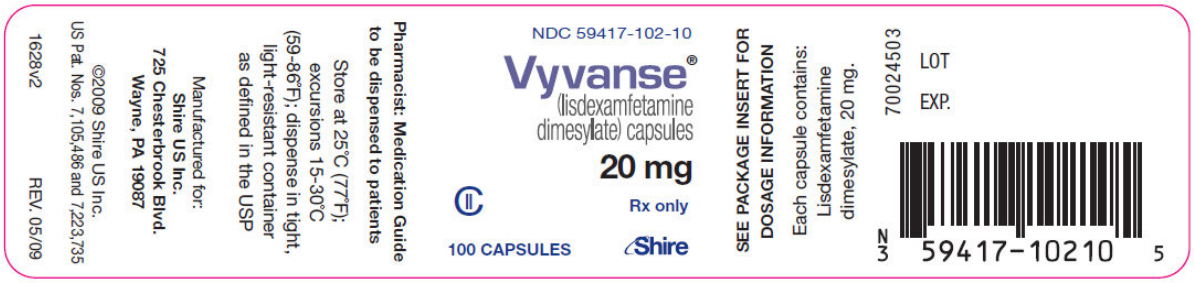
- No pending labeling supplements for NDA 021977.

NDA 021977 Vyvanse 20 mg Container Labels (Annual Report-6, 4/23/13 submission)

DSM Pharmaceuticals



Patheon Pharmaceuticals



2. **USP 36** (Checked June 19, 2013): None

3. **PATENT AND EXCLUSIVITY** (Checked Orange Book on June 19, 2013)
Patent Data – NDA 021977

No	Expiration	Use Code	How filed	Labeling Impact
7105486	Jun 29, 2023	U - 727	IV	None
7223735	Jun 29, 2023		IV	None
7655630	Feb 24, 2023		IV	None
7659253	Feb 24, 2023	U - 727	IV	None
7659254	Feb 24, 2023	U - 1034	IV	None
7662787	Feb 24, 2023		IV	None
7662788	Feb 24, 2023	U - 727	IV	None
7671030	Feb 24, 2023	U - 727	IV	None
7671031	Feb 28, 2023	U - 727	IV	None
7674774	Mar 18, 2023	U - 842	IV	None
7678770	Mar 25, 2023	U - 842	IV	None
7678771	Mar 25, 2023	U - 842	IV	None
7687466	Feb 24, 2023		IV	None
7687467	Apr 8, 2023	U - 842	IV	None
7700561	Jun 29, 2023		IV	None
7713936	Feb 24, 2023	U - 727	IV	None
7718619	Feb 24, 2023	U - 842	IV	None
7723305	Feb 24, 2023	U - 842	IV	None
U - 727	FOR THE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)			
U - 1034	TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN ADULTS			
U - 842	INDICATED FOR THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)			

Exclusivity Data– NDA 021977

Code	Reference	Expiration	Labeling impact
I - 645	MAINTENANCE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN ADULTS	**Jan 31, 2015**	**Carve out**
NPP	NEW PATIENT POPULATION	**Nov 10, 2013**	**Will not market before expiration**

4. **INACTIVE INGREDIENTS** (2.3.P.1 QOS and 3.2.P.1.1 February 6, 2013 amendment)

The listing of inactive ingredients in the DESCRIPTION section of the package insert is consistent with the listing of inactive ingredients found in the statement of components and composition.

Lisdexamfetamine dimesylate capsules contain 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg of lisdexamfetamine dimesylate and the following inactive ingredients: ammonium hydroxide, calcium phosphate, gelatin, iron oxide black, isopropyl alcohol, magnesium stearate, microcrystalline cellulose, n-butyl alcohol, propylene glycol, shellac glaze, sodium starch glycolate, and titanium dioxide.

(b) (4)

5. **MANUFACTURING FACILITY** (3.2.P.3 Quality, February 23, 2011 submission)

Lisdexamfetamine Dimesylate Capsules 20, 30, 40, 50, 60, and 70mg will be manufactured at the (b) (4).

6. **FINISHED PRODUCT DESCRIPTION** (2.3.P.5 QOS)

The product has been accurately described in the HOW SUPPLIED section of the labeling as required by 21 CFR 206, et al.

RLD:

Vyvanse capsules 20 mg	ivory body/ivory cap (imprinted with S489 and 20 mg)
Vyvanse capsules 30 mg	white body/orange cap (imprinted with S489 and 30 mg)
Vyvanse capsules 40 mg	white body/blue green cap (imprinted with S489 and 40 mg)
Vyvanse capsules 50 mg	white body/blue cap (imprinted with S489 and 50 mg)
Vyvanse capsules 60 mg	aqua blue body/aqua blue cap (imprinted with S489 and 60 mg)
Vyvanse capsules 70 mg	blue body/orange cap (imprinted with S489 and 70 mg)

ANDA:

Lisdexamfetamine dimesylate capsules 20 mg	ivory body/ivory cap (imprinted with 54 990)
Lisdexamfetamine dimesylate capsules 30 mg	white body/orange cap (imprinted with 54 682)
Lisdexamfetamine dimesylate capsules 40 mg	white body/light green cap (imprinted with 54 098)
Lisdexamfetamine dimesylate capsules 50 mg	white body/blue cap (imprinted with 54 296)
Lisdexamfetamine dimesylate capsules 60 mg	blue body/blue cap (imprinted with 54 338)
Lisdexamfetamine dimesylate capsules 70 mg	orange body/blue cap (imprinted with 54 818)

(b) (4)

7. **STORAGE STATEMENT AND DISPENSING RECOMMENDATIONS**

RLD: Dispense in a tight, light-resistant container as defined in the USP. Store at 25º C (77º F). Excursions permitted to 15-30º C (59-86º F) *[see USP Controlled Room Temperature]*.

ANDA: Dispense in a tight, light-resistant container as defined in the USP. Store at 25°C (77°F). Excursions permitted to 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature.]

Stability (2.3.P.8 OOS)

(b) (4)

8. **PRODUCT LINE**

RLD: 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg – Bottles of 100.

ANDA: 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg – Bottles of 30 and 100.

9. **CONTAINER/CLOSURE** (3.2.P.1.1, Quality February 6, 2013 submission)

Bottles of 30 Capsules (20, 30, 40, 50, 50, 60 and 70 mg)

(b) (4)

10. **MEDICATION GUIDES**

- 3 copies of Medication Guide attached to the end of the professional insert/outsert.

➢ Will ask firm to update Medication Guide to RLD NDA 021977/S-028, approved June14, 2013.

11. **MEDWATCH** (Checked June 20, 2013): No updates

12. **RELATED APPLICATIONS:** None

13. **SPL DATA ELEMENTS**

- Data Elements are satisfactory in February 6, 2013 submission.

14. **CITIZENS PETITION/PROPRIETARY NAME/CONSULTS:** None

15. **CONTAINER LABELS** (Bottles of 30 and 100)

- Acceptable in August 14, 2012 submission.
- No updates to container labels in this amendment.

Date of Review: June 20, 2013

Primary Reviewer: Alison Park

Team Leader: Koung Lee

Rev #3

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALISON J PARK
06/20/2013

KOUNG U LEE
06/25/2013

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 202827

Date of Submission: August 14, 2012 (amendement)

Applicant's Name: Roxane Laboratories, Inc.

Established Name: Lisdexamfetamine Dimesylate Capsules, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg

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Labeling Comments below are considered:

☐ NOT easily correctable (applicant cannot respond within 10 business days)

☒ Easily correctable (respond within 10 business days)

☐ No Comments **(**Labeling Approval Summary or Tentative Approval Summary)

RPM Note - Labeling comments to be sent to the firm start below:

Labeling Deficiencies determined on November 12, 2012 based on your submission dated August 14, 2012:

1. **GENERAL COMMENT**
   To assist in our review, we request that labeling also be submitted in MS Word format.

2. **PRESCRIBING INFORMATION/PHYSICIAN INSERT:**
   a. FULL PRESCRIBING INFORMATION: CONTENTS: Please ensure that your section titles match the section titles in the approved labeling of the innovator. There are some slight inconsistencies. For example, the title for section 5.1 should read, "Serious Cardiovascular Reactions" not [redacted] (b) (4)
   b. We believe the following information in 14 CLINICAL STUDIES to be protected under the I-645 exclusivity (MAINTENANCE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN ADULTS):

   Maintenance of Efficacy Study (Study 7): A double-blind, placebo-controlled, randomized withdrawal design study was conducted in adults ages 18 to 55 (N=123) who had a documented diagnosis of ADHD or met DSM-IV with adult prompts criteria for ADHD. At study entry, patients must have had documentation of treatment with lisdexamfetamine dimesylate for a

minimum of 6 months and had to demonstrate treatment response as defined by CGI-S ≤3 and Total Score on the ADHD-RS with adult prompts <22. ADHD-RS Total Score is a measure of core symptoms of ADHD. Patients that maintained treatment response at week 3 of open label treatment phase (N=116) were eligible to be randomized to ongoing treatment with the same dose of lisdexamfetamine dimesylate (N=56) or switched to placebo (N=60) during the doubleblind phase. Patients were observed for relapse (treatment failure) during the 6 week double blind phase. Maintenance of efficacy for patients treated with lisdexamfetamine dimesylate was demonstrated by the significantly lower proportion of treatment failure (8.9%) compared to patients receiving placebo (75%) at endpoint during the double-blind randomized withdrawal phase (Figure 3). The endpoint measurement was defined as the last post-randomization treatment week at which a valid ADHD-RS with adult prompts total score and CGI-S were observed. Treatment failure was defined as a ≥50% increase (worsening) in the ADHD-RS with adult prompts Total Score and ≥2-point increase in the CGI-S score compared to scores at entry into the double-blind randomized withdrawal phase (Study 7, Figure 3).

Revise to remove from your prescribing information.

c. Please also remove, (b) (4)

3. SPL

The SPL provided does not contain the most recently approved language as found in the innovators labeling. Please revise

Submit your revised labeling electronically in final print format.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained.

Prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the Electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

Note RPM - Labeling comments end here

REMS required? ☐ Yes ☒ No

MedGuides and/or PPIs (505-1(e)) ☐ Yes ☒ No

Communication plan (505-1(e)) ☐ Yes ☒ No

Elements to assure safe use (ETASU) (505-1(f)(3)) ☐ Yes ☒ No

Implementation system if certain ETASU (505-1(f)(4)) ☐ Yes ☒ No

Timetable for assessment (505-1(d)) ☐ Yes ☒ No

ANDA REMS acceptable?
☐ Yes ☐ No ☒ n/a

	Date submitted	Final or Draft	Recommendation
CONTAINER (Bottles of 30 and 100)	August 14, 2012	Final	Recommended for Approval
PRESCRIBING INFORMATION	August 14, 2012		See above Comments
MEDICATION GUIDE	August 14, 2012		See above Comments
SPL	August 14, 2012		See above Comments

REVISIONS NEEDED POST APPROVAL? N/A

NOTES/QUESTIONS TO THE CHEMIST/BIO REVIEWER/MICRO REVIEWER: None

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FOR THE RECORD:

1. **MODEL LABELING**
   The model labeling used for this review is Vyvanase NDA 21977/S-022 by Shire approved January 31, 2012.
   Additional notes:
   - First Generic
   - Innovator has several pending labeling supplements
     - S-021: Modification of the full prescribing information section 6.2 Postmarketing
     - S-024: The purpose of this submission is to provide a prior approval supplement (PAS) to revise the DOSAGE AND ADMINISTRATION section of the USPI and the corresponding section of the Medication Guide with additional information for patients regarding the opening of Vyvanse capsules for use in water.
     - S-025: The purpose of this submission is to provide a prior approval supplement (PAS) to update the CLINICAL PHARMACOLOGY and USE IN SPECIFIC POPULATIONS sections of the USPI. The Drug Interactions Studies and Special

Populations subsections of Section 12 (Clinical Pharmacology) were updated based on newly available data obtained from the completion of a venlafaxine drug interaction study and geriatric PK study, respectively. In addition, the Geriatric Use subsection of Section 8 was updated to provide for an additional cross-reference to the Pharmacokinetics, Section 12.3 of the USPI.

2. **USP & PF** -None

3. **PATENT AND EXCLUSIVITY**

Patent Data – NDA

Patent No	Patent Expiration	Patent Use Code	Certification	Labeling Impact
7105486	Jun 29, 2023	U - 727	IV	None
7223735	Jun 29, 2023		IV	None
7655630	Feb 24, 2023		IV	None
7659253	Feb 24, 2023	U - 727	IV	None
7659254	Feb 24, 2023	U - 1034	IV	None
7662787	Feb 24, 2023		IV	None
7662788	Feb 24, 2023	U - 727	IV	None
7671030	Feb 24, 2023	U - 727	IV	None
7671031	Feb 28, 2023	U - 727	IV	None
7674774	Mar 18, 2023	U - 842	IV	None
7678770	Mar 25, 2023	U - 842	IV	None
7678771	Mar 25, 2023	U - 842	IV	None
7687466	Feb 24, 2023		IV	None
7687467	Apr 8, 2023	U - 842	IV	None
7700561	Jun 29, 2023		IV	None
7713936	Feb 24, 2023	U - 727	IV	None
7718619	Feb 24, 2023	U - 842	IV	None
7723305	Feb 24, 2023	U - 842	IV	None

U-727	FOR THE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)
U-842	INDICATED FOR THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)
U-1034	TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN ADULTS

Exclusivity Data– NDA

EXCLUSIVITY DATA – NDA 21977			
Code	**Reference**	**Expiration**	**Labeling Impact**
M-82	LABELING REVISIONS RELATED TO CLINICAL STUDIES	**Apr 5, 2013**	Does not intend to market prior to the expiration of exclusivity
I-645	MAINTENANCE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN ADULTS	**Jan 31, 2015**	Carve out
NPP	New Patient Population	**Nov 10, 2013**	Does not intend to market prior to the expiration of exclusivity

4. **INACTIVE INGREDIENTS**

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing in section 2.3.p.1

- Elemental Iron (Acceptable) – Firm correspondence dated February 23, 2011

Lisdexamfetamine dimesylate capsules contain 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg of lisdexamfetamine dimesylate and the following inactive ingredients: ammonium hydroxide, calcium phosphate, gelatin, iron oxide black, isopropyl alcohol, magnesium stearate, microcrystalline cellulose, n-butyl alcohol, propylene glycol, shellac glaze, sodium starch glycolate, and titanium dioxide. In addition, the 20 mg capsule also contains yellow iron oxide. The 30 mg capsule also contains FD&C yellow #6. The 40 mg capsule also contains FD&C blue #1 and FD&C green #3. The 50 mg and 60 mg capsules also contain D&C red #28 and FD&C blue #1. The 70 mg capsule also contains D&C red #28, FD&C blue #1, and FD&C yellow #6.

5. **MANUFACTURING FACILITY**

- Manufacturing Process
  Lisdexamfetamine Dimesylate Capsules 20, 30, 40, 50, 60 and 70 mg (b) (4)
  (b) (4)

6. **FINISHED PRODUCT DESCRIPTION- Satisfactory**

RLD:

Generic:

Lisdexamfetamine dimesylate capsules 20 mg: ivory body/ivory cap (imprinted with 54 990)
Lisdexamfetamine dimesylate capsules 30 mg: white body/orange cap (imprinted with 54 682)
Lisdexamfetamine dimesylate capsules 40 mg: white body/light green cap (imprinted with 54 098)
Lisdexamfetamine dimesylate capsules 50 mg: white body/blue cap (imprinted with 54 296)

Lisdexamfetamine dimesylate capsules 60 mg: blue body/blue cap (imprinted with 54 338)
Lisdexamfetamine dimesylate capsules 70 mg: orange body/blue cap (imprinted with 54 818)

ANDA:

BRAND
Vyvanse capsules 20 mg: ivory body/ivory cap (imprinted with NRP104 or S489 and 20 mg), bottles of 100, NDC 59417-102-10
Vyvanse capsules 30 mg: white body/orange cap (imprinted with NRP104 or S489 and 30 mg), bottles of 100, NDC 59417-103-10
Vyvanse capsules 40 mg: white body/blue green cap (imprinted with NRP104 or S489 and 40 mg), bottles of 100, NDC 59417-
Vyvanse capsules 50 mg: white body/blue cap (imprinted with NRP104 or S489 and 50 mg), bottles of 100, NDC 59417-
Vyvanse capsules 60 mg: aqua blue body/aqua blue cap (imprinted with NRP104 or S489 and 60 mg), bottles of 100,
Vyvanse capsules 70 mg: blue body/orange cap (imprinted with NRP104 or S489 and 70 mg), bottles of 100, NDC 59417-107-10

7. **STORAGE STATEMENT AND DISPENSING RECOMMENDATIONS**
RLD: Dispense in a tight, light-resistant container as defined in the USP. Store at 25º C (77º F). Excursions permitted to 15-30º C (59-86º F) [see USP Controlled Room Temperature]

ANDA: Dispense in a tight, light-resistant container as defined in the USP.
Store at 25°C (77°F). Excursions permitted to 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature.]

8. **PRODUCT LINE**
RLD: Bottles of 100
ANDA: Bottles of 30 and 100

9. **CONTAINER/CLOSURE**
(b) (4)

10. **MEDICATION GUIDES/PATIENT PACKAGE INSERT**

11. **RELATED APPLICATIONS:** None

12. **SPL DATA ELEMENTS:** appears satisfactory in the February 23, 2011 submission

13. **CITIZENS PETITION/PROPRIETARY NAME/CONSULTS**: No

Date of Review: 11/12/2012

Primary Reviewer: Kendra Stewart

Team Leader: Lillie Golson

RV #2

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KENDRA S STEWART
11/24/2012

LILLIE D GOLSON
11/26/2012

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	202827
Date of Submission:	February 23, 2011 (original)
Applicant's Name:	Roxane Laboratories, Inc.
Established Name:	Lisdexamfetamine Dimesylate Capsules, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg

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LABELING DEFICIENCIES:

1. **GENERAL COMMENT:**
   Please ensure you have certified to all patents and exclusivities as listed in the Orange Book.

2. **CONTAINER:** (Bottles of 30 and 100)
   a. Revise to read, "Dispense in a tight, light-resistant…"
   b. Please further revise your pharmacist dispensing statement to one of the following statements; whichever is applicable.
      PHARMACIST: Dispense the enclosed Medication Guide to each patient.
      PHARMACIST: Dispense the accompanying Medication Guide to each patient.
      PHARMACIST: Dispense the Medication Guide provided separately to each patient.
   c. Please add the statement, "Keep out of reach of children" to the container label.

3. **PRESCRIBING INFORMATION:**
   Please revise your insert in accordance with the insert of the innovator, Vyvanase®, NDA 021977 /S-022; approved January 31, 2012.

4. **MEDICATION GUIDE:**
   Please revise your insert in accordance with the insert of the innovator, Vyvanase®, NDA 021977 /S-022; approved January 31, 2012.

Revise your labeling, as instructed above, and submit final printed labeling electronically. In addition, please review the guidance for industry titled "Providing Regulatory Submissions in Electronic Format-Content of Labeling".

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -
http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained.

Labeling Summary:	
CONTAINER: (Bottles of 30 and 1000)	See Comments Above
PRESCRIBING INFORMATION:	See Comment Above
MEDICATION GUIDE:	See Comment Above

BASIS OF APPROVAL:

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Lisdexamfetamine Dimesylate Capsules
NDA Number: 21977
NDA Drug Name: Vyvanase
NDA Firm: Shire
Date of Approval of NDA Insert and supplement #: 21977/S-022 by Shire approved January 31, 2012

Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No

NOTE TO THE CHEMIST: None

FOR THE RECORD:

1. MODEL LABELING:
   The model labeling used for this review is Vyvanase NDA 21977/S-022 by Shire approved January 31, 2012.
   Additional notes:
   - First Generic
   - Innovator has several pending labeling supplements
     - S-021: Modification of the full prescribing information section 6.2 Postmarketing
     - S-024: The purpose of this submission is to provide a prior approval supplement (PAS) to revise the DOSAGE AND ADMINISTRATION section of the USPI and the corresponding section of the Medication Guide with additional information for patients regarding the opening of Vyvanse capsules for use in water.
     - S-025: The purpose of this submission is to provide a prior approval supplement (PAS) to update the CLINICAL PHARMACOLOGY and USE IN SPECIFIC POPULATIONS sections of the USPI. The Drug Interactions Studies and Special Populations subsections of Section 12 (Clinical Pharmacology) were updated based on newly available data obtained from the completion of a venlafaxine drug interaction study and geriatric PK study, respectively. In addition, the Geriatric Use subsection of Section 8 was updated to provide for an additional cross-reference to the Pharmacokinetics, Section 12.3 of the USPI.

2. PATENT AND EXCLUSIVITY:
   - **Please provide an updated list of all patents and exclusivities**

Patent No	Patent Expiration	Patent Use Code	Certification	Labeling Impact
7105486	Jun 29, 2023	U - 727	IV	None
7223735	Jun 29, 2023		IV	None
7655630	Feb 24, 2023		IV	None

7659253	Feb 24, 2023	U - 727	IV	None
7659254	Feb 24, 2023	U - 1034	IV	None
7662787	Feb 24, 2023		IV	None
7662788	Feb 24, 2023	U - 727		
7671030	Feb 24, 2023	U - 727	IV	
7671031	Feb 28, 2023	U - 727	IV	None
7674774	Mar 18, 2023	U - 842	IV	None
7678770	Mar 25, 2023	U - 842	IV	None
7678771	Mar 25, 2023	U - 842	IV	
7687466	Feb 24, 2023		IV	None
7687467	Apr 8, 2023	U - 842	IV	
7700561	Jun 29, 2023		IV	None
7713936	Feb 24, 2023	U - 727		
7718619	Feb 24, 2023	U - 842	IV	
7723305	Feb 24, 2023	U - 842	IV	

U-727	FOR THE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)
U-842	INDICATED FOR THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)
U-1034	TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN ADULTS

EXCLUSIVITY DATA – NDA 21977			
Code	**Reference**	**Expiration**	**Labeling Impact**
M-82	LABELING REVISIONS RELATED TO CLINICAL STUDIES	**Apr 5, 2013**	Does not intend to market prior to the expiration of exclusivity
I-645	MAINTENANCE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN ADULTS	**Jan 31, 2015**	Does not intend to market prior to the expiration of exclusivity
NPP	New Patient Population	**Nov 10, 2013**	Does not intend to market prior to the expiration of exclusivity

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM: 2.3.P.3

   - Manufacturing Process
     Lisdexamfetamine Dimesylate Capsules 20, 30, 40, 50, 60 and 70 mg (b) (4)
     (b) (4)

4. USP: Not USP

5. PF: Not PF

6. INGREDIENTS: 2.3.P.1
   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing in section 2.3.p.1

   - Elemental Iron (Acceptable) – Firm correspondence dated February 23, 2011

Lisdexamfetamine dimesylate capsules contain 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg of lisdexamfetamine dimesylate and the following inactive ingredients: ammonium hydroxide, calcium phosphate, gelatin, iron oxide black, isopropyl alcohol, magnesium

stearate, microcrystalline cellulose, n-butyl alcohol, propylene glycol, shellac glaze, sodium starch glycolate, and titanium dioxide. In addition, the 20 mg capsule also contains yellow iron oxide. The 30 mg capsule also contains FD&C yellow #6. The 40 mg capsule also contains FD&C blue #1 and FD&C green #3. The 50 mg and 60 mg capsules also contain D&C red #28 and FD&C blue #1. The 70 mg capsule also contains D&C red #28, FD&C blue #1, and FD&C yellow #6.

7. PACKAGING CONFIGURATIONS/PRODUCT LINE:
   RLD: Bottles of 100
   ANDA: Bottles of 30 and 100

8. DISPENSING/STORAGE TEMPERATURE STATEMENT COMPARISON – 2.3.P.8
   RLD: Dispense in a tight, light-resistant container as defined in the USP. Store at 25º C (77º F). Excursions permitted to 15-30º C (59-86º F) [see USP Controlled Room Temperature]

   ANDA: Dispense in a tight, light-resistant container as defined in the USP.
   Store at 25°C (77°F). Excursions permitted to 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature.]

9. CONTAINER CLOSURE: 2.3.P.7

(b) (4)

10. FINISHED PRODUCT DESCRIPTION:
The product has been accurately described in the How supplied section of the labeling as required by 21 CFR 206, et. al section 2.3.p.5.

Generic:

Lisdexamfetamine dimesylate capsules 20 mg: ivory body/ivory cap (imprinted with 54 990)

Lisdexamfetamine dimesylate capsules 30 mg: white body/orange cap (imprinted with 54 682)

Lisdexamfetamine dimesylate capsules 40 mg: white body/light green cap (imprinted with 54 098)

Lisdexamfetamine dimesylate capsules 50 mg: white body/blue cap (imprinted with 54 296)

Lisdexamfetamine dimesylate capsules 60 mg: blue body/blue cap (imprinted with 54 338)

Lisdexamfetamine dimesylate capsules 70 mg: orange body/blue cap (imprinted with 54 818)

BRAND
Vyvanse capsules 20 mg: ivory body/ivory cap (imprinted with NRP104 or S489 and 20 mg), bottles of 100, NDC 59417-102-10
Vyvanse capsules 30 mg: white body/orange cap (imprinted with NRP104 or S489 and 30 mg), bottles of 100, NDC 59417-103-10
Vyvanse capsules 40 mg: white body/blue green cap (imprinted with NRP104 or S489 and 40 mg), bottles of 100, NDC 59417-
Vyvanse capsules 50 mg: white body/blue cap (imprinted with NRP104 or S489 and 50 mg), bottles of 100, NDC 59417-
Vyvanse capsules 60 mg: aqua blue body/aqua blue cap (imprinted with NRP104 or S489 and 60 mg), bottles of 100,
Vyvanse capsules 70 mg: blue body/orange cap (imprinted with NRP104 or S489 and 70

mg), bottles of 100, NDC 59417-107-10

14. SPL DATA ELEMENTS: appears satisfactory in the February 23, 2011 submission

15. MEDWATCH: December 12, 2011

    - **No pending labeling supplements pertaining to this alert**

    FDA Drug Safety Communication: Safety Review Update of Medications used to treat Attention-Deficit/Hyperactivity Disorder (ADHD) in adults

16. REMS: No

17. MEDICATION GUIDE:

18. TALL MAN LETTERS: N/A

19. PROPRIETARY NAME: N/A

20. CITIZEN'S PETITION/SUITABILITY PETITION: None

Date of Review: 7/12/2012

Primary Reviewer: Kendra Stewart

Team Leader: Lillie Golson

NA- #1

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KENDRA S STEWART
07/30/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202827Orig1s000

BIOEQUIVALENCE REVIEW(s)

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	202827	
Drug Product Name	Lisdexamfetamine Dimesylate Capsules	
Strength(s)	20, 30, 40, 50, 60, and 70 mg	
Applicant Name	Roxane Laboratories, Inc.	
Address	1809 Wilson Road, Columbus, OH 43228	
Applicant's Point of Contact	Elizabeth Ernst, Director – Drug Regulatory Affairs and Medical Affairs	
Contact's Telephone Number	(614) 272-4785	
Contact's Fax Number	(614) 276-2470	
Original Submission Date(s)	February 23, 2011	
Submission Date(s) of Amendment(s) Under Review	November 8, 2011 December 22, 2011	
Reviewer	Svetlana Cherstniakova, Ph.D.	
Study Number (s)	LISD-C70-PVFS-1	LISD-C70-PVFD-1
Study Type (s)	Fasting	Fed
Strength (s)	70 mg	70 mg
Clinical Site	Novum Pharmaceutical Research Services	
Clinical Site Address	3760 Pecos McLeod, Las Vegas, NV 89121	
Analytical Site	(b) (4)	
Analytical Site Address		

OVERALL REVIEW RESULT	**ADEQUATE**		
OSI REPORT RESULT	**ADEQUATE**		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1	**FASTING STUDY**	**70 MG**	**ADEQUATE**
1	**FED STUDY**	**70 MG**	**ADEQUATE**
1	**DISSOLUTION**	**20 MG**	**ADEQUATE**
1	**DISSOLUTION**	**30 MG**	**ADEQUATE**
1	**DISSOLUTION**	**40 MG**	**ADEQUATE**
1	**DISSOLUTION**	**50 MG**	**ADEQUATE**
1	**DISSOLUTION**	**60 MG**	**ADEQUATE**
1	**DISSOLUTION**	**70 MG**	**ADEQUATE**

Review of a Study Amendment

1 EXECUTIVE SUMMARY

This is a bioequivalence amendment for Lisdexamfetamine Dimesylate Capsules, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg in response to a deficiency letter from the Division of Bioequivalence II, dated December 13, 2011.

The original submission, dated February 23, 2011, contained fasting and fed bioequivalence (BE) studies comparing a test product Lisdexamfetamine Dimesylate Capsules, 70 mg to the corresponding reference product Vyvanse® (lisdexamfetamine dimesylate) Capsules, 70 mg.[1] The application was incomplete due to analytical deficiencies (i.e., the firm was requested to (1) submit original data and chromatograms for all repeated samples and (2) explain the repeat of samples due to unacceptable internal standard response).

In the current amendment the firm submitted original data and chromatograms for all repeated samples. Reanalysis of samples were performed according to the SOP. The firm's response is acceptable.

The DB II grants the waiver requests of in vivo BE study requirements for the 20 mg, 30 mg, 40 mg, 50 mg, and 60 mg strengths based on criteria set forth in 21 CFR § 320.22 (d) (2).

No Office of Scientific Investigations (OSI) inspection is pending or necessary.

The application is acceptable.

[1] DARRTS N 202827 REV-BIOEQ-01(General Review), 11/30/2011

2 TABLE OF CONTENTS

1 Executive Summary 2
2 Table of Contents 3
3 Submission Summary 4
3.1 Review of Submission 4
Deficiency Comment 1: 4
Deficiency Comment 2: 5
3.2 Deficiency Comments 5
3.3 Recommendations 5
3.4 Comments for Other OGD Disciplines 6
3.5 Additional Attachments 7
3.6 Outcome Page 9
4 *Completed Assignment for 202827 ID: 16196* 9

3 SUBMISSION SUMMARY

3.1 Review of Submission

Deficiency Comment 1:

For Lisdexamfetamine, you re-assayed a total of 319 samples due to unacceptable internal standard response (i.e., 134 samples in the fasting BE study No. LISD-C70-PVFS-1 and 185 samples in the fed BE study No. LISD-C70-PVFD-1). Please investigate and justify the high number of samples repeated due to internal standard response.

Firm's Response:

Sample analysis was conducted using an internal standard (IS) acceptance criterion of 30 to 170 % of the average IS response from the run's acceptable calibrators and quality controls. PPD understands this criterion to be within the industry's currently accepted expectation for IS response evaluation. There are several factors inherent to the method of analysis which contribute to increased variability in the response of the lisdexamfetamine IS, lisdexamfetamine-d3, thereby leading to a high number of repeats due to IS responses outside the established study criterion. Analytes and internal standards are isolated from human plasma samples by liquid-liquid extraction with ethyl acetate saturated with water. Following vortexing and centrifugation, the ethyl acetate layer is transferred to a clean tube, dried under vacuum, and reconstituted in mobile phase for analysis by LC/MS/MS. As samples are vortexed in the extraction procedure, emulsions often form and remain between the plasma and ethyl acetate layers, leading to sample-to-sample variation in the amount of ethyl acetate transferred for drying. Use of multiple evaporators for batch processing can also lead to differences between dried extracts. These variations in combination with relatively low general recovery of lisdexamfetamine-d3 lead to more variability of IS response across an analytical batch. However, as the IS is a stable isotope labeled version of the analyte, the extraction recovery variability does not negatively impact the assay's ability to provide accurate incurred sample results. As seen in the accompanying tables for the response to deficiency finding #2, far greater than two-thirds of the re-assayed samples show agreement within 20% relative percent difference between values rejected based on unacceptable IS response and the reported re-assay result. The lisdexamfetamine method proves reproducible; nonetheless, PPD hesitates to broaden the pre-established IS re-assay criteria as a wider criterion may not reflect industry expectation.

Reviewer's Comments:

The original data for majority of the repeated samples show that re-assayed samples are within 20% relative percent difference between values rejected based on unacceptable IS response and the reported re-assay result. The recalculated plasma concentration data will not change study outcome. The firm's response is acceptable.

Deficiency Comment 2:

In the Tables 2A and 2B (Reassayed Samples) of the analytical reports (Project AFUB) for both the fasting and fed BE studies, you did not provide the original values for the reassayed samples, instead citing NRR (No Recorded Result). Please provide original values and chromatograms for all repeated samples.

Firm's Response:

The original data and chromatograms are submitted in Section 5 of the current amendment.

Reviewer's Comments:

Reanalysis of samples were performed according to the SOP. The firm's response is acceptable.

3.2 Deficiency Comments

None

3.3 Recommendations

1. The Division of Bioequivalence accepts the fasting BE study (LISD-C70-PVFS-1) conducted by the Roxane Laboratories, Inc. on its Lisdexamfetamine Dimesylate Capsules, 70 mg, lot # 4000324 comparing it to Shire's Vyvanse® (lisdexamfetamine dimesylate) Capsules, 70 mg, lot #3074098.

2. The Division of Bioequivalence accepts the fed BE study (LISD-C70-PVFD-1) conducted by the Roxane Laboratories, Inc. on its Lisdexamfetamine Dimesylate Capsules, 70 mg, lot # 4000324 comparing it to Shire's Vyvanse® (lisdexamfetamine dimesylate) Capsules, 70 mg, lot #3074098.

3. The firm's in vitro dissolution testing is acceptable. The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37ºC $\pm$ 0.5ºC using USP apparatus 2 (paddle) with sinker at 50 rpm. The test product should meet the following specification:

   NLT (b)(4)% (Q) in 15 minutes

The formulations for the 20 mg, 30 mg, 40 mg, 50 mg, and 60 mg strengths are proportionally similar to the 70 mg strength of the test product which underwent bioequivalence testing. The DB II grants waivers of in vivo bioequivalence study requirements for the 20 mg, 30 mg, 40 mg, 50 mg, and 60 mg strengths of the test product under the Section 21 CFR § 320.22 (d) (2).

The Division of Bioequivalence II deems the test product Lisdexamfetamine Dimesylate Capsules, manufactured by Roxane Laboratories, Inc., to be bioequivalent to the reference product, Vyvanse® (lisdexamfetamine dimesylate) Capsules, manufactured by Shire.

3.4 Comments for Other OGD Disciplines

Discipline	Comment
	None

3.5 Additional Attachments

None

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 202827

APPLICANT: Roxane Laboratories, Inc.

DRUG PRODUCT: Lisdexamfetamine Dimesylate Capsules, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg

The Division of Bioequivalence II (DB II) has completed its review and has no further questions at this time.

We acknowledge that you will conduct dissolution testing using the following dissolution method and specification. The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37°C ± 0.5°C using USP apparatus 2 (paddle) with sinker at 50 rpm. The test product should meet the following specification:

NLT (b)(4)% (Q) in 15 minutes

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

3.6 Outcome Page

ANDA: 202827

4 *COMPLETED ASSIGNMENT FOR 202827 ID: 16196*

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
16196	12/22/2011	Other	Study Amendment	1	1
				Bean Total:	1

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY

Study Amendment	
Study Amendment	1
Total Complexity Points	***1***

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SVETLANA A CHERSTNIAKOVA
02/28/2012

MOHEB H MAKARY
02/28/2012

BARBARA M DAVIT
02/28/2012

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	202827	
Drug Product Name	Lisdexamfetamine Dimesylate Capsules	
Strength(s)	20, 30, 40, 50, 60, and 70 mg	
Applicant Name	Roxane Laboratories, Inc.	
Address	1809 Wilson Road, Columbus, OH 43228	
Applicant's Point of Contact	Elizabeth Ernst, Director – Drug Regulatory Affairs and Medical Affairs	
Contact's Telephone Number	(614) 272-4785	
Contact's Fax Number	(614) 276-2470	
Original Submission Date(s)	February 23, 2011	
Submission Date(s) of Amendment(s) Under Review	November 8, 2011	
Reviewer	Svetlana Cherstniakova, Ph.D.	
Study Number (s)	LISD-C70-PVFS-1	LISD-C70-PVFD-1
Study Type (s)	Fasting	Fed
Strength (s)	70 mg	70 mg
Clinical Site	Novum Pharmaceutical Research Services	
Clinical Site Address	3760 Pecos McLeod, Las Vegas, NV 89121	
Analytical Site	(b) (4)	
Analytical Site Address		
OVERALL REVIEW RESULT	**INADEQUATE**	
OSI REPORT RESULT	**ADEQUATE**	

BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
1	FASTING STUDY	70 MG	INADEQUATE
1	FED STUDY	70 MG	INADEQUATE
1	DISSOLUTION	20 MG	ADEQUATE
1	DISSOLUTION	30 MG	ADEQUATE
1	DISSOLUTION	40 MG	ADEQUATE
1	DISSOLUTION	50 MG	ADEQUATE
1	DISSOLUTION	60 MG	ADEQUATE
1	DISSOLUTION	70 MG	ADEQUATE

1 EXECUTIVE SUMMARY

This application contains the results of fasting and fed bioequivalence (BE) studies comparing a test product Lisdexamfetamine Dimesylate Capsules, 70 mg to the corresponding reference product Vyvanse® (lisdexamfetamine dimesylate) Capsules, 70 mg. Each of the BE studies was designed as a single-dose, two-way crossover study in healthy male and female subjects. The results are summarized in the tables below.

Lisdexamfetamine, 70 mg
Fasting Bioequivalence Study No. LISD-C70-PVFS-1, N=35 (Male=26 and Female=9)
Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals

Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (ng·hr/mL)	52.79	52.24	1.01	93.67	109.02
AUC∞ (ng·hr/mL)	52.71	52.76	1.00	89.09	112.03
Cmax (ng/mL)	42.75	39.65	1.08	97.27	119.51

Lisdexamfetamine, 70 mg
Fed Bioequivalence Study No. LISD-C70-PVFD-1, N=32 (Male=19 and Female=13)
Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals

Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (ng·hr/mL)	47.88	48.18	0.99	93.99	105.09
AUC∞ (ng·hr/mL)	46.98	47.68	0.99	91.40	106.23
Cmax (ng/mL)	19.15	18.39	1.04	92.34	117.47

In the BE studies, the pharmacokinetic (PK) parameters of the test and reference for the active metabolite (dextroamphetamine) were comparable. Therefore the metabolite data are supportive; however, the studies are incomplete due to analytical deficiencies (i.e., the firm is requested to (1) submit original data and chromatograms for all repeated samples and (2) explain the repeat of 319 samples due to unacceptable internal standard response).

The firm has conducted acceptable comparative dissolution testing on all strengths using the FDA-recommended dissolution method, (DARRTS N 202827 REV-BIOEQ-02(Dissolution Review), 09/23/2011). On November 8, 2011, the firm has acknowledged the FDA-recommended dissolution method and specification.

The DB II denies the waiver requests for in vivo BE study requirements for the 20 mg, 30 mg, 40 mg, 50 mg, and 60 mg strengths based on criteria set forth in 21 CFR § 320.22 (d)(2).

No Office of Scientific Investigations (OSI) inspection is pending or necessary.

The application is incomplete.

2 TABLE OF CONTENTS

1 Executive Summary 2
2 Table of Contents 3
3 Submission Summary 4
3.1 Drug Product Information 4
3.2 PK/PD Information 4
3.3 OGD Recommendations for Drug Product 5
3.4 Contents of Submission 6
3.5 Pre-Study Bioanalytical Method Validation 7
3.6 In Vivo Studies 8
3.7 Formulation 14
3.8 In Vitro Dissolution 14
3.9 Waiver Request(s) 14
3.10 Deficiency Comments 15
3.11 Recommendations 16
3.12 Comments for Other OGD Disciplines 16
4 Appendix 17
4.1 Individual Study Reviews 17
4.1.1 Single-dose Fasting Bioequivalence Study 17
4.1.1.1 Study Design 17
4.1.1.2 Clinical Results 19
4.1.1.3 Bioanalytical Results 22
4.1.1.4 Pharmacokinetic Results 24
4.1.2 Single-dose Fed Bioequivalence Study 29
4.1.2.1 Study Design 29
4.1.2.2 Clinical Results 31
4.1.2.3 Bioanalytical Results 35
4.1.2.4 Pharmacokinetic Results 37
4.2 Formulation Data 42
4.3 Dissolution Data 45
4.4 Detailed Regulatory History (If Applicable) 46
4.5 Consult Reviews 46
4.6 SAS Output 47
4.6.1 Fasting Study Data 47
4.6.2 Fasting Study Codes 55
4.6.3 Fasting Study Output 60
4.6.4 Fed Study Data 70
4.6.5 Fed Study Codes 77
4.6.6 Fed Study Output 77
4.7 Additional Attachments 88
4.8 Outcome Page 90

3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Lisdexamfetamine dimesylate Capsules, 20, 30, 40, 50, 60, and 70 mg
Reference Product	Vyvanse® (lisdexamfetamine dimesylate) Capsules, 70 mg (also available in 20, 30, 40, 50, 60 mg capsules)
RLD Manufacturer	Shire LLC
NDA No.	021977
RLD Approval Date	February 23, 2007 (30 mg, 50 mg, 70 mg capsules) December 10, 2007 (20 mg, 40 mg, 60 mg capsules)
Indication	Indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD)

3.2 PK/PD Information[1]

Bioavailability	After oral administration, lisdexamfetamine is rapidly absorbed from the gastrointestinal tract.
Food Effect	Food does not affect the observed AUC and Cmax of dextroamphetamine in healthy adults after single-dose oral administration of 70 mg of Vyvanse capsules but prolongs Tmax by approximately 1 hour (from 3.8 hrs at fasted state to 4.7 hrs after a high fat meal). After an 8-hour fast, the AUCs for dextroamphetamine following oral administration of lisdexamfetamine dimesylate in solution and as intact capsules were equivalent.
Tmax	Lisdexamfetamine: 1 hour Dextroamphetamine: 3.5 hours
Metabolism	After oral administration, lisdexamfetamine is rapidly absorbed from the gastrointestinal tract. Lisdexamfetamine is converted to dextroamphetamine and l-lysine primarily in blood due to the hydrolytic activity of red blood cells. 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 the 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. Plasma concentrations of unconverted lisdexamfetamine are low and transient, generally becoming non-quantifiable by 8 hours after administration.
Half-life	The plasma elimination half-life of lisdexamfetamine typically averaged less than one hour in studies of lisdexamfetamine dimesylate in volunteers.
Drug Specific Issues (if any)	**WARNING: POTENTIAL FOR ABUSE** • Amphetamines have a high potential for abuse; prolonged administration may lead to dependence

[1] Vyvanse®label

	• Misuse of amphetamines may cause sudden death and serious cardiovascular adverse events

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	2, fasting and fed

1.	**Type of study:**	Fasting
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	70 mg
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	

2.	**Type of study:**	Fed
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	70 mg
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	

Analytes to measure (in plasma/serum/blood):	Lisdexamfetamine and its active metabolite, dextroamphetamine in plasma
Bioequivalence based on:	(90% CI) Lisdexamfetamine
Waiver request of in-vivo testing:	20 mg, 30 mg, 40 mg, 50 mg, 60 mg
Source of most recent recommendations:	Draft Guidance on Lisdexamfetamine Dimesylate (dated Sept 2008) at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm086296.pdf

Summary of OGD or DBE History (for details, see Appendix 4.4):	Active ingredient: Lisdexamfetamine Dimesylate Form/Route: Capsules/Oral Recommended studies: 2 studies 1. Type of study: Fasting Design: Single-dose, two-way crossover in vivo Strength: 70 mg Subjects: Normal healthy adult males and females, general population. Additional comments: Females should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study. _____ 1.Type of study: Fed Design: Single-dose, two-way, crossover in-vivo Strength: 70 mg Subjects: Normal healthy males and females, general population Additional comments: Please see comment above. _____ Analytes to measure: Lisdexamfetamine and its active metabolite, dextroamphetamine in plasma Please submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and Cmax. Bioequivalence based on (90% CI): Lisdexamfetamine Waiver request of in-vivo testing: 20 mg, 30 mg, 40 mg, 50 mg, and 60 mg based on (i) acceptable bioequivalence studies on the 70 mg strength, (ii) acceptable dissolution testing across all strengths, and (iii) proportional similarity in the formulations across all strengths. Dissolution test method and sampling times: Please note that a Dissolution Methods Database is available to the public at the OGD website at http://www.fda.gov/cder/ogd/index.htm. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the application.

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	Yes	1
Steady-state		
In vitro dissolution	Yes	6
Waiver requests	Yes	5
BCS Waivers		
Clinical Endpoints		
Failed Studies		
Amendments	Yes	1

3.5 Pre-Study Bioanalytical Method Validation

Information Requested	Data
Bioanalytical method validation report location	PPD validation report AFTJ2
Analyte	Lisdexamfetamine and d-Amphetamine
Internal standard (IS)	Lisdexamfetamine-d_3 and ± Amphetamine-D_{11}
Method description	LC-MS/MS, Liquid-liquid extraction
Limit of quantitation	Lisdexamfetamine = 0.100 ng/mL d-Amphetamine = 0.200 ng/mL
Average recovery of drug (%)	Lisdexamfetamine = 11.3% d-Amphetamine = 66.8%
Average recovery of IS (%)	Lisdexamfetamine IS = 6.03% d-Amphetamine IS = 64.8%
Standard curve concentrations (units/mL)	Lisdexamfetamine = 0.100, 0.200, 0.400, 1.60, 6.00, 24.0, 80.0, and 100 ng/mL d-Amphetamine = 0.200, 0.400, 0.800, 3.20, 12.0, 48.0, 160, and 200 ng/mL
QC concentrations (units/mL)	Lisdexamfetamine = 0.100, 0.300, 0.800, 3.00, 12.0, and 75.0 ng/mL d-Amphetamine = 0.200, 0.600, 1.60, 6.00, 24.0, and 150 ng/mL
QC Intraday precision range (%)	Lisdexamfetamine = 0.569 to 6.89% d-Amphetamine = 0.896 to 2.06%
QC Intraday accuracy range (%)	Lisdexamfetamine = -2.77 to 0.908% d-Amphetamine = -2.67 to 3.61%
QC Interday precision range (%)	Lisdexamfetamine = 1.66 to 9.28% d-Amphetamine = 2.43 to 5.00%
QC Interday accuracy range (%)	Lisdexamfetamine = -3.01 to 1.15% d-Amphetamine = -4.21 to 2.79%
Bench-top stability (hrs)	27.25 hours at room temperature
Stock stability (days)	43 days at -20 ºC
Processed stability (hrs)	158 hours at 4 ºC
Freeze-thaw stability (cycles)	5 cycles at –20 ºC
Long-term storage stability (days)	42 days at -20 ºC
Dilution integrity	Lisdexamfetamine = 3.00 ng/mL diluted 8-fold Lisdexamfetamine = 400 ng/mL diluted 8-fold. d-Amphetamine = 6.00 ng/mL diluted 8-fold d-Amphetamine = 800 ng/mL diluted 8-fold
Selectivity	No interfering peaks noted in blank plasma samples

SOPs submitted	Yes
Bioanalytical method is acceptable	Yes, September 16, 2010

Comments on the Pre-Study Method Validation: Acceptable.

3.6 In Vivo Studies

Table 1. Summary of all in vivo Bioequivalence Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (Total No. (M/F)) Type Age: Mean (Range)	Mean Parameters (+/- SD) for *Lisdexamfetamine*						Study Rpt Loc
					C_{max} (ng/mL) (%CV) (N)	T_{max} (hr) (Median) (N)	$AUC_{(0-t)}$ (h*ng/mL) (%CV) (N)	AUC_{∞} (h*ng/mL) (%CV) (N)	$t_{1/2}$ (hr) (%CV) (N)	Kel* (hr^{-1}) (%CV) (N)	
LISD-C70-PVFS-1	A Single Dose, Two-Period, Two-Treatment, Two-Way Crossover Bioequivalence Study of Lisdexamfetamine Dimesylate 70 mg Capsules Under Fasted Conditions	Single-Dose, Randomized, Two-Treatment, Two-Period, Open-Label, Crossover Design Study (Fasting)	**Test product** Lisdexamfetamine Dimesylate Capsules, 70 mg Oral Lot No.: 4000324B	35 Healthy Subjects (26M, 9F) Mean Age: 27.77 ± 7.13 Range: 18 – 44	47.2 ± 24.4 (51.70%) (35)	1.25 [0.8 – 1.8] (35)	57.3 ± 25.6 (44.60%) (35)	50.7 ± 14.8 (29.24%) (27)	1.45 ± 0.37 (25.78%) (27)	0.5137 ± 0.1553 (30.24%) (27)	Section 5.3
			Ref. product VYVANSE® (lisdexamfetamine dimesylate) Capsules, 70 mg Oral Lot No.: 3074098		43.7 ± 19.7 (45.03%) (35)	1.00 [0.8 – 2.0] (35)	56.7 ± 23.5 (41.33%) (35)	59.0 ± 25.2 (42.61%) (29)	2.20 ± 3.16 (143.71%) (29)	0.4760 ± 0.2121 (44.56%) (29)	
LISD-C70-PVFD-1	A Single Dose, Two-Period, Two-Treatment, Two-Way Crossover Bioequivalence Study of Lisdexamfetamine Dimesylate 70 mg Capsules Under Fed Conditions	Single-Dose, Randomized, Two-Treatment, Two-Period, Open-Label, Crossover Design Study (Fed)	**Test product** Lisdexamfetamine Dimesylate Capsules, 70 mg Oral Lot No.: 4000324B	32 Healthy Subjects (19M, 13F) Mean Age: 31.25 ± 8.70 Range: 19 – 45	20.4 ± 6.97 (34.22%) (32)	3.00 [1.0 – 5.0] (32)	49.4 ± 13.5 (27.39%) (32)	47.0 ± 12.7 (26.97%) (26)	1.38 ± 0.53 (38.23%) (26)	0.5706 ± 0.2086 (36.56%) (26)	Section 5.3
			Ref. product VYVANSE® (lisdexamfetamine dimesylate) Capsules, 70 mg Oral Lot No.: 3074098		19.8 ± 8.22 (41.51%) (32)	2.50 [1.3 – 5.0] (32)	50.0 ± 15.0 (29.93%) (32)	50.6 ± 14.6 (28.96%) (24)	1.65 ± 1.23 (74.30%) (24)	0.5541 ± 0.2438 (43.99%) (24)	

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (Total No. (M/F)) Type Age: Mean (Range)	Mean Parameters (+/- SD) for *d-Amphetamine*						Study Rpt Loc
					C_{max} (ng/mL) (%CV) (N)	T_{max} (hr) (Median) (N)	$AUC_{(0-t)}$ (h*ng/mL) (%CV) (N)	AUC_{∞} (h*ng/mL) (%CV) (N)	$t_{1/2}$ (hr) (%CV) (N)	Kel* (hr^{-1}) (%CV) (N)	
LISD-C70-PVFS-1	A Single Dose, Two-Period, Two-Treatment, Two-Way Crossover Bioequivalence Study of Lisdexamfetamine Dimesylate 70 mg Capsules Under Fasted Conditions	Single-Dose, Randomized, Two-Treatment, Two-Period, Open-Label, Crossover Design Study (Fasting)	**Test product** Lisdexamfetamine Dimesylate Capsules, 70 mg Oral Lot No.: 4000324B	35 Healthy Subjects (26M, 9F) Mean Age: 27.77 ± 7.13 Range: 18 – 44	61.5 ± 12.1 (19.77%) (34)	3.50 [2.5 – 7.0] (34)	1,178 ± 250 (21.21%) (34)	1,201 ± 249 (20.71%) (34)	11.4 ± 2.14 (18.73%) (34)	0.0627 ± 0.0106 (16.93%) (34)	Section 5.3
			Ref. product VYVANSE® (lisdexamfetamine dimesylate) Capsules, 70 mg Oral Lot No.: 3074098		63.1 ± 12.5 (19.83%) (34)	3.50 [2.5 – 8.0] (34)	1,208 ± 241 (19.94%) (34)	1,232 ± 247 (20.04%) (34)	12.0 ± 2.38 (19.75%) (34)	0.0597 ± 0.0110 (18.40%) (34)	
LISD-C70-PVFD-1	A Single Dose, Two-Period, Two-Treatment, Two-Way Crossover Bioequivalence Study of Lisdexamfetamine Dimesylate 70 mg Capsules Under Fed Conditions	Single-Dose, Randomized, Two-Treatment, Two-Period, Open-Label, Crossover Design Study (Fed)	**Test product** Lisdexamfetamine Dimesylate Capsules, 70 mg Oral Lot No.: 4000324B	32 Healthy Subjects (19M, 13F) Mean Age: 31.25 ± 8.70 Range: 19 – 45	58.7 ± 9.28 (15.80%) (32)	5.02 [3.5 – 10.0] (32)	1,098 ± 240 (21.86%) (32)	1,113 ± 248 (22.29%) (32)	11.0 ± 1.34 (12.21%) (32)	0.0638 ± 0.0075 (11.78%) (32)	Section 5.3
			Ref. product VYVANSE® (lisdexamfetamine dimesylate) Capsules, 70 mg Oral Lot No.: 3074098		61.0 ± 10.8 (17.69%) (32)	5.00 [3.5 – 8.0] (32)	1,145 ± 244 (21.34%) (32)	1,173 ± 284 (24.18%) (32)	11.6 ± 2.65 (22.89%) (32)	0.0621 ± 0.0102 (16.38%) (32)	

Table 2. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

Lisdexamfetamine, 70 mg Fasting Bioequivalence Study No. LISD-C70-PVFS-1, N=35 (Male=26 and Female=9) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	52.79	52.24	1.01	93.67	109.02
AUC∞ (ng·hr/mL)	52.71	52.76	1.00	89.09	112.03
Cmax (ng/mL)	42.75	39.65	1.08	97.27	119.51

Lisdexamfetamine, 70 mg Fed Bioequivalence Study No. LISD-C70-PVFD-1, N=32 (Male=19 and Female=13) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	47.88	48.18	0.99	93.99	105.09
AUC∞ (ng·hr/mL)	46.98	47.68	0.99	91.40	106.23
Cmax (ng/mL)	19.15	18.39	1.04	92.34	117.47

Table 3. Reanalysis of Study Samples

Lisdexamfetamine	Study No. LISD-C70-PVFS-1							
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.000	0.000	0	0	0.000	0.000
Result above upper limit of quantitation	3	0	0.195	0	3	0	0.195	0
Sample lost during analysis	27	29	1.76	1.89	27	29	1.76	1.89
Unacceptable internal standard response	58	76	3.78	4.95	58	76	3.78	4.95
Total	88	105	5.74	6.84	88	105	5.74	6.84

d-Amphetamine	Study No. LISD-C70-PVFS-1							
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.000	0.000	0	0	0.000	0.000
Peak of interest with 2 apexes	1	0	0.0651	0	1	0	0.0651	0
Sample lost during analysis	27	29	1.76	1.89	27	29	1.76	1.89
Unacceptable internal standard response	1	0	0.0651	0	1	0	0.0651	0
Total	29	29	1.89	1.89	29	29	1.89	1.89

Lisdexamfetamine	Study No. LISD-C70-PVFD-1							
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.000	0.000	0	0	0.000	0.000
No peaks detected	0	2	0	0.142	0	2	0	0.142
Unacceptable internal standard response	91	94	6.47	6.68	91	94	6.47	6.68
Unacceptable matrix blanks; result possibly affected.	4	2	0.284	0.142	4	2	0.284	0.142
Sample lost during analysis	0	1	0	0.0711	0	1	0	0.0711
Insufficient volume for full volume reassay in original sample tube	0	3	0	0.213	0	3	0	0.213
Total	95	102	6.75	7.25	95	102	6.75	7.25

d-Amphetamine	Study No. LISD-C70-PVFD-1							
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.000	0.000	0	0	0.000	0.000
No peaks detected	0	3	0	0.213	0	3	0	0.213
Insufficient volume for full volume reassay in original sample tube	3	0	0.213	0	3	0	0.213	0
Total	3	3	0.213	0.213	3	3	0.213	0.213

Did use of recalculated plasma concentration data change study outcome? No

Comments from the Reviewer:

For Lisdexamfetamine, 134 samples in the fasting BE study No. LISD-C70-PVFS-1 and 185 samples in the fed BE study No. LISD-C70-PVFD-1 were repeated due to unacceptable internal standard response. The firm should investigate and provide

clarification regarding internal standard response. Also, in the tables 2A and 2B (Reassayed Samples) for both studies, the firm did not provide the original data citing NRR (No Recorded Result) instead of Initial Result Value. The firm should provide original data and chromatograms.

3.7 Formulation

Location in appendix	Section 4.2, Page 42
If a tablet, is the RLD scored?	NA
If a tablet, is the test product biobatch scored	NA
Is the formulation acceptable?	**FORMULATION ACCEPTABLE**
If not acceptable, why?	

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	DARRTS N 202827REV-BIOEQ-02(Dissolution Review), 09/23/2011
Source of Method (USP, FDA or Firm)	FDA
Medium	0.1N HCl
Volume (mL)	900
USP Apparatus type	2
Rotation (rpm)	50
DBE-recommended specifications	NLT (b) (4)% (Q) in 15 min
If a modified-release tablet, was testing done on ½ tablets?	
F2 metric calculated?	No
If no, reason why F2 not calculated	(b) (4)
Is method acceptable?	**METHOD ACCEPTABLE**
If not then why?	

3.9 Waiver Request(s)

Strengths for which waivers are requested	20 mg, 30 mg, 40 mg, 50 mg, 60 mg
Proportional to strength tested in vivo?	Yes
Is dissolution acceptable?	Yes
Waivers granted?	**WAIVERS DENIED**
If not then why?	Pending analytical deficiency

3.10 Deficiency Comments

1. For Lisdexamfetamine, the firm re-assayed total of 319 samples due to unacceptable internal standard response (i.e., 134 samples in the fasting BE study No. LISD-C70-PVFS-1 and 185 samples in the fed BE study No. LISD-C70-PVFD-1). The firm should investigate and justify the high number of samples repeated due to internal standard response.
2. In the tables 2A and 2B (Reassayed Samples) for both fasting and fed BE studies, the firm did not provide the original data citing NRR (No Recorded Result) instead of Initial Result Value. The firm should provide original data and chromatograms for all repeated samples.

3.11 Recommendations

1. The Division of Bioequivalence finds the fasting BE study (LISD-C70-PVFS-1) incomplete due to the deficiencies mentioned above. Roxane Laboratories, Inc. conducted the fasting BE study on its Lisdexamfetamine Dimesylate Capsules, 70 mg, lot # 4000324 comparing it to Shire's Vyvanse® (lisdexamfetamine dimesylate) Capsules, 70 mg, lot #3074098.

2. The Division of Bioequivalence finds the fed BE study (LISD-C70-PVFD-1) incomplete due to the deficiencies mentioned above. Roxane Laboratories, Inc. conducted the fed BE study on its Lisdexamfetamine Dimesylate Capsules, 70 mg, lot # 4000324 comparing it to Shire's Vyvanse® (lisdexamfetamine dimesylate) Capsules, 70 mg, lot #3074098.

3. The firm's in vitro dissolution testing is acceptable. The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37ºC ± 0.5ºC using USP apparatus 2 (paddle) with sinker at 50 rpm. The test product should meet the following specification(s):

   NLT (b)(4)% (Q) in 15 minutes

The dissolution testing conducted by Roxane Laboratories, Inc. on its Lisdexamfetamine Dimesylate Capsules, 20 mg, lot # 4000480, 30 mg, lot # 4000481, 40 mg, lot # 4000482, 50 mg, lot # 4000483, 60 mg, lot # 4000484, and 70 mg, lot # 4000324, is acceptable. The firm has conducted in vivo bioequivalence testing (submission date February 23, 2011) comparing 70 mg capsules of the test product with 70 mg of the reference product Vyvanse® manufactured by Shire. The formulations for the 20 mg, 30 mg, 40 mg, 50 mg, and 60 mg strengths are proportionally similar to the 70 mg strength of the test product which underwent bioequivalence testing. The DB II denies waivers of in vivo bioequivalence study requirements for the 20 mg, 30 mg, 40 mg, 50 mg, and 60 mg strengths of the test product under the Section 21 CFR § 320.22 (d) (2) due to the deficiencies cited above.

3.12 Comments for Other OGD Disciplines

Discipline	Comment
	None

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

Table 4 Study Information

Study Number	LISD-C70-PVFS-1 (Novum Study No. 11014207)	
Study Title	A Single Dose, Two-Period, Two-Treatment, Two-Way Crossover Bioequivalence Study of Lisdexamfetamine Dimesylate 70 mg Capsules Under Fasted Conditions	
Clinical Site (Name, Address, Phone #)	Novum Pharmaceutical Research Services 3760 Pecos McLeod Las Vegas, NV 89121 702-435-3739	
Principal Investigator	Carmelo V. Rillera, M.D.	
Dosing Dates	Period I:	07/20/10
	Period II:	07/27/10
Analytical Site (Name, Address, Phone #)	(b) (4)	
Analysis Dates		
Analysis Director		
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	37 days	

Table 5. Product information

Product	Test	Reference
Treatment ID	A	B
Product Name	Lisdexamfetamine Dimesylate Capsules, 70mg	Vyvanse® (Lisdexamfetamine Dimesylate) Capsules 70 mg
Manufacturer	BIRI	Shire US Inc.
Batch/Lot No.	4000324	3074098
Manufacture Date	6/4/2010	N/A
Expiration Date	N/A	07/2011
Strength	70 mg	70 mg
Dosage Form	Oral Capsule	Oral Capsule
Bio-Batch Size	(b) (4) apsules	N/A
Production Batch Size	capsules	N/A

Potency (Assay)	99.4%	99.5%
Content Uniformity (mean, %CV)	AV = 2.5	N/A
Dose Administered	70 mg	70 mg
Route of Administration	Oral	Oral

Table 6. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	36 enrolled 35 completed
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme	AB: 1,2,3,7,9,10,13,14,17,19,20,22,27,28,29,31,35,36 BA: 4,5,6,8,11,12,15,16,18,21,23,24,25,26,30,32,33,34
Blood Sampling Times	Pre-dose and at 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 16, 24, 48, and 72 hours after dosing
Blood Volume Collected/Sample	6 mL/K_2EDTA
Blood Sample Processing/Storage	-19°C
IRB Approval	Yes, 07/06/10
Informed Consent	Yes
Length of Fasting	10 hours
Length of Confinement	34 hours
Safety Monitoring	Blood pressure, pulse, and temperature (sitting) were measured approximately 1 and 3.5 hours (± 30 minutes) after dosing and prior to release from the clinical facility.

Comments on Study Design:

The study design is acceptable.

4.1.1.2 Clinical Results

Table 7. Demographics Profile of Subjects Completing the Bioequivalence Study

LISD-C70-PVFS-1 (Novum Study No. 11014207)			
		Treatment Groups	
		Test A Roxane Product N = 35	Reference B VYVANSE N = 36
Age (years)	Mean ± SD	27.77 ± 7.13	27.69 ± 7.04
	Range	18 – 44	18 – 44
Age Groups	< 18	0 (0.00%)	0 (0.00%)
	18 – 40	34 (97.14%)	35 (97.22%)
	41 – 64	1 (2.86%)	1 (2.78%)
	65 – 75	0 (0.00%)	0 (0.00%)
	> 75	0 (0.00%)	0 (0.00%)
Sex	Male	26 (74.29%)	27 (75.00%)
	Female	9 (25.71%)	9 (25.00%)
Ethnicity	Hispanic/Latino	4 (11.43%)	4 (11.11%)
	Not Hispanic/Latino	31 (88.57%)	32 (88.88%)
Race	American Indian or Alaskan Native	0 (0.00%)	0 (0.00%)
	Asian	1 (2.86%)	1 (2.78%)
	Black or African American	15 (42.86%)	16 (44.44%)
	Native Hawaiian or Other Pacific Islander	0 (0.00%)	0 (0.00%)
	White	11 (31.43%)	11 (30.56%)
	Other	8 (22.86%)	8 (22.22%)
Height (cm)	Mean ± SD	173.45 ± 8.94	173.50 ± 8.82
	Range	154.94 – 195.58	154.94 – 195.58
Weight (kg)	Mean ± SD	76.71 ± 11.55	76.91 ± 11.45
	Range	53.55 – 94.50	53.55 – 94.50
Other Factors			
BMI (kg/m^2)	Mean ± SD	25.41 ± 2.61	25.46 ± 2.60
	Range	20.3 – 29.9	20.3 – 29.9
Tobacco Users	Yes	0 (0.00%)	0 (0.00%)
	No	35 (100.00%)	36 (100.00%)

Table 8. Dropout Information, Fasting Bioequivalence Study

LISD-C70-PVFS-1 (Novum Study No. 11014207)				
Subject No	Reason for dropout/replacement*	Period	Replaced?	Replaced with
(b) (6)	Voluntary Withdrawal (family emergency) Withdrew consent at Period II check-in Period I: Reference B	I	No	N/A

Table 9. Study Adverse Events, Fasting Bioequivalence Study

Body System/Adverse Event	Bioequivalence Study LISD-C70-PVFS-1 (Novum Study No. 11014207)	
	Test A Roxane Product N (%)	Reference B VYVANSE N (%)
Cardiac Disorders		
Palpitations	1 (2.86%)	1 (2.78%)
Gastrointestinal Disorders		
Abdominal discomfort	1 (2.86%)	1 (2.78%)
Diarrhoea	1 (2.86%)	0 (0.00%)
Dry mouth	0 (0.00%)	2 (5.56%)
Oral herpes	0 (0.00%)	1 (2.78%)
Vomiting	2 (5.71%)	1 (2.78%)
General Disorders and Administration Site Conditions		
Fatigue	1 (2.86%)	0 (0.00%)
Feeling hot	2 (5.71%)	2 (5.56%)
Investigations		
Aspartate aminotransferase increased	0 (0.00%)	1 (2.78%)
Blood pressure increased	6 (17.14%)	5 (13.89%)
Haematology test abnormal	1 (2.86%)	0 (0.00%)
Heart rate increased	1 (2.86%)	2 (5.56%)
Metabolism and Nutrition Disorders		
Decreased appetite	1 (2.86%)	2 (5.56%)
Nervous System Disorders		
Dizziness	4 (11.43%)	3 (8.33%)
Headache	3 (8.57%)	6 (16.67%)
Hypoaesthesia	0 (0.00%)	1 (2.78%)
Paraesthesia	1 (2.86%)	0 (0.00%)
Restlessness	0 (0.00%)	1 (2.78%)
Total N%	**14 (40.00%)**	**17 (47.22%)**

N% = (Number of subjects reporting AE / number of subjects dosed with respective study drug) x 100.
Total N%= (Number of subjects that reported at least one AE / number of subjects dosed with respective study drug) x 100.
Test product A = 35 subjects dosed. Reference product B = 36 subjects dosed.

Table 10. Protocol Deviations, Fasting Bioequivalence Study

Type	Subject #s (Test)	Subject #s (Ref.)
None		

Comments on Dropouts/Adverse Events/Protocol Deviations:

Of the 36 subjects who were dosed, 35 completed both study periods. Subject No. (b) (6) withdrew at Period 2 check-in due to family emergency. The data from this subject was not included in statistical analysis. There were 3 episodes of vomiting (i.e., Subject Nos.

11 (07/27/2010, 21:45) and 15 (07/20/2010, 15:50 and 07/29/2010, 08:30); all of them occurred at above 2 median T_{max}. There was no protocol deviations reported. The reported adverse events were judged to have no significant impact on determination of bioequivalence.

4.1.1.3 Bioanalytical Results

Table 11. Assay Validation – Within the Fasting Bioequivalence Study

Bioequivalence Study No. LISD-C70-PVFS-1 Analyte Name: Lisdexamfetamine								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	0.10	0.200	0.400	1.60	6.00	24.0	80.0	100
Inter day Precision (%CV)	6.02	6.01	3.90	3.83	2.70	3.49	2.80	3.38
Inter day Accuracy (%Actual)	99.5	100	101	101	102	101	98.7	97.7
Linearity	(Range of R^2 values) 0.9970 to 0.9996							
Linearity Range (ng/mL)	0.100 to 100							
Sensitivity/LOQ (ng/mL)	0.100							

Bioequivalence Study No. LISD-C70-PVFS-1 Analyte Name: Lisdexamfetamine					
Parameter	**Quality Control Samples**				
Concentration (ng/mL)	0.300	0.800	3.00	12.0	75.0
Inter day Precision (%CV)	7.85	3.68	3.05	1.87	3.25
Inter day Accuracy (%Actual)	103	102	100	100	97.2

Bioequivalence Study No. LISD-C70-PVFS-1 Analyte Name: d-Amphetamine								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	0.20	0.400	0.800	3.20	12.0	48.0	160	200
Inter day Precision (%CV)	7.57	4.78	4.00	4.50	4.05	3.26	5.19	5.39
Inter day Accuracy (%Actual)	91.1	97.5	103	106	104	99.1	98.6	101
Linearity	(Range of R^2 values) 0.9972 to 0.9999							
Linearity Range (ng/mL)	0.200 to 200							
Sensitivity/LOQ (ng/mL)	0.200							

Bioequivalence Study No. LISD-C70-PVFS-1 Analyte Name: d-Amphetamine					
Parameter	**Quality Control Samples**				
Concentration (ng/mL)	0.600	1.60	6.00	24.0	150
Inter day Precision (%CV)	9.30	4.52	4.64	4.03	5.29
Inter day Accuracy (%Actual)	101	105	104	101	95.8

Comments on Study Assay Validation:

Acceptable.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms:

Acceptable.

Table 12. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
(b) (4)		Defining Assignable Cause for Sample Reanalysis and Excluding Results from Bioanalytical Data Sets
		Conduct of an Analytical Study

Table 13. Additional Comments on Repeat Assays

Were all SOPs followed?	Unable to verify repeat samples
Did recalculation of PK parameters change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	No
If no, reason for disagreement	The firm did not provide original data and chromatograms for the repeated samples.

Summary/Conclusions, Study Assays: Incomplete. The long-term stability data (42 days) cover the entire duration of the study sample storage (37 days). For Lisdexamfetamine, 134 samples in the fasting BE study No. LISD-C70-PVFS-1 were repeated due to unacceptable internal standard response. The firm should investigate and provide clarification regarding internal standard response. Also, in the tables 2A and 2B (Reassayed Samples), the firm did not provide the original data citing NRR (No Recorded Result) instead of Initial Result Value. The firm should provide original data and chromatograms for all repeated samples.

4.1.1.4 Pharmacokinetic Results

Table 14. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 18 and Figure 1

Lisdexamfetamine

Fasting Bioequivalence Study, Study No. LISD-C70-PVFS-1, N=35									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	57.349	44.60	25.10	152.13	56.749	41.33	26.44	109.08	1.01
AUC∞ (hr *ng/ml)	50.659	29.24	25.43	78.27	59.037	42.61	26.73	109.62	0.86
Cmax (ng/ml)	47.194	51.70	21.40	148.00	43.749	45.03	14.20	95.90	1.08
Tmax* (hr)	1.250	.	0.75	1.77	1.000	.	0.75	2.03	1.25
Kel (hr^{-1})	0.514	30.24	0.32	0.90	0.476	44.56	0.04	1.29	1.08
T1/2 (hr)	1.455	25.78	0.77	2.17	2.198	143.71	0.54	18.23	0.66

* Tmax values are presented as median, range

d-Amphetamine

Fasting Bioequivalence Study, Study No. LISD-C70-PVFS-1, N=35									
Parameter (units)	Test				Reference				T/R
	Mean	% CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/ml)	1216.734	22.28	487.13	1990.10	1220.268	18.34	868.36	1706.68	1.00
AUC∞ (hr *ng/ml)	1241.783	22.23	583.65	2085.77	1245.566	18.45	879.92	1731.47	1.00
Cmax (ng/ml)	61.918	19.41	39.90	83.30	63.274	19.56	39.70	82.90	0.98
Tmax* (hr)	3.750	.	2.50	7.00	3.500	.	2.50	8.00	1.07
Kel (hr^{-1})	0.062	17.35	0.04	0.08	0.059	17.83	0.04	0.08	1.05
T1/2 (hr)	11.634	19.31	8.24	18.90	12.177	19.02	8.71	18.30	0.96

* Tmax values are presented as median, range

Table 15. Geometric Means and 90% Confidence Intervals - Firm Calculated

Lisdexamfetamine, 70 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. LISD-C70-PVFS-1, N=35					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (hr *ng/ml)	52.79	52.24	101.05	93.67	109.02
AUC∞ (hr *ng/ml)	52.71	52.76	99.90	89.09	112.03
Cmax (ng/ml)	42.75	39.65	107.82	97.27	119.51

d-Amphetamine, 70 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. LISD-C70-PVFS-1, N=35					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	1,164.11	1,180.06	98.65	93.17	104.45
AUC∞ (hr *ng/ml)	1,190.48	1,204.42	98.84	93.52	104.46
Cmax (ng/ml)	60.26	61.51	97.96	95.13	100.87

Table 16. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Lisdexamfetamine, 70 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. LISD-C70-PVFS-1, N=35					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	52.79	52.24	1.01	93.67	109.02
AUC∞ (hr *ng/ml)	52.71	52.76	1.00	89.09	112.03
Cmax (ng/ml)	42.75	39.65	1.08	97.27	119.51

Table 17. Additional Study Information, Fasting Study No. LISD-C70-PVFS-1

Root mean square error, AUC0-t	0.1874	
Root mean square error, AUC∞	0.2145	
Root mean square error, Cmax	0.2544	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	27	29
Do you agree or disagree with firm's decision?	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	27	0.99	0.98	1.00
Reference	29	0.99	0.96	1.00

Comments on Pharmacokinetic and Statistical Analysis:

1. The pharmacokinetic measures (AUC_t, AUC_i, C_{max}) and confidence intervals of AUC_t, AUC_i and C_{max} for lisdexamfetamine and dextroamphetamine as calculated by the reviewer were in agreement with the values reported by the firm.

2. The 90% confidence intervals for lisdexamfetamine of ln-transformed AUC_t, AUC_i, and C_{max} ratios are within the acceptable limits of 80-125%.

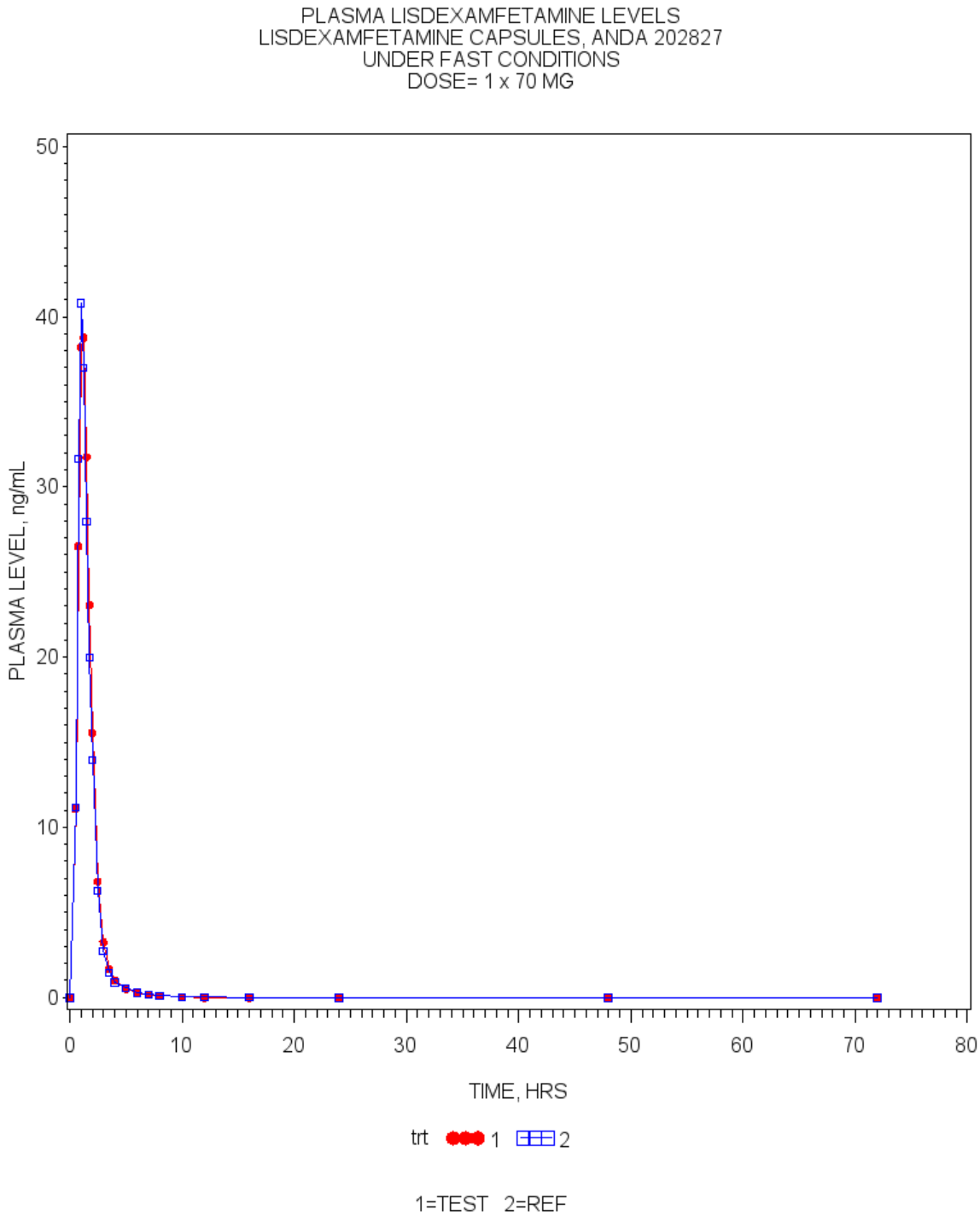
Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

The fasting *in vivo* bioequivalence study is incomplete due to analytical deficiency.

Table 18. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

	Test (n=35)		Reference (n=35)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
0.50	11.10	208.87	11.16	73.46	0.99
0.75	26.51	106.14	31.67	60.58	0.84
1.00	38.19	57.52	40.82	50.24	0.94
1.25	38.78	40.36	37.00	46.02	1.05
1.50	31.76	40.51	27.96	46.43	1.14
1.75	23.07	48.99	20.00	54.40	1.15
2.00	15.57	60.34	13.96	75.06	1.12
2.50	6.84	77.42	6.27	89.08	1.09
3.00	3.26	73.74	2.76	79.76	1.18
3.50	1.70	79.99	1.49	70.94	1.14
4.00	1.01	80.86	0.90	71.18	1.12
5.00	0.52	78.25	0.57	140.74	0.90
6.00	0.28	78.78	0.29	98.40	0.96
7.00	0.16	99.66	0.18	127.10	0.93
8.00	0.10	137.87	0.10	162.78	0.97
10.00	0.02	316.54	0.03	304.03	0.66
12.00	0.00	.	0.03	591.61	0.00
16.00	0.00	.	0.01	591.61	0.00
24.00	0.00	.	0.00	.	.
48.00	0.00	.	0.00	583.10	0.00
72.00	0.00	.	0.00	.	.

Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study



4.1.2 Single-dose Fed Bioequivalence Study

4.1.2.1 Study Design

Table 19. Study Information

Study Number	LISD-C70-PVFD-1 (Novum Study No. 11014208)	
Study Title	A Single Dose, Two-Period, Two-Treatment, Two-Way Crossover Bioequivalence Study of Lisdexamfetamine Dimesylate 70 mg Capsules Under Fed Conditions	
Clinical Site (Name, Address, Phone #)	Novum Pharmaceutical Research Services 3760 Pecos McLeod Las Vegas, NV 89121 702-435-3739	
Principal Investigator	Carmelo V. Rillera, M.D.	
Dosing Dates	Period I:	7/17/10
	Period II:	7/24/10
Analytical Site (Name, Address, Phone #)	(b) (4)	
Analysis Dates		
Analytical Director		
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	40 days	

Table 20. Product Information

Product	**Test**	**Reference**
Treatment ID	A	B
Product Name	Lisdexamfetamine Dimesylate Capsules, 70mg	Vyvanse® (Lisdexamfetamine Dimesylate) Capsules 70 mg
Manufacturer	BIRI	Shire US Inc.
Batch/Lot No.	4000324	3074098
Manufacture Date	6/4/2010	N/A
Expiration Date	N/A	07/2011
Strength	70 mg	70 mg
Dosage Form	Oral Capsule	Oral Capsule
Bio-Batch Size	(b) (4) apsules	N/A
Production Batch Size	capsules	N/A
Potency (Assay)	99.4%	99.5%
Content Uniformity (mean, %CV)	AV = 2.5	N/A
Dose Administered	70 mg	70 mg
Route of Administration	Oral	Oral

Table 21. Study Design, Single-Dose Fed Bioequivalence Study

No. of Subjects	36 enrolled 32 completed
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme	AB: 3,4,6,8,9,11,14,15,18,21,23,24,25,28,29,31,32,33 BA: 1,2,5,7,10,12,13,16,17,19,20,22,26,27,30,34,35,36
Blood Sampling Times	Pre-dose and at 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 16, 24, 48, and 72 hours after dosing
Blood Volume Collected/Sample	6 mL/K_2EDTA
Blood Sample Processing/Storage	-19°C
IRB Approval	Yes, 07/06/10
Informed Consent	Yes
Length of Fasting Before Meal	10 hours
Length of Confinement	34.5 hours
Safety Monitoring	Blood pressure, pulse, and temperature (sitting) were measured approximately 1 and 3.5 hours (± 30 minutes) after dosing and prior to release from the clinical facility.

Standard FDA Meal Used?	Yes

Comments on Study Design:

The study design is acceptable.

4.1.2.2 Clinical Results

Table 22. Demographics Profile of Subjects Completing the Bioequivalence Study

LISD-C70-PVFD-1 (Novum Study No. 11014208)			
		Treatment Groups	
		Test A Roxane Product N = 35	Reference B VYVANSE N = 35
Age (years)	Mean ± SD	31.29 ± 8.59	30.69 ± 8.55
	Range	19 – 45	19 – 45
Age Groups	< 18	0 (0.00%)	0 (0.00%)
	18 – 40	27 (77.14%)	28 (80.00%)
	41 – 64	8 (22.86%)	7 (20.00%)
	65 – 75	0 (0.00%)	0 (0.00%)
	> 75	0 (0.00%)	0 (0.00%)
Sex	Male	21 (60.00%)	21 (60.00%)
	Female	14 (40.00%)	14 (40.00%)
Ethnicity	Hispanic/Latino	6 (17.14%)	5 (14.29%)
	Not Hispanic/Latino	29 (82.86%)	30 (85.71%)
Race	American Indian or Alaskan Native	0 (0.00%)	0 (0.00%)
	Asian	1 (2.86%)	1 (2.86%)
	Black or African American	14 (40.00%)	15 (42.86%)
	Native Hawaiian or Other Pacific Islander	0 (0.00%)	0 (0.00%)
	White	14 (40.00%)	14 (40.00%)
	Other	6 (17.14%)	5 (14.29%)
Height (cm)	Mean ± SD	172.43 ± 8.60	172.65 ± 8.50
	Range	157.48 – 190.50	157.48 – 190.50
Weight (kg)	Mean ± SD	78.16 ± 12.39	77.84 ± 12.61
	Range	46.35 – 103.20	46.35 – 103.20
Other Factors			
BMI (kg/m^2)	Mean ± SD	26.17 ± 3.06	26.00 ± 3.14
	Range	18.1 – 30.0	18.1 – 30.0
Tobacco Users	Yes	0 (0.00%)	0 (0.00%)
	No	35 (100.00%)	35 (100.00%)

Table 23. Dropout Information, Fed Bioequivalence Study

LISD-C70-PVFD-1 (Novum Study No. 11014208)				
Subject No (b) (6)	Reason for dropout/replacement*	Period	Replaced?	Replaced with
	Inability to obtain blood samples Withdrawn by Investigator approx. 7 hours after dosing in Period II Period I: Reference B; Period II: Test A	II	No	N/A

(b) (6)				
	Voluntary Withdrawal Withdrew consent approx. 3 hours after dosing in Period II Period I: Reference B; Period II: Test A	II	No	N/A
	Voluntary Withdrawal Withdrew consent at Period II check-in Period I: Test A	I	No	N/A
	Adverse Event (vomiting) Approx. 3 hours prior to scheduled dosing time in Period II (Did not dose in Period II) Period I: Reference B	I	No	N/A

Table 24. Study Adverse Events, Fed Bioequivalence Study

Body System/Adverse Event	Bioequivalence Study LISD-C70-PVFD-1 (Novum Study No. 11014208)	
	Test A Roxane Product N (%)	Reference B VYVANSE N (%)
Gastrointestinal Disorders		
Abdominal pain upper	2 (5.71%)	0 (0.00%)
Dry mouth	0 (0.00%)	1 (2.86%)
Dyspepsia	1 (2.86%)	1 (2.86%)
Nausea	0 (0.00%)	3 (8.57%)
Vomiting	0 (0.00%)	3 (8.57%)
General Disorders and Administration Site Conditions		
Hyperhidrosis	0 (0.00%)	1 (2.86%)
Injection site haemorrhage	1 (2.86%)	0 (0.00%)
Irritability	1 (2.86%)	1 (2.86%)
Investigations		
Blood pressure increased	14 (40.00%)	12 (34.29%)
Haematology test abnormal	2 (5.71%)	0 (0.00%)
Heart rate increased	6 (17.14%)	6 (17.14%)
Laboratory test abnormal	0 (0.00%)	1 (2.86%)
Urine analysis abnormal	0 (0.00%)	1 (2.86%)
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	1 (2.86%)	0 (0.00%)
Nervous System Disorders		
Dizziness	2 (5.71%)	2 (5.71%)
Headache	2 (5.71%)	1 (2.86%)
Restlessness	1 (2.86%)	2 (5.71%)
Presyncope	1 (2.86%)	0 (0.00%)
Psychiatric Disorders		
Anxiety	1 (2.86%)	0 (0.00%)
Depressed mood	1 (2.86%)	0 (0.00%)
Euphoric mood	0 (0.00%)	1 (2.86%)
Skin and Subcutaneous Tissue Disorders		
Pruritus	1 (2.86%)	0 (0.00%)
Vascular Disorders		
Flushing	1 (2.86%)	0 (0.00%)
Total N%	**26 (74.29%)**	**19 (54.29%)**

N% = (Number of subjects reporting AE / number of subjects dosed with respective study drug) x 100.
Total N%= (Number of subjects that reported at least one AE / number of subjects dosed with respective study drug) x 100.
Test product A = 35 subjects dosed. Reference product B = 35 subjects dosed.

Table 25. Protocol Deviations, Fed Bioequivalence Study

LISD-C70-PVFD-1 (Novum Study No. 11014208)		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
Blood sample could not be obtained at the final study visit for PK or safety analysis.	-	208

Comments on Adverse Events/Protocol Deviations:

Of the 36 subjects who were dosed, 32 completed both study periods. Subject No. 7 withdrew 7 hours post-dose in Period 2 due to the inability to obtain blood samples. Subject Nos (b) (6) withdrew in period 2 for personal reasons. Subject No (b) (6) experienced emesis 3 hours before dosing in Period 2 and was discontinued. The data from these subjects were not included in statistical analysis. The reported adverse events and protocol deviations were judged to have no significant impact on determination of bioequivalence.

4.1.2.3 Bioanalytical Results

Table 26. Assay Validation – Within the Fed Bioequivalence Study

Bioequivalence Study No. LISD-C70-PVFD-1 Analyte Name: Lisdexamfetamine								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	0.10	0.200	0.400	1.60	6.00	24.0	80.0	100
Inter day Precision (%CV)	5.63	5.38	6.15	2.74	2.92	2.98	2.50	2.93
Inter day Accuracy (%Actual)	99.4	99.9	102	101	101	101	98.6	97.4
Linearity	(Range of R^2 values) 0.9967 to 0.9995							
Linearity Range (ng/mL)	0.100 to 100							
Sensitivity/LOQ (ng/mL)	0.100							

Bioequivalence Study No. LISD-C70-PVFD-1 Analyte Name: Lisdexamfetamine					
Parameter	**Quality Control Samples**				
Concentration (ng/mL)	0.300	0.800	3.00	12.0	75.0
Inter day Precision (%CV)	18.0[1]	5.35	5.84	3.55	3.81
Inter day Accuracy (%Actual)	104[2]	101	100	99.3	96.9

1 - Interday precision after exclusion of one statistical outlier = 6.27%
2 - Interday accuracy after exclusion of one statistical outlier = 101%

Bioequivalence Study No. LISD-C70-PVFD-1 Analyte Name: d-Amphetamine								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	0.200	0.400	0.800	3.20	12.0	48.0	160	200
Inter day Precision (%CV)	5.24	2.85	3.30	2.88	2.90	2.44	3.09	4.25
Inter day Accuracy (%Actual)	90.0	98.1	104	106	103	99.1	98.8	101
Linearity	(Range of R^2 values) 0.9978 to 1.000							
Linearity Range (ng/mL)	0.200 to 200							
Sensitivity/LOQ (ng/mL)	0.200							

Bioequivalence Study No. LISD-C70-PVFD-1 Analyte Name: d-Amphetamine					
Parameter	**Quality Control Samples**				
Concentration (ng/mL)	0.600	1.60	6.00	24.0	150
Inter day Precision (%CV)	18.6[1]	4.40	6.97	3.75	3.36

Inter day Accuracy (%Actual)	103[2]	105	105	99.8	95.7

1 - Interday precision after exclusion of one statistical outlier = 4.94%
2 - Interday accuracy after exclusion of one statistical outlier = 99.8%

Note: Based on firm's (b) (4), "quality controls are acceptable if the calculated concentrations are within fifteen percent (15.0%) of the theoretical value. An analytical run is considered acceptable when two-thirds of the quality controls analyzed in the run meet the acceptance criteria. In addition, at least 50% of the quality control results analyzed for each level must be within the acceptance limits for a run to be acceptable."
In the run No. 1AFUA1, one out of two QCs (i.e., QC at the 0.2 ng/mL level for lisdexamfetamine) was above 15% of the theoretical value (i.e., 0.61 ng/mL) and, therefore, was not acceptable. However, the run No. 1AFUA1 was acceptable because the other QC was within 15% of the theoretical value (0.298 ng/mL), and, therefore 50 % of QCs at the 0.2 ng/mL level were acceptable.
In the run No. 1AFUA2, one out of two QCs (i.e., QC at the 0.6 ng/mL level for dextroamphetamine) was above 15% of the theoretical value (i.e., 1.21 ng/mL) and, therefore, was not acceptable. However, the run No. 1AFUA2 was acceptable because the other QC was within 15% of the theoretical value (0.599 ng/mL), and, therefore 50 % of QCs at the 0.6 ng/mL level were acceptable.

Comments on Study Assay Validation:

Acceptable.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms:

Acceptable.

Table 27. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
(b) (4)		Defining Assignable Cause for Sample Reanalysis and Excluding Results from Bioanalytical Data Sets
		Conduct of an Analytical Study

Table 28. Additional Comments on Repeat Assays

Were all SOPs followed?	Unable to verify repeat samples
Did recalculation of PK parameters change the study outcome?	No
Does the reviewer agree with the outcome of	No

the repeat assays?	
If no, reason for disagreement	The firm did not provide original data and chromatograms for the repeated samples.

Summary/Conclusions, Study Assays: Incomplete. The long-term stability data (42 days) cover the entire duration of the study sample storage (40 days). For Lisdexamfetamine, 185 samples in the fed BE study No. LISD-C70-PVFD-1 were repeated due to unacceptable internal standard response. The firm should investigate and provide clarification regarding internal standard response. Also, in the tables 2A and 2B (Reassayed Samples), the firm did not provide the original data citing NRR (No Recorded Result) instead of Initial Result Value. The firm should provide original data and chromatograms for all repeated samples.

4.1.2.4 Pharmacokinetic Results

Table 29. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 33 and Figure 2

Lisdexamfetamine

Fed Bioequivalence Study, Study No. LISD-C70-PVFD-1, N=32									
Parameter (units)	**Test**				**Reference**				**T/R**
	Mean	**%CV**	**Min**	**Max**	**Mean**	**% CV**	**Min**	**Max**	
AUC0-t (hr *ng/ml)	49.401	27.39	28.88	82.21	50.031	29.93	27.80	82.82	0.99
AUC∞ (hr *ng/ml)	47.032	26.97	29.13	82.58	50.572	28.96	30.18	83.14	0.93
Cmax (ng/ml)	20.362	34.22	7.61	34.30	19.798	41.51	9.14	44.10	1.03
Tmax* (hr)	3.000	.	1.00	5.00	2.500	.	1.25	5.00	1.20
Kel (hr^{-1})	0.571	36.56	0.26	1.13	0.554	43.99	0.11	1.01	1.03
T1/2 (hr)	1.381	38.23	0.61	2.71	1.653	74.30	0.68	6.45	0.83

* Tmax values are presented as median, range

d-Amphetamine

Fed Bioequivalence Study, Study No. LISD-C70-PVFD-1, N=32									
Parameter (units)	**Test**				**Reference**				**T/R**
	Mean	**%CV**	**Min**	**Max**	**Mean**	**% CV**	**Min**	**Max**	
AUC0-t (hr *ng/ml)	1097.839	21.86	747.67	1935.83	1144.738	21.34	766.44	1874.09	0.96
AUC∞ (hr *ng/ml)	1112.932	22.29	754.55	1984.37	1173.449	24.18	771.43	2139.19	0.95
Cmax (ng/ml)	58.712	15.80	41.60	78.80	60.988	17.69	44.10	87.10	0.96
Tmax* (hr)	5.017	.	3.50	10.00	5.000	.	3.50	8.00	1.00

Kel (hr^{-1})	0.064	11.78	0.05	0.08	0.062	16.48	0.03	0.08	1.03
T1/2 (hr)	11.012	12.21	9.11	13.90	11.559	22.89	8.83	23.40	0.95

* Tmax values are presented as median, range

Table 30. Geometric Means and 90% Confidence Intervals - Firm Calculated

Lisdexamfetamine, 70 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. LISD-C70-PVFD-1, N=32					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	47.88	48.18	99.39	93.99	105.09
AUC∞ (hr *ng/ml)	46.98	47.68	98.54	91.40	106.23
Cmax (ng/ml)	19.15	18.39	104.15	92.34	117.47

d-Amphetamine, 70 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. LISD-C70-PVFD-1, N=32					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	1,074.91	1,122.39	95.77	93.15	98.47
AUC∞ (hr *ng/ml)	1,088.88	1,145.58	95.05	92.26	97.93
Cmax (ng/ml)	58.08	60.06	96.71	93.91	99.59

Table 31. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Lisdexamfetamine, 70 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. LISD-C70-PVFD-1, N=32					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	47.88	48.18	0.99	93.99	105.09
AUC∞ (hr *ng/ml)	46.98	47.68	0.99	91.40	106.23
Cmax (ng/ml)	19.15	18.39	1.04	92.34	117.47

Table 32. Additional Study Information

Root mean square error, AUC0-t	0.1312	
Root mean square error, AUC∞	0.1407	
Root mean square error, Cmax	0.2831	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	26	24
Do you agree or disagree with firm's decision?	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	26	0.99	0.98	1.00
Reference	24	0.99	0.96	1.00

Comments on Pharmacokinetic and Statistical Analysis:

1. The pharmacokinetic measures (AUC_t, AUC_i, C_{max}) and confidence intervals of AUC_t, AUC_i and C_{max} for lisdexamfetamine and dextroamphetamine as calculated by the reviewer were in agreement with the values reported by the firm.

2. The 90% confidence intervals for lisdexamfetamine of ln-transformed AUC_t, AUC_i, and C_{max} ratios are within the acceptable limits of 80-125%.

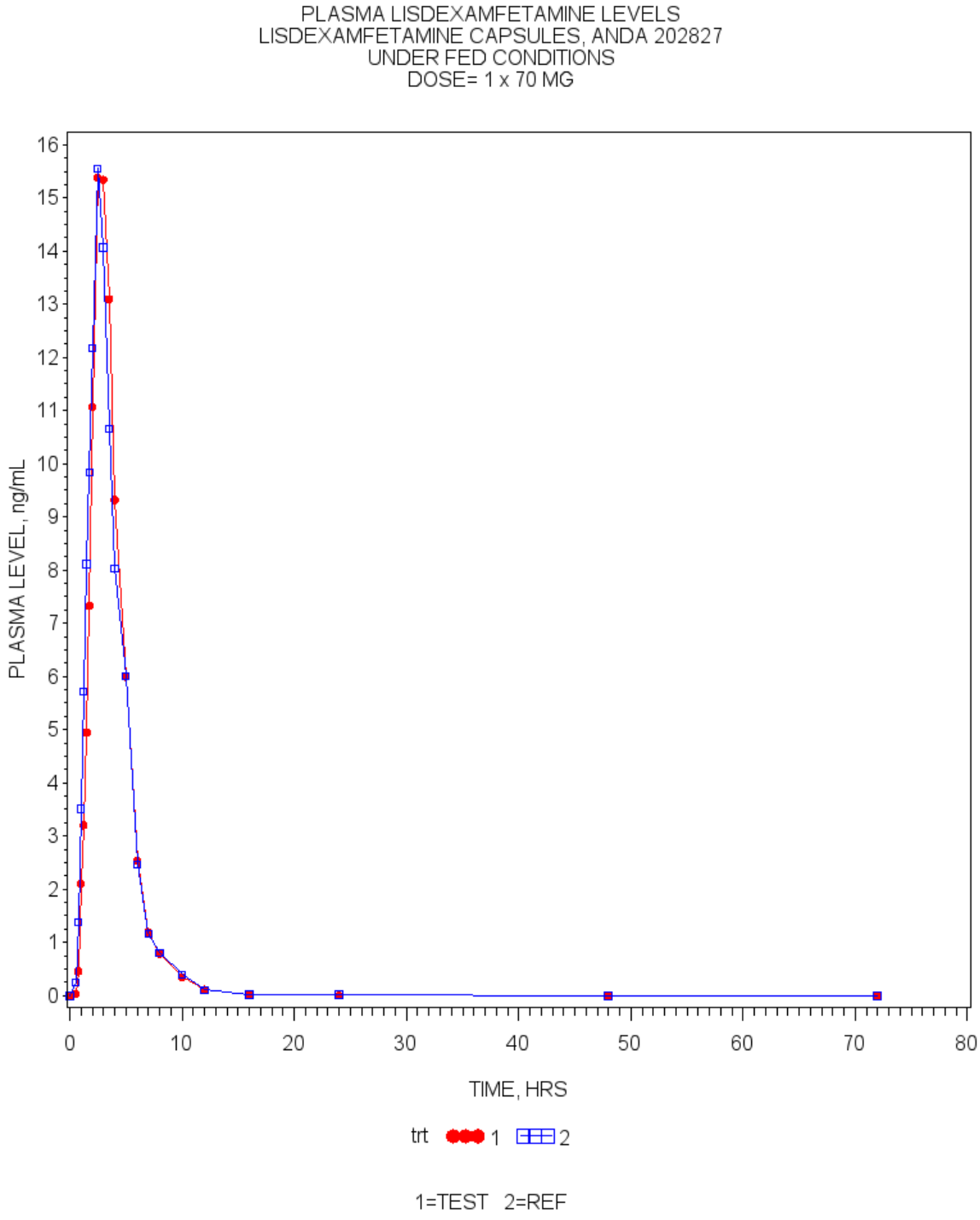
Summary/Conclusions, Single-Dose Fed Bioequivalence Study:

The fed *in vivo* bioequivalence study is incomplete due to analytical deficiency

Table 33. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

	Test (n=32)		Reference (n=32)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
0.50	0.03	297.14	0.26	181.08	0.13
0.75	0.46	207.53	1.39	152.17	0.33
1.00	2.11	247.71	3.52	136.48	0.60
1.25	3.20	172.86	5.72	120.74	0.56
1.50	4.95	133.57	8.12	92.34	0.61
1.75	7.33	90.55	9.84	73.49	0.75
2.00	11.07	74.61	12.18	69.24	0.91
2.50	15.38	55.45	15.56	65.00	0.99
3.00	15.35	42.82	14.08	47.07	1.09
3.50	13.10	49.29	10.66	48.95	1.23
4.00	9.32	44.41	8.04	49.88	1.16
5.00	6.00	70.19	6.01	70.50	1.00
6.00	2.53	79.32	2.47	86.92	1.02
7.00	1.20	80.40	1.16	86.31	1.03
8.00	0.79	123.06	0.80	104.14	0.99
10.00	0.34	128.30	0.39	141.87	0.88
12.00	0.12	197.52	0.11	194.68	1.05
16.00	0.02	397.84	0.02	384.62	0.85
24.00	0.01	565.69	0.02	422.45	0.23
48.00	0.00	.	0.00	.	.
72.00	0.00	.	0.00	.	.

Figure 2. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study



4.2 Formulation Data

		Quality		mg/capsule					
INGREDIENTS – Part A	**Function**	**Standard**	**% w/w**	**20 mg**	**30 mg**	**40 mg**	**50 mg**	**60 mg**	**70 mg**
Lisdexamfetamine Dimesylate	Active		(b) (4)	20.000	30.000	40.000	50.000	60.000	70.000
Microcrystalline Cellulose, NF (b) (4)	(b) (4)								(b) (4)
(b) (4) **Calcium Phosphate** (b) (4) **USP**									
(b) (4)									
Sodium Starch Glycolate, NF									
Magnesium Stearate, NF									
									(b) (4)

(b) (4)

Gelatin	(b) (4)
Titanium Dioxide	
Yellow Iron Oxide *[2]	
FD&C Yellow #6	
FD&C Blue #1	
FD&C Green #3	
D&C Red #28	
Ink – Black (b) (4) *[2]	

*[1] This component is listed in the IIG but no maximum potency is provided.

*[2] Sources of iron in the capsule are Yellow Iron Oxide and the Ink. Total iron content contained in each capsule is below the 5 mg/day limit (per 21 CFR 73.1200).

Is there an overage of the active pharmaceutical ingredient (API)?	NO
If the answer is yes, has the appropriate chemistry division been notified?	N/A

If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Comments on the drug product formulation:	Acceptable. All strengths are dose proportional in composition. All excipients are below IIG levels.

4.3 Dissolution Data

Dissolution Review Path	DARRTS N 202827REV-BIOEQ-02(Dissolution Review), 09/23/2011

The dissolution testing data were reviewed previously. The firm has conducted acceptable comparative dissolution testing on all strengths using the FDA-recommended dissolution method. The firm was requested to acknowledge the following dissolution method and specification. The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37ºC ± 0.5ºC using USP apparatus 2 (paddle) with sinker at 50 rpm. The test product should meet the following specification(s):

NLT (b)(4)% (Q) of the labeled amount of Lisdexamfetamine is dissolved in 15 minutes

On November 8, 2011, the firm has acknowledged the FDA-recommended dissolution method and specification.

Table 34. Dissolution Data

DARRTS N 202827REV-BIOEQ-02(Dissolution Review), 09/23/2011

Figure 3. Dissolution Profiles

None

4.4 Detailed Regulatory History (If Applicable)

None

4.5 Consult Reviews

None

4.6 SAS Output

4.6.1 Fasting Study Data

FAST CONCENTRATION DATASET

Obs	sub	seq	per	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17
1	(b) (6)	1	1	1	0	2.590	13.70	25.80	27.7	32.1	21.20	13.90	5.32	2.350	1.830	1.210	0.574	0.235	0.189	0.109	0.000
2		1	2	1	0	6.750	15.50	17.70	16.8	12.1	11.20	8.01	3.30	1.110	0.600	0.425	0.196	0.148	0.000	0.000	0.000
3		1	1	1	0	2.580	14.50	37.50	40.5	26.9	17.50	9.75	3.99	2.040	0.896	0.534	0.198	0.128	0.000	0.548	0.000
4		1	2	1	0	14.400	40.20	46.10	33.8	25.8	15.60	9.30	3.03	1.170	0.625	0.430	0.256	0.148	0.116	0.000	0.000
5		1	1	1	0	3.250	22.30	44.80	58.9	52.0	32.70	18.00	5.02	2.080	0.723	0.441	0.238	0.150	0.000	0.000	0.000
6		1	2	1	0	23.100	85.70	81.90	57.4	33.9	18.20	9.62	3.05	1.390	0.648	0.406	0.262	0.132	0.110	0.000	0.000
7		2	1	1	0	6.030	23.50	29.80	27.2	28.0	28.10	25.70	11.60	4.360	1.920	1.160	0.532	0.448	0.256	0.290	0.372
8		2	2	1	0	1.850	5.98	14.90	30.1	38.0	39.50	35.70	14.10	5.170	2.030	1.190	0.579	0.452	0.322	0.179	0.000
9		2	1	1	0	24.500	37.50	42.10	27.5	17.0	10.30	6.58	2.48	1.120	0.829	0.493	0.311	0.237	0.144	0.118	0.000
10		2	2	1	0	0.634	5.16	26.10	46.6	45.0	35.30	23.60	8.42	3.090	1.380	0.883	0.475	0.305	0.251	0.129	0.000
11		2	1	1	0	4.140	15.70	20.60	16.9	14.1	8.92	6.15	2.82	1.350	0.759	0.659	0.274	0.218	0.141	0.000	0.000
12		2	2	1	0	3.360	9.86	20.90	31.5	22.1	17.20	11.10	5.00	3.270	1.930	1.200	0.403	0.155	0.109	0.000	0.000
13		1	1	1	0	0.293	5.15	19.20	31.3	37.0	33.10	26.30	12.70	5.010	2.230	1.160	0.443	0.265	0.160	0.140	0.000
14		1	2	1	0	6.750	24.20	33.30	32.5	20.9	12.90	7.86	6.62	3.210	2.400	1.510	0.558	0.256	0.141	0.149	0.000
15		2	1	1	0	12.900	38.00	47.30	43.2	29.2	18.20	11.20	3.93	2.030	1.890	1.150	0.650	0.288	0.149	0.149	0.000
16		2	2	1	0	3.520	25.00	40.70	37.1	28.9	18.40	11.70	6.13	3.450	2.290	1.840	0.981	0.517	0.227	0.205	0.000
17		1	1	1	0	10.300	28.60	44.40	39.3	33.0	20.90	11.90	3.72	1.270	0.759	0.439	0.218	0.180	0.103	0.000	0.000
18		1	2	1	0	11.700	23.20	30.40	62.6	65.6	51.90	29.70	8.11	2.530	1.340	0.720	0.419	0.253	0.120	0.000	0.000
19		1	1	1	0	2.750	32.20	64.70	70.3	52.8	34.20	19.10	6.44	2.770	1.520	0.756	0.276	0.172	0.000	0.000	0.000

Obs	sub	seq	per	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17
20	(b) (6)	1	2	1	0	13.800	47.90	73.50	67.5	47.6	34.60	25.00	11.30	5.390	2.280	1.390	0.481	0.220	0.164	0.134	0.000
21		2	1	1	0	12.100	46.20	49.30	37.0	23.7	15.50	8.43	3.09	1.440	0.458	0.333	0.189	0.000	0.000	0.000	0.000
22		2	2	1	0	15.400	42.70	50.60	36.4	25.7	13.80	7.34	1.98	0.941	0.487	0.365	0.208	0.123	0.000	0.000	0.000
23		1	1	1	0	0.112	4.87	15.80	30.6	31.0	37.50	31.20	20.90	10.500	7.460	4.530	2.240	1.280	0.866	0.556	0.285
24		1	2	1	0	1.660	8.86	14.60	32.1	31.6	31.00	29.80	19.10	9.500	5.560	3.670	2.190	0.965	0.558	0.327	0.134
25		1	1	1	0	30.800	42.40	37.10	28.8	19.7	12.10	7.15	2.55	1.200	0.749	0.433	0.263	0.181	0.106	0.000	0.000
26		1	2	1	0	8.280	27.40	40.80	39.6	34.0	25.50	15.80	5.42	2.020	1.300	0.601	0.304	0.205	0.181	0.103	0.000
27		2	1	1	0	1.860	9.74	16.10	17.5	17.2	13.20	8.19	4.91	3.340	1.740	1.000	0.615	0.393	0.160	0.000	0.000
28		2	2	1	0	1.010	4.57	9.75	16.7	21.6	21.10	13.90	6.27	2.210	0.926	0.624	0.301	0.194	0.142	0.000	0.000
29		2	1	1	0	1.430	8.84	15.80	20.4	24.1	20.90	17.50	9.80	3.270	1.470	0.840	0.340	0.181	0.162	0.204	0.000
30		2	2	1	0	14.400	30.50	30.10	20.6	13.8	8.33	4.97	1.91	0.963	0.574	0.423	0.276	0.144	0.133	0.000	0.000
31		1	1	1	0	0.176	7.67	29.70	28.8	25.3	16.70	9.67	3.53	1.840	0.788	0.475	0.226	0.173	0.000	0.000	0.000
32		1	2	1	0	1.400	17.40	27.10	24.1	17.8	10.10	6.83	3.35	1.660	0.781	0.440	0.222	0.154	0.000	0.000	0.000
33		2	1	1	0	10.900	27.80	47.80	51.5	41.6	45.10	55.80	30.30	10.400	4.000	1.690	0.626	0.277	0.141	0.114	0.000
34		2	2	1	0	128.000	148.00	103.00	56.5	34.9	20.20	10.30	4.96	5.860	1.510	0.992	0.431	0.251	0.183	0.134	0.114
35		1	1	1	0	2.090	11.30	32.20	41.3	35.5	23.40	14.90	6.58	3.050	2.520	1.160	0.389	0.353	0.274	0.108	0.000
36		1	2	1	0	12.400	31.80	33.30	31.1	25.0	18.60	11.90	5.01	3.680	2.050	1.260	0.611	0.421	0.281	0.241	0.190
37		1	1	1	0	58.800	85.10	85.20	62.4	43.1	25.20	14.60	6.54	4.170	2.010	0.581	0.690	0.466	0.128	0.105	0.000
38		1	2	1	0	24.900	47.30	62.80	53.2	43.8	35.40	29.10	12.60	5.090	1.900	0.948	0.331	0.222	0.107	0.000	0.000
39		2	1	1	0	4.570	20.90	39.50	34.3	27.9	18.60	11.90	5.24	2.410	1.550	1.040	0.457	0.306	0.167	0.000	0.000
40		2	2	1	0	0.260	2.61	11.00	23.6	30.1	32.00	29.70	16.80	7.170	3.790	2.570	1.110	0.643	0.325	0.274	0.109
41		1	1	1	0	4.010	13.60	27.10	30.7	24.0	15.10	9.18	2.79	0.933	0.465	0.268	0.131	0.000	0.000	0.000	0.000
42		1	2	1	0	2.400	9.59	21.50	32.6	36.4	25.10	18.90	9.59	5.730	3.120	1.140	0.261	0.141	0.000	0.000	0.000
43		2	1	1	0	9.470	34.90	27.20	22.6	14.2	8.30	5.04	2.35	1.300	0.830	0.586	0.291	0.227	0.123	0.000	0.000
44		2	2	1	0	8.750	27.60	30.70	24.3	16.8	10.20	6.73	3.37	1.590	1.060	0.666	0.321	0.200	0.147	0.000	0.000
45		2	1	1	0	9.650	27.90	28.90	21.3	14.4	9.42	4.59	2.92	1.200	1.020	0.323	0.404	0.235	0.159	0.119	0.000

46	(b) (6)	2	2	1	0	10.400	21.30	21.40	15.7	10.7	5.71	3.33	1.20	0.902	0.438	0.328	0.228	0.000	0.000	0.000	0.000
47		2	1	1	0	12.200	23.10	30.20	19.2	10.2	5.71	2.84	1.25	1.000	0.469	0.360	0.347	0.224	0.161	0.166	0.000
48		2	2	1	0	2.140	7.75	16.60	22.1	18.9	11.80	6.74	1.96	0.934	0.510	0.416	0.222	0.182	0.125	0.000	0.000
49		2	1	1	0	5.320	25.30	39.90	34.2	28.5	19.80	11.40	5.00	2.340	2.110	1.560	1.060	0.512	0.299	0.163	0.000
50		2	2	1	0	13.600	27.60	58.00	41.9	28.1	19.00	13.80	6.26	4.810	2.680	1.500	0.779	0.347	0.250	0.000	0.000
51		1	1	1	0	6.630	34.90	52.70	47.9	29.2	17.80	11.40	3.61	1.810	1.110	0.525	0.354	0.235	0.121	0.000	0.000
52		1	2	1	0	25.600	37.50	37.70	26.7	16.3	9.21	5.56	2.46	0.959	0.531	0.295	0.203	0.106	0.000	0.000	0.000
53		1	1	1	0	20.300	43.20	42.30	32.8	22.3	14.90	10.80	6.31	4.840	2.690	1.460	0.884	0.346	0.171	0.136	0.000
54		1	2	1	0	0.000	1.03	8.84	14.2	13.3	11.40	6.35	3.93	1.800	0.949	1.800	4.710	1.630	1.290	0.899	0.245
55		1	1	1	0	8.350	49.50	63.20	45.3	23.2	13.80	7.61	3.04	1.660	0.658	0.611	0.352	0.216	0.118	0.000	0.000
56		1	2	1	0	11.100	42.80	47.10	35.4	23.3	12.70	8.69	3.23	1.520	0.848	0.507	0.213	0.176	0.000	0.000	0.000
57		2	1	1	0	9.550	29.60	44.30	38.8	26.5	16.10	10.20	4.08	1.760	1.040	0.616	0.305	0.194	0.118	0.000	0.000
58		2	2	1	0	2.390	11.10	24.90	29.3	26.0	18.80	12.10	4.29	1.480	0.929	0.501	0.322	0.159	0.000	0.113	0.000
59		1	1	1	0	1.520	12.50	26.90	46.5	44.2	40.00	28.40	12.10	4.970	2.740	2.080	1.190	0.289	0.371	0.133	0.000
60		1	2	1	0	6.360	17.90	38.70	34.7	22.7	18.10	13.40	3.45	1.660	0.810	0.652	0.304	0.177	0.122	0.000	0.000
61		2	1	1	0	19.100	55.30	74.70	75.2	46.7	28.70	16.60	6.11	2.260	1.110	0.797	0.365	0.342	0.185	0.112	0.000
62		2	2	1	0	0.455	14.40	34.10	54.6	60.5	50.80	38.40	23.10	10.100	3.890	1.400	0.773	0.325	0.266	0.146	0.117
63		2	1	1	0	8.430	37.70	64.80	61.8	40.1	25.60	13.70	5.37	2.170	1.230	0.690	0.408	0.183	0.135	0.118	0.000
64		2	2	1	0	12.600	68.80	74.30	48.3	31.0	17.00	10.60	5.16	2.630	1.390	0.725	0.454	0.275	0.156	0.131	0.000
65		2	1	1	0	28.000	59.60	67.60	55.5	40.7	29.30	16.50	6.24	2.810	1.650	0.685	0.429	0.177	0.142	0.000	0.000
66		2	2	1	0	2.370	10.40	23.20	45.2	43.9	35.80	28.00	11.90	4.520	2.020	1.340	0.521	0.333	0.256	0.165	0.000
67		1	1	1	0	5.290	24.60	72.10	87.8	66.1	44.90	26.90	8.75	3.350	1.780	0.975	0.664	0.332	0.219	0.197	0.000
68		1	2	1	0	30.800	84.50	95.90	73.9	50.5	29.00	16.70	6.53	2.950	1.560	1.120	0.673	0.378	0.301	0.218	0.000
69		1	1	1	0	7.420	18.60	25.80	25.9	18.2	11.40	6.03	2.65	1.110	0.715	0.644	0.322	0.146	0.000	0.000	0.000
70		1	2	1	0	9.080	24.00	31.40	22.6	14.0	7.62	3.70	2.04	0.829	0.725	0.269	0.167	0.000	0.000	0.000	0.000

1	0.00	0.000	0	0.000	0	13	22	1
2	0.00	0.000	0	0.000	0	13	22	2
3	0.00	0.000	0	0.000	0	13	22	1
4	0.00	0.000	0	0.000	0	13	22	2
5	0.00	0.000	0	0.000	0	13	22	1
6	0.00	0.000	0	0.000	0	13	22	2
7	0.00	0.000	0	0.000	0	13	22	2
8	0.00	0.000	0	0.000	0	13	22	1
9	0.00	0.000	0	0.000	0	13	22	2
10	0.00	0.000	0	0.000	0	13	22	1
11	0.00	0.000	0	0.000	0	13	22	2
12	0.00	0.000	0	0.000	0	13	22	1
13	0.00	0.000	0	0.000	0	13	22	1
14	0.00	0.000	0	0.000	0	13	22	2
15	0.00	0.000	0	0.000	0	13	22	2
16	0.00	0.000	0	0.000	0	13	22	1
17	0.00	0.000	0	0.000	0	13	22	1
18	0.00	0.000	0	0.000	0	13	22	2
19	0.00	0.000	0	0.000	0	13	22	1
20	0.00	0.000	0	0.000	0	13	22	2
21	0.00	0.000	0	0.000	0	13	22	2
22	0.00	0.000	0	0.000	0	13	22	1
23	0.00	0.000	0	0.000	0	13	22	1
24	0.00	0.000	0	0.000	0	13	22	2
25	0.00	0.000	0	0.000	0	13	22	1
26	0.00	0.000	0	0.000	0	13	22	2

27	0.00	0.000	0	.	0	13	22	2
28	0.00	0.000	0	.	.	13	22	1
29	0.00	0.000	0	0.000	0	13	22	2
30	0.00	0.000	0	.	0	13	22	1
31	0.00	0.000	0	0.000	0	13	22	1
32	0.00	0.000	0	0.000	0	13	22	2
33	0.00	0.000	0	0.000	0	13	22	2
34	0.00	0.000	0	0.000	0	13	22	1
35	0.00	0.000	0	0.000	0	13	22	1
36	0.00	0.000	0	0.000	0	13	22	2
37	0.00	0.000	0	0.000	0	13	22	1
38	0.00	0.000	0	0.000	0	13	22	2
39	1.21	0.000	0	0.117	0	13	22	2
40	0.00	0.000	0	0.000	0	13	22	1
41	0.00	0.000	0	0.000	0	13	22	1
42	0.00	0.000	0	0.000	0	13	22	2
43	0.00	0.000	0	0.000	0	13	22	2
44	0.00	0.000	0	0.000	0	13	22	1
45	0.00	0.000	0	0.000	0	13	22	2
46	0.00	0.000	0	0.000	0	13	22	1
47	0.00	0.000	0	0.000	0	13	22	2
48	0.00	0.000	0	0.000	0	13	22	1
49	0.00	0.000	0	0.000	0	13	22	2
50	0.00	0.000	0	0.000	0	13	22	1
51	0.00	0.000	0	0.000	0	13	22	1
52	0.00	0.000	0	0.000	0	13	22	2

53	0.00	0.000	0	0.000	0	13	22	1
54	0.00	0.000	0	0.000	0	13	22	2
55	0.00	0.000	0	0.000	0	13	22	1
56	0.00	0.000	0	0.000	0	13	22	2
57	0.00	0.000	0	0.000	0	13	22	2
58	0.00	0.000	0	0.000	0	13	22	1
59	0.00	0.000	0	0.000	0	13	22	1
60	0.00	0.000	0	0.000	0	13	22	2
61	0.00	0.000	0	0.000	0	13	22	2
62	0.00	0.000	0	0.000	0	13	22	1
63	0.00	0.000	0	0.000	0	13	22	2
64	0.00	0.000	0	0.000	0	13	22	1
65	0.00	0.000	0	0.000	0	13	22	2
66	0.00	0.000	0	0.000	0	13	22	1
67	0.00	0.000	0	0.000	0	13	22	1
68	0.00	0.000	0	0.000	0	13	22	2
69	0.00	0.000	0	0.000	0	13	22	1
70	0.00	0.441	0	0.000	0	13	22	2

FAST PHARMACOKINETIC DATASET

Obs	sub	seq	per	GRP	AUCT	AUCI	CMAX	TMAX	KE	THALF	TRT
1	(b) (4)	1	1	1	42.856	43.066	32.1	1.45000	0.52017	1.3325	1
2		1	2	1	26.954	27.234	17.7	1.00000	0.52744	1.3142	2
3		1	1	1	43.529	.	40.5	1.25000	.	.	1
4		1	2	1	52.460	52.719	46.1	1.00000	0.44786	1.5477	2
5		1	1	1	65.199	65.477	58.9	1.25000	0.53920	1.2855	1
6		1	2	1	84.843	85.081	85.7	0.75000	0.46032	1.5058	2
7		2	1	1	57.982	.	29.8	1.00000	.	.	2
8		2	2	1	58.472	58.935	39.5	1.76667	0.38609	1.7953	1
9		2	1	1	48.590	48.937	42.1	1.00000	0.34056	2.0353	2
10		2	2	1	56.831	57.145	46.6	1.25000	0.41054	1.6884	1
11		2	1	1	26.435	26.725	20.6	1.00000	0.48545	1.4278	2
12		2	2	1	37.425	37.546	31.5	1.25000	0.90251	0.7680	1
13		1	1	1	53.220	53.659	37.0	1.50000	0.31904	2.1726	1
14		1	2	1	44.716	.	33.3	1.00000	.	.	2
15		2	1	1	58.979	.	47.3	1.00000	.	.	2
16		2	2	1	52.375	52.726	40.7	1.00000	0.58427	1.1864	1
17		1	1	1	53.105	53.380	44.4	1.00000	0.37488	1.8490	1
18		1	2	1	81.218	81.424	65.6	1.50000	0.58254	1.1899	2
19		1	1	1	78.038	78.270	70.3	1.25000	0.74027	0.9363	1
20		1	2	1	93.785	94.325	73.5	1.00000	0.24789	2.7961	2
21		2	1	1	53.462	53.784	49.3	1.00000	0.58670	1.1814	2
22		2	2	1	53.075	53.298	50.6	1.00000	0.55075	1.2585	1
23		1	1	1	70.017	70.717	37.5	1.75000	0.40716	1.7024	1
24		1	2	1	65.296	65.534	32.1	1.26667	0.56243	1.2324	2
25		1	1	1	52.328	52.558	42.4	0.75000	0.45956	1.5083	1
26		1	2	1	56.417	56.723	40.8	1.00000	0.33714	2.0560	2
27		2	1	1	29.037	29.306	17.5	1.25000	0.59456	1.1658	2
28		2	2	1	29.758	30.136	21.6	1.50000	0.37564	1.8452	1
29		2	1	1	38.479	.	24.1	1.50000	.	.	2
30		2	2	1	36.167	36.469	30.5	0.75000	0.44071	1.5728	1
31		1	1	1	34.483	34.825	29.7	1.00000	0.50501	1.3725	1
32		1	2	1	30.736	31.029	27.1	1.00000	0.52491	1.3205	2
33		2	1	1	103.097	103.353	55.8	2.03333	0.44391	1.5615	2
34		2	2	1	152.128	.	148.0	0.80000	.	.	1
35		1	1	1	50.311	.	41.3	1.25000	.	.	1
36		1	2	1	52.242	53.264	33.3	1.00000	0.18587	3.7292	2

Obs	sub	seq	per	GRP	AUCT	AUCI	CMAX	TMAX	KE	THALF	TRT
37	(b) (4)	1	1	1	112.348	.	85.2	1.00000	.	.	1
38		1	2	1	92.146	92.335	62.8	1.00000	0.56464	1.2276	2
39		2	1	1	75.031	78.109	39.5	1.00000	0.03802	18.2315	2
40		2	2	1	54.468	54.708	32.0	1.75000	0.45382	1.5274	1
41		1	1	1	34.932	35.090	30.7	1.25000	0.82616	0.8390	1
42		1	2	1	49.692	49.800	36.4	1.50000	1.29452	0.5354	2
43		2	1	1	35.500	35.750	34.9	0.75000	0.49318	1.4055	2
44		2	2	1	37.309	37.685	30.7	1.00000	0.39050	1.7750	1
45		2	1	1	34.729	35.022	28.9	1.00000	0.40576	1.7083	2
46		2	2	1	25.485	26.017	21.4	1.00000	0.42812	1.6191	1
47		2	1	1	30.187	30.840	30.2	1.00000	0.25423	2.7265	2
48		2	2	1	25.098	25.426	22.1	1.25000	0.38058	1.8213	1
49		2	1	1	51.043	51.329	39.9	1.00000	0.56987	1.2163	2
50		2	2	1	63.176	63.543	58.0	1.00000	0.68108	1.0177	1
51		1	1	1	56.695	56.946	52.7	1.00000	0.48125	1.4403	1
52		1	2	1	45.990	46.197	37.7	1.00000	0.51177	1.3544	2
53		1	1	1	60.052	60.251	43.2	0.75000	0.68084	1.0181	1
54		1	2	1	28.487	28.918	14.2	1.25000	0.56747	1.2215	2
55		1	1	1	58.499	58.717	63.2	1.00000	0.54216	1.2785	1
56		1	2	1	51.227	.	47.1	1.00000	.	.	2
57		2	1	1	50.691	50.940	44.3	1.00000	0.47481	1.4598	2
58		2	2	1	37.358	.	29.3	1.25000	.	.	1
59		1	1	1	67.405	.	46.5	1.25000	.	.	1
60		1	2	1	44.405	44.625	38.7	1.00000	0.55482	1.2493	2
61		2	1	1	90.245	90.445	75.2	1.26667	0.55816	1.2419	2
62		2	2	1	89.927	.	60.5	1.50000	.	.	1
63		2	1	1	71.490	72.028	64.8	1.00000	0.21940	3.1593	2
64		2	2	1	74.634	74.988	74.3	1.00000	0.37079	1.8694	1
65		2	1	1	86.413	86.665	67.6	1.00000	0.56339	1.2303	2
66		2	2	1	62.431	62.876	45.2	1.25000	0.37124	1.8671	1
67		1	1	1	94.931	.	87.8	1.25000	.	.	1
68		1	2	1	109.084	109.618	95.9	1.00000	0.40778	1.6998	2
69		1	1	1	33.138	33.333	25.9	1.25000	0.74840	0.9262	1
70		1	2	1	35.124	.	31.4	1.00000	.	.	2

4.6.2 Fasting Study Codes

```
**** NODATE OPTION generates error in word document.. with bodytitle ods
****;

**********FOLLOW THE STEPS 1-15 TO RUN THIS PROGRAM**********;

OPTIONS PS=60;

****** STEP 1:  LOCATION OF MACRO FILE (MACROLIB.SAS). CHANGE LOCATION IF
APPLICABLE ********;
%INCLUDE "C:\Documents and Settings\cherstniakov\My
Documents\SAS\MACROLIB.SAS";

/*********************************************************
  ASSIGN WHETHER HAVE GROUP EFFECT:
   TRTGROUP = 1      TRT*GROUP INTERACTION IN GLM MODEL
   TRTGROUP = 2      TRT*GROUP INTERACTION NOT IN GLM MODEL
   TRTGROUP =        NO GROUP EFFECT IN STUDY
 NOTE:  group variable has to be named GRP in the dataset.
*********************************************************/;

*****STEP 2:  ASSIGN FLAG FROM ABOVE FOR TREAT*GROUP INTERACTION*****;
%let trtgroup=;

*****STEP 3: ENTER ANDA INFORMATION *****;
%let level = LISDEXAMFETAMINE;
%let drug=LISDEXAMFETAMINE CAPSULES;
%let dose= 1 x 70 MG;
%let anda=202827;
%let studytype=FAST;

***** STEP 4: ENTER LOCATION OF DATASETS AND LOCATION FOR SAVING OUTPUT
REPORTS *****;
%let studydir=C:\Documents and Settings\cherstniakov\My
Documents\Reviews\Lisdexamfetamine\202827\fastlis;

*****STEP 5: ENTER UNITS FOR PK PARAMETERS *****;
%let aucunit = ng hr/mL;
%let cmaxunit = ng/mL;
%let timeunit = hr;

**** DO NOT CHANGE: NAME OF MS WORD STATISTICAL OUTPUT FILE ****;
%LET ODSFILE=&studydir\&anda._&studytype._stat_&level..doc;

**** DO NOT CHANGE: NAME OF MS WORD REVIEW TABLES OUTPUT FILE ****;
%LET ODSFILE1=&studydir\&anda._&studytype._table_&level..doc;

**** DO NOT CHANGE: NAME OF PLASMA CONCENTRATION PLOT IN CGM GRAPHIC
FILE****;
%LET PLOTFILE=&studydir\&anda._&studytype._plot_&level..png;
```

```
**** DO NOT CHANGE: NAME OF CONC AND PK DATASETS OUTPUT ****;
%LET CONCOUTPUT=&studydir\&anda._&studytype._Datasets_&level..doc;


%LET VARSORT=SUB PER;

%GLOBAL SUB PER SEQ TRT GRP TREAT C T AUCT CMAX TMAX AUCI KE DF NNAME
THALF CLAST KE_FIRST KE_LAST OLDNAME NEWNAME;


*****STEP 6: SELECT TYPE OF ANALYSIS FROM BOTTOM******;

/***SELECT CALCKE.SAS IF YOU WANT TO CALCULATE KE AND OTHER PARAMETERS ***/
/***SELECT CONTINU.SAS IF YOU DO NOT WANT TO RECALCULATE KE.  SPONSOR'S KE
WILL BE
USED FOR CALCULATION OF OTHER PARAMETERS WITH STATISTICS ON SPONSOR SUPPLIED
PARAMETERS.  FOR STATISTICS ON CALCULATED PARAMETERS USE CONTINU2.SAS ***/

%LET FNAME=%QUOTE(C:\Documents and Settings\cherstniakov\My
Documents\SAS\CONTINU.SAS);
*%LET FNAME=%QUOTE(DESKTOP\CONTINU2.SAS);
/*** WRITE DATA FILE NAMES  ***/

*****STEP 7: BLOOD LEVEL DATA: NEED FILE NAME, FIRST OBSERVATION AND VARIABLE
LIST *****;

/*** IF NO BLOOD DATA, BLOCK READDATA AND SORTDS AND GO TO STEP 3 ***/
/*** IF DATA ON EXCEL WORKSHEET ACTIVATE THE LINE WITH DDE AND CLOSE THE NEXT
LINE */
FILENAME ORGPLASM DDE 'EXCEL|Plasma!R2C1:R71C29';
* FILENAME ORGPLASM "&studydir.\&plasmadata";
 *%LET FIRSTOBS=1; /* FIRST OBSERVATION */
 *%LET VARPLASM=SUB SEQ PER TRT c1-c22;  /* VARIABLE LIST FOR THE PLASMA DATA
FILE */
%LET PLASMLS=900;   /* INCREASE LINE SIZE IF NEEDED */
 *%READDATA(ORGPLASM,PLASMA,&FIRSTOBS,&VARPLASM,&PLASMLS)
 *RUN;


*** IF EXCEL FILE, ACTIVATE THESE STATEMENTS ***;
 *FILENAME ORGPLASM DDE 'EXCEL|conc!R2C1:R73C26';
 *%LET FIRSTOBS=1; /* FIRST OBSERVATION */

** IF INPUT FILE IS A SAS DATASET **;
** SPECIFIY LIBNAME WHERE THE SAS DATASET IS SAVED **;
LIBNAME libdata "&studydir";

** STEP 8:  ENSURE TREATMENT AND OTHER VARIABLES ARE PROPERLY FORMATTED..CHAR
OR NUMERIC **;
DATA PLASMA;

*** STANDARD NAMES:  SUB SEQ PER GRP TRT c1-c23  ****;
```

```
** ENSURE THAT THE DATASET HAS TWO COLUMNS: KE_FIRST AND KE_LAST SPECIFYING
DATA POINTS TO BE USED FOR CALCULATION OF KE **;
  infile ORGPLASM ls=&plasmls;
  input sub seq per GRP treat $ c1-c22 KE_FIRST KE_LAST;

  if treat = "A" then trt=1;
  else trt=2;
  DROP TREAT;
RUN;

proc print data=plasma;
run;


%SORTDS(PLASMA, &VARSORT)
RUN;



*****STEP 9:PK PARAMETER DATA: NEED FILE NAME, FIRST OBSERVATION AND VARIABLE
LIST *****;

/***IF NO PK PARAMETER DATA, BLOCK READDATA AND SORTDS AND GO TO STEP 4 ***/
/*** IF DATA ON EXCEL WORKSHEET ACTIVATE THE LINE WITH DDE AND CLOSE THE NEXT
LINE */
FILENAME ORGPARAM DDE 'EXCEL|pk!R2C1:R71C11';
* FILENAME ORGPARAM "&studydir.\&pkdata";
*%LET FIRSTOBS=1; /* FIST OBSERVATION */
*%LET VARPARAM=SUB SEQ PER TRT AUCT AUCI CMAX TMAX KE THALF; /* VARIABLE LIST
*/
%LET PARAMLS=500;  /* INCREASE LINE SIZE IF NEEDED */
*%READDATA(ORGPARAM,PARAME,&FIRSTOBS,&VARPARAM,&PARAMLS)
*RUN;


*** IF EXCEL FILE, ACTIVATE THESE STATEMENTS ***;
 *FILENAME ORGPARAM DDE 'EXCEL|PK!R2C1:R73C26';
 *%LET FIRSTOBS=1; /* FIRST OBSERVATION */

DATA PARAME;

** IF USING EXCEL FILE ACTIVATE THESE STATEMENTS **;
infile ORGPARAM ls=&paramls;
input sub seq per GRP TREAT $   AUCT AUCI CMAX TMAX KE THALF;

  IF TREAT = "A" THEN TRT=1;
  ELSE TRT=2;

  DROP TREAT;

 RUN;
```

```
%SORTDS(PARAME, &VARSORT)
RUN;



*****STEP 10: ADD OR REDUCE THE BLOOD SAMPLE NUMBER TO FIT THE STUDY *****;
%LET CONCENT=%STR(C1, C2, C3, C4, C5, C6, C7, C8, C9, C10,
             C11, C12, C13, C14, C15, C16, C17, C18, C19, C20, C21, C22);


/***STEP : USE THIS STEP IF COMMON SAMPLING TIMES ARE USED,
                   ADD OR REDUCE THE SAMPLING TIME POINTS AND CHANGE THE
TIME,
                   OR ADD FEW DEVIATED SAMPLING TIME POINTS,
                   ALSO MAKE SURE TO DEACTIVATE "SET TIME" AND ACTIVATE
"&TIME" UNDER STEP 15***/

%LET TIME=%STR(T1=0; T2=0.5; T3=0.75; T4=1; T5=1.25;
T6=1.5; T7=1.75; T8=2; T9=2.5; T10=3; T11=3.5; T12=4;
T13=5; T14=6; T15=7; T16=8; T17=10; T18=12; T19=16; T20=24; T21=48; T22=72);

*IF SUB=1 AND PER=2 THEN T12=5;
*IF SUB=12 AND PER=2 THEN T7=1.8);*/

/***STEP 11A:  USE THIS STEP INSTEAD OF STEP 11 IF ACTUAL SAMPLING TIME
DATASET INCLUDED
                   IN THE CONCENTRATION DATASET,
                  ALSO, MAKE SURE TO ACTIVATE "SET TIME" AND DEACTIVATE
"&TIME" UNDER STEP 15***/;
/*
DATA TIME;
SET PLASMA;
*FILE'DESKTOP\TIME';
PUT SUB TRT SEQ PER GRP;
KEEP SUB TRT SEQ PER GRP;

PROC PRINT DATA=TIME;RUN;
*/
*****STEP 12: WRITE THE TOTAL NUMBER OF SAMPLING TIME POINTS *****;
%LET NO_ASSAY=22;


*****STEP 13 : INITIALIZE KE_FIRST AND KE_LAST FOR KE CALCULATION IF THESE
ARE NOT
IN THE DATA SUBMITTED. *****;
*%LET KE_FIRST=&NO_ASSAY-2;
*%LET KE_LAST=&NO_ASSAY;


*****STEP 14: SUBJECTS/RECORDS TO BE REMOVED FROM CALCULATION *****;
/***VARIOUS SCREENING CONDITIONS CAN BE APPLIED FOR SUBJECT REMOVAL***/
/***LEAVE AS IT IS IF NO CHANGE IS DESIRED***/
```

```
/* %LET REMOVSUB=%STR(IF SUB^=10;IF SUB^=15;IF SUB^=34;IF SUB^=37;IF
SUB^=49); */
*%LET REMOVSUB=%STR(IF SUB^=205);


*****STEP 15: IF SEQ, PER, TRT OR OTHER VARIABLES TO BE ADDED OR MODIFIED
*****;
/***CREATING NUMERIC VARIABLES FROM CHARACTER VARIABLES, ETC  ***/
/***  IF KE_FIRST AND KE_LAST ARE SUBMITTED IN THE DATA SET , KEEP THEM
CLOSED ***/
/* %LET ADD_VAR=%STR(KE_FIRST=&KE_FIRST; KE_LAST=&KE_LAST
IF TREAT='A' THEN TRT=1; ELSE TRT=2 );  */



DATA ORIGIN;
       ARRAY C(&NO_ASSAY) C1-C&NO_ASSAY;
       ARRAY T(&NO_ASSAY) T1-T&NO_ASSAY;
SET PLASMA;
SET PARAME;
* SET TIME;
*SET MERGED;
&TIME;
*KE_FIRST=0;
*KE_LAST=0;
CLAST=C&NO_ASSAY;
NEWCMAX=MAX(&CONCENT);


/***DO NOT CHANGE: TITLES FOR TABLES***/
%LET TITLE1=MEAN PLASMA &level LEVELS;
%LET TITLE2=MEAN PLASMA &level LEVELS FOR TEST AND REFERENCE PRODUCTS;

/*** DESCRIBE TITLES, FOOTNOTES AND LABELS FOR GRAPH ***/
%LET TITLE3=PLASMA &level LEVELS;
%LET TITLE4= &drug, ANDA &anda;
%LET TITLE5=UNDER &STUDYTYPE CONDITIONS;
%LET TITLE6=DOSE= &dose;
%LET FOOTNOT1=1=TEST   2=REF;
%LET FOOTNOT2=Tmax values are presented as median, range.;
%LET FOOTNOT3=;
%LET FOOTNOT4=;
%LET FOOTNOT5=;
%LET LABEL1=PLASMA LEVEL, &cmaxunit;
%LET LABEL2=TIME, HRS;
%LET LABEL3=TEST;
%LET LABEL4=REFERENCE;


%COPYDS(ORIGIN, NEW)
RUN;
```

```
*****STEP 14: OPEN IF YOU WANT TO REMOVE, ADD OR EDIT*****;
*%REMUVSUB(NEW, NEW)
RUN;
```

4.6.3 Fasting Study Output

FAST STATISTICAL OUTPUT

The GLM Procedure

Class Level Information		
Class	**Levels**	**Values**
sub	35	101 102 103 104 105 106 107 108 109 110 111 113 114 115 116 117 118 119 120 121 122 123 124 125 126 127 128 129 130 131 132 133 134 135 136
trt	2	1 2
per	2	1 2
seq	2	1 2

Data for Analysis of AUCT CMAX LAUCT LCMAX	
Number of Observations Read	70
Number of Observations Used	70

Data for Analysis of AUCI LAUCI	
Number of Observations Read	70
Number of Observations Used	56

Note: Variables in each group are consistent with respect to the presence or absence of missing values.

FAST STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	36	10.09549037	0.28043029	7.98	<.0001
Error	33	1.15896916	0.03512028		
Corrected Total	69	11.25445953			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.897021	4.729852	0.187404	3.962155

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.11138138	0.11138138	3.17	0.0841
sub(seq)	33	9.96131472	0.30185802	8.59	<.0001
per	1	0.02087450	0.02087450	0.59	0.4462
trt	1	0.00191977	0.00191977	0.05	0.8166

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.11138138	0.11138138	3.17	0.0841
sub(seq)	33	9.96131472	0.30185802	8.59	<.0001
per	1	0.02049743	0.02049743	0.58	0.4503
trt	1	0.00191977	0.00191977	0.05	0.8166

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	**DF**	**Type III SS**	**Mean Square**	**F Value**	**Pr > F**
seq	1	0.11138138	0.11138138	0.37	0.5477

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	0.01047810	0.04481643	0.23	0.8166

FAST STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	36	11.22309095	0.31175253	4.82	<.0001
Error	33	2.13594662	0.06472566		
Corrected Total	69	13.35903757			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.840112	6.841169	0.254412	3.718844

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.12573705	0.12573705	1.94	0.1727
sub(seq)	33	10.96989158	0.33242096	5.14	<.0001
per	1	0.02840518	0.02840518	0.44	0.5123
trt	1	0.09905715	0.09905715	1.53	0.2248

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.12573705	0.12573705	1.94	0.1727
sub(seq)	33	10.96989158	0.33242096	5.14	<.0001
per	1	0.02543296	0.02543296	0.39	0.5351
trt	1	0.09905715	0.09905715	1.53	0.2248

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	**DF**	**Type III SS**	**Mean Square**	**F Value**	**Pr > F**
seq	1	0.12573705	0.12573705	0.38	0.5428

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	0.07526641	0.06084103	1.24	0.2248

FAST STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	36	7.35635197	0.20434311	4.44	0.0005
Error	19	0.87393897	0.04599679		
Corrected Total	55	8.23029094			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.893814	5.450132	0.214469	3.935108

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.17093414	0.17093414	3.72	0.0690
sub(seq)	33	7.17556887	0.21744148	4.73	0.0004
per	1	0.00983908	0.00983908	0.21	0.6490
trt	1	0.00000988	0.00000988	0.00	0.9885

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.09329405	0.09329405	2.03	0.1706
sub(seq)	33	7.02672701	0.21293112	4.63	0.0004
per	1	0.00978713	0.00978713	0.21	0.6498
trt	1	0.00000988	0.00000988	0.00	0.9885

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	**DF**	**Type III SS**	**Mean Square**	**F Value**	**Pr > F**
seq	1	0.09329405	0.09329405	0.44	0.5126

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.00097107	0.06626162	-0.01	0.9885

AUCT/AUCI RATIO FOR INDIVIDUAL SUBJECTS

Obs	sub	trt	AUCRATIO
1	(b) (4)	1	1.00
2		1	.
3		1	1.00
4		1	0.99
5		1	0.99
6		1	1.00
7		1	0.99
8		1	0.99
9		1	0.99
10		1	1.00
11		1	1.00
12		1	0.99
13		1	1.00
14		1	0.99
15		1	0.99
16		1	0.99
17		1	.
18		1	.
19		1	.
20		1	1.00
21		1	1.00
22		1	0.99
23		1	0.98
24		1	0.99
25		1	0.99
26		1	1.00
27		1	1.00
28		1	1.00
29		1	.
30		1	.
31		1	.
32		1	1.00
33		1	0.99
34		1	.
35		1	0.99
36		2	0.99

Obs	sub	trt	AUCRATIO
37	(b) (4)	2	1.00
38		2	1.00
39		2	.
40		2	0.99
41		2	0.99
42		2	.
43		2	.
44		2	1.00
45		2	0.99
46		2	0.99
47		2	1.00
48		2	0.99
49		2	0.99
50		2	.
51		2	0.99
52		2	1.00
53		2	0.98
54		2	1.00
55		2	0.96
56		2	1.00
57		2	0.99
58		2	0.99
59		2	0.98
60		2	0.99
61		2	1.00
62		2	0.99
63		2	.
64		2	1.00
65		2	1.00
66		2	1.00
67		2	0.99
68		2	1.00
69		2	1.00
70		2	.

TEST PRODUCT/REFERENCE PRODUCT RATIOS FOR INDIVIDUAL SUBJECTS

sub	seq	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
(b) (6)	1	1.59	1.58	1.81	1.45	0.99	1.01
	1	0.83	.	0.88	1.25	.	.
	1	0.77	0.77	0.69	1.67	1.17	0.85
	2	1.01	.	1.33	1.77	.	.
	2	1.17	1.17	1.11	1.25	1.21	0.83
	2	1.42	1.40	1.53	1.25	1.86	0.54
	1	1.19	.	1.11	1.50	.	.
	2	0.89	.	0.86	1.00	.	.
	1	0.65	0.66	0.68	0.67	0.64	1.55
	1	0.83	0.83	0.96	1.25	2.99	0.33
	2	0.99	0.99	1.03	1.00	0.94	1.07
	1	1.07	1.08	1.17	1.38	0.72	1.38
	1	0.93	0.93	1.04	0.75	1.36	0.73
	2	1.02	1.03	1.23	1.20	0.63	1.58
	2	0.94	.	1.27	0.50	.	.
	1	1.12	1.12	1.10	1.00	0.96	1.04
	2	1.48	.	2.65	0.39	.	.
	1	0.96	.	1.24	1.25	.	.
	1	1.22	.	1.36	1.00	.	.
	2	0.73	0.70	0.81	1.75	11.9	0.08
	1	0.70	0.70	0.84	0.83	0.64	1.57
	2	1.05	1.05	0.88	1.33	0.79	1.26
	2	0.73	0.74	0.74	1.00	1.06	0.95
	2	0.83	0.82	0.73	1.25	1.50	0.67
	2	1.24	1.24	1.45	1.00	1.20	0.84
	1	1.23	1.23	1.40	1.00	0.94	1.06
	1	2.11	2.08	3.04	0.60	1.20	0.83
	1	1.14	.	1.34	1.00	.	.
	2	0.74	.	0.66	1.25	.	.
	1	1.52	.	1.20	1.25	.	.
	2	1.00	.	0.80	1.18	.	.
	2	1.04	1.04	1.15	1.00	1.69	0.59
	2	0.72	0.73	0.67	1.25	0.66	1.52
	1	0.87	.	0.92	1.25	.	.
	1	0.94	.	0.82	1.25	.	.

RATIO OF SPONSOR/REVIEWER CALCULATED PARAMETERS

Obs	sub	seq	per	trt	AUCTO_N	AUCIO_N	CMAXO_N	TMAXO_N
1	(b) (6)	1	1	1	1.00	1.00	1	0.97
2		1	1	1	1.01	.	1	1.00
3		1	1	1	1.00	1.00	1	1.00
4		2	2	1	0.99	0.99	1	1.01
5		2	2	1	1.00	1.00	1	1.00
6		2	2	1	1.00	1.00	1	1.00
7		1	1	1	1.00	1.00	1	1.00
8		2	2	1	1.00	1.00	1	1.00
9		1	1	1	0.99	0.99	1	1.00
10		1	1	1	1.00	1.00	1	1.00
11		2	2	1	1.00	1.00	1	1.00
12		1	1	1	1.00	1.00	1	1.00
13		1	1	1	1.00	1.00	1	1.00
14		2	2	1	1.00	1.00	1	1.00
15		2	2	1	1.02	1.02	1	1.00
16		1	1	1	1.00	1.00	1	1.00
17		2	2	1	1.01	.	1	1.07
18		1	1	1	1.00	.	1	1.00
19		1	1	1	1.01	.	1	1.00
20		2	2	1	1.00	1.00	1	1.00
21		1	1	1	1.00	1.00	1	1.00
22		2	2	1	1.00	1.00	1	1.00
23		2	2	1	1.00	1.00	1	1.00
24		2	2	1	1.00	1.00	1	1.00

Obs	sub (b) (6)	seq	per	trt	AUCTO_N	AUCIO_N	CMAXO_N	TMAXO_N
25		2	2	1	1.00	1.00	1	1.00
26		1	1	1	1.00	1.00	1	1.00
27		1	1	1	1.00	1.00	1	1.00
28		1	1	1	1.00	1.00	1	1.00
29		2	2	1	1.00	.	1	1.00
30		1	1	1	1.00	.	1	1.00
31		2	2	1	1.01	.	1	1.00
32		2	2	1	1.00	1.00	1	1.00
33		2	2	1	1.00	1.00	1	1.00
34		1	1	1	1.00	.	1	1.00
35		1	1	1	1.00	1.00	1	1.00
36		1	2	2	1.00	1.00	1	1.00
37		1	2	2	1.00	1.00	1	1.00
38		1	2	2	1.00	1.00	1	1.00
39		2	1	2	1.00	.	1	1.00
40		2	1	2	1.00	1.00	1	1.00
41		2	1	2	1.00	1.00	1	1.00
42		1	2	2	1.00	.	1	1.00
43		2	1	2	1.00	.	1	1.00
44		1	2	2	1.00	1.00	1	1.00
45		1	2	2	1.00	1.00	1	1.00
46		2	1	2	1.00	1.00	1	1.00
47		1	2	2	1.00	1.00	1	1.01
48		1	2	2	1.00	1.00	1	1.00
49		2	1	2	1.00	1.00	1	1.00
50		2	1	2	1.00	.	1	1.00

Obs	sub	seq	per	trt	AUCTO_N	AUCIO_N	CMAXO_N	TMAXO_N
51	(b) (6)	1	2	2	1.00	1.00	1	1.00
52		2	1	2	1.00	1.00	1	1.02
53		1	2	2	1.00	1.00	1	1.00
54		1	2	2	1.00	1.00	1	1.00
55		2	1	2	1.42	1.40	1	1.00
56		1	2	2	1.00	1.00	1	1.00
57		2	1	2	1.00	1.00	1	1.00
58		2	1	2	1.01	1.01	1	1.00
59		2	1	2	1.00	1.00	1	1.00
60		2	1	2	1.00	1.00	1	1.00
61		1	2	2	1.00	1.00	1	1.00
62		1	2	2	1.00	1.00	1	1.00
63		1	2	2	1.00	.	1	1.00
64		2	1	2	1.00	1.00	1	1.00
65		1	2	2	1.00	1.00	1	1.00
66		2	1	2	1.00	1.00	1	1.01
67		2	1	2	1.00	1.00	1	1.00
68		2	1	2	1.00	1.00	1	1.00
69		1	2	2	1.00	1.00	1	1.00
70		1	2	2	1.07	.	1	1.00

4.6.4 Fed Study Data

FED CONCENTRATION DATASET

Obs	sub	seq	per	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17
1	(b) (6)	2	1	1	0	1.310	5.300	8.470	12.200	13.400	12.500	13.100	15.70	14.100	8.66	4.97	5.690	1.940	0.706	0.611	0.395
2		2	2	1	0	0.133	1.200	2.410	2.400	2.570	3.840	5.790	12.90	19.700	13.20	8.51	6.070	1.550	0.463	0.217	0.186
3		2	1	1	0	0.000	0.000	5.170	0.102	0.301	0.446	0.460	12.50	21.900	19.40	13.80	7.050	1.780	1.270	0.808	0.255
4		2	2	1	0	0.000	0.127	0.576	1.140	2.000	3.540	4.780	14.00	18.000	12.50	6.97	2.980	1.250	0.918	0.585	0.306
5		1	1	1	0	0.107	1.820	3.200	11.400	15.000	14.100	14.400	11.90	9.640	6.32	4.32	2.180	1.060	0.491	0.173	0.000
6		1	2	1	0	0.000	0.000	0.204	0.640	1.320	2.060	2.720	5.92	8.770	9.14	8.72	5.060	1.580	0.453	0.357	0.000
7		1	1	1	0	0.000	0.171	2.350	0.495	0.758	1.140	1.700	7.84	15.600	18.30	12.60	6.320	3.920	1.520	0.835	0.515
8		1	2	1	0	0.000	0.113	0.266	1.020	2.450	3.390	4.270	6.17	10.600	15.10	15.40	8.640	3.170	1.100	0.641	0.766
9		2	1	1	0	0.235	1.500	0.000	5.850	7.400	7.850	8.040	10.40	12.200	9.86	11.40	11.500	3.970	1.660	0.877	0.448
10		2	2	1	0	0.000	0.000	0.203	0.589	1.260	1.980	3.600	7.02	18.700	24.90	13.70	6.650	2.380	0.747	0.412	0.147
11		1	1	1	0	0.000	0.000	0.000	0.000	0.974	7.270	21.100	27.40	17.700	8.78	5.40	3.400	1.280	0.467	0.279	0.126
12		1	2	1	0	0.000	0.272	1.200	2.300	4.070	5.390	6.260	11.90	14.100	9.57	4.57	2.820	0.980	0.468	0.385	0.225
13		1	1	1	0	0.000	0.224	1.380	0.858	1.080	2.890	3.800	5.04	7.170	6.55	7.03	7.610	7.600	4.160	4.980	2.090
14		1	2	1	0	0.663	4.800	7.870	10.900	12.100	10.400	8.890	7.42	7.040	5.51	4.69	5.900	6.210	3.460	3.010	1.810
15		1	1	1	0	0.000	0.767	3.960	6.320	10.000	11.600	13.800	17.10	24.400	29.50	16.00	5.280	3.310	1.870	0.563	0.212
16		1	2	1	0	0.627	3.040	6.650	8.650	9.450	10.200	10.100	16.50	20.400	13.00	6.40	3.380	1.530	0.555	0.299	0.125
17		2	1	1	0	0.000	0.471	2.160	5.300	6.270	7.380	8.400	10.30	7.040	3.53	2.84	5.250	1.690	0.805	0.573	0.326
18		2	2	1	0	0.000	0.000	0.800	3.430	9.300	18.100	18.500	12.40	6.180	3.32	2.39	2.240	0.947	0.718	0.424	0.202
19		1	1	1	0	0.000	0.000	0.000	0.000	0.198	0.335	0.887	7.28	11.300	20.80	14.20	7.700	1.750	1.220	0.644	0.174
20		1	2	1	0	0.000	0.625	3.260	6.670	10.500	10.800	10.700	16.30	10.100	6.07	2.64	0.949	0.282	0.135	0.000	0.000
21		2	1	1	0	0.000	0.000	0.000	0.000	0.000	0.000	0.392	3.62	9.920	13.30	10.20	9.020	3.270	1.690	0.637	0.107
22		2	2	1	0	0.000	0.000	0.125	0.682	3.200	6.310	9.500	15.00	16.900	12.50	8.63	3.870	2.130	1.220	0.566	0.111
23		2	1	1	0	0.000	0.355	0.766	0.995	1.480	2.770	3.570	12.10	16.100	16.80	15.20	8.140	4.260	1.210	0.757	0.803

Obs	sub	seq	per	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17
24	(b) (6)	2	2	1	0	0.000	0.000	0.178	0.790	2.410	5.860	8.950	20.90	27.900	20.50	12.10	6.460	1.630	0.625	0.243	0.238
25		1	1	1	0	0.506	1.710	4.200	8.850	12.400	10.200	8.950	7.25	9.530	9.65	6.95	3.080	0.854	0.294	0.180	0.000
26		1	2	1	0	0.000	0.000	0.111	0.194	0.265	0.263	0.424	1.47	3.620	6.82	8.38	10.000	3.540	2.000	1.460	0.510
27		1	1	1	0	0.000	0.132	0.647	2.290	3.920	11.100	22.400	24.30	11.200	4.94	2.53	1.730	0.509	0.283	0.182	0.000
28		1	2	1	0	0.000	0.520	2.170	4.810	11.900	12.400	16.400	13.00	7.200	4.64	3.35	5.120	1.260	0.475	0.303	0.238
29		2	1	1	0	0.000	0.000	0.467	1.960	4.910	11.600	18.800	28.10	21.000	16.40	9.74	3.450	0.967	0.497	0.290	0.000
30		2	2	1	0	0.000	0.000	0.676	2.090	2.740	3.850	6.770	12.70	16.600	16.30	12.60	6.640	3.100	2.380	1.600	0.740
31		2	1	1	0	0.348	2.310	7.360	13.400	17.300	22.700	28.400	32.90	25.200	17.80	11.40	5.610	1.870	0.914	0.584	0.191
32		2	2	1	0	0.135	1.670	9.380	16.500	26.100	28.800	31.900	30.80	22.100	14.30	10.50	4.570	1.740	0.782	0.425	0.180
33		1	1	1	0	0.000	0.000	0.208	0.139	0.000	0.000	0.280	4.97	13.000	17.00	15.80	8.830	5.960	1.710	0.756	0.434
34		1	2	1	0	0.375	0.670	1.600	3.520	5.770	8.160	11.800	16.90	17.000	11.30	9.43	4.450	1.230	0.761	0.520	0.237
35		2	1	1	0	1.750	1.190	0.508	0.255	0.123	0.000	0.298	6.15	18.400	22.90	17.30	12.300	5.610	2.690	2.300	0.604
36		2	2	1	0	0.000	0.000	0.000	0.000	0.103	0.505	2.010	5.65	11.800	15.10	14.50	11.800	7.590	3.440	2.130	0.670
37		2	1	1	0	0.000	0.166	0.390	0.971	1.800	2.810	7.430	9.73	16.200	13.30	13.40	12.200	5.310	4.020	3.460	2.490
38		2	2	1	0	0.000	0.403	0.727	1.390	3.080	5.600	10.600	17.00	18.300	18.80	14.80	11.400	5.220	3.140	2.700	1.190
39		1	1	1	0	0.000	0.000	0.000	0.179	0.917	3.600	9.670	22.50	22.800	20.30	14.40	8.570	2.080	0.922	0.666	0.267
40		1	2	1	0	0.000	0.901	4.790	9.180	13.500	17.200	21.200	26.50	23.800	18.10	9.74	6.000	1.630	0.736	0.510	0.218
41		2	1	1	0	0.000	0.736	2.380	5.210	12.100	20.100	26.000	34.60	28.900	16.30	10.50	5.490	2.000	0.777	0.427	0.163
42		2	2	1	0	0.000	0.000	0.138	1.120	3.940	9.110	17.800	26.30	21.200	18.50	13.20	6.810	2.410	1.120	0.787	0.256
43		1	1	1	0	0.000	0.000	0.279	1.090	2.480	3.050	3.970	7.15	7.110	7.67	6.42	5.860	2.290	1.000	0.390	0.152
44		1	2	1	0	0.000	0.827	3.290	6.240	10.800	11.300	11.900	12.30	7.650	4.11	3.47	1.120	0.606	0.488	0.295	0.159
45		1	1	1	0	0.000	0.000	0.000	0.252	0.807	2.500	6.690	13.90	13.800	8.29	6.29	3.610	0.808	0.404	0.244	0.000
46		1	2	1	0	1.450	9.210	21.400	33.000	32.900	27.000	18.500	8.88	4.630	2.79	1.73	0.953	0.331	0.124	0.000	0.000
47		1	1	1	0	0.000	0.000	0.000	0.239	1.540	5.780	14.600	22.90	19.300	11.20	7.23	3.010	1.370	0.790	0.444	0.172
48		1	2	1	0	0.154	0.218	0.738	2.480	7.250	12.900	19.800	24.30	16.700	6.77	6.27	3.280	1.680	0.640	0.281	0.117
49		2	1	1	0	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.00	0.441	2.17	6.45	21.900	10.700	3.620	1.350	0.216

Obs	sub	seq	per	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17
50	(b) (6)	2	2	1	0	0.000	0.000	0.000	0.410	1.730	5.370	7.480	11.10	12.900	14.60	13.10	7.450	1.870	0.603	0.250	0.000
51		1	1	1	0	0.000	0.149	0.712	2.100	4.980	11.100	17.000	14.00	10.600	7.53	7.19	3.820	1.330	0.433	0.266	0.000
52		1	2	1	0	0.000	0.413	1.940	3.480	6.990	11.400	16.300	14.20	13.300	8.12	6.90	6.370	1.970	0.749	0.352	0.114
53		1	1	1	0	0.000	0.000	0.305	0.614	1.110	2.180	10.900	34.30	33.500	18.70	9.44	2.460	1.170	0.558	0.311	0.119
54		1	2	1	0	0.000	0.130	0.359	0.788	3.280	11.700	25.000	29.60	18.100	10.80	6.68	4.470	1.430	0.807	0.390	0.000
55		2	1	1	0	0.116	0.371	0.808	2.670	4.250	8.680	11.800	15.10	14.700	10.50	5.62	2.220	0.750	0.359	0.217	0.000
56		2	2	1	0	0.000	1.130	4.290	7.380	11.200	12.500	12.800	12.40	10.000	7.22	5.72	2.630	0.684	0.356	0.240	0.000
57		1	1	1	0	0.000	0.000	0.000	0.000	0.000	0.181	0.433	2.08	3.250	2.88	3.28	24.000	7.000	2.070	1.190	0.534
58		1	2	1	0	0.000	0.827	3.260	6.540	13.800	13.900	17.300	13.70	10.800	7.86	5.88	3.050	1.450	0.701	0.585	0.291
59		1	1	1	0	0.000	4.670	28.600	25.600	24.900	21.600	24.100	18.00	11.100	5.82	3.74	1.970	1.130	0.644	0.448	0.840
60		1	2	1	0	0.538	5.210	16.100	20.800	26.100	24.800	26.200	44.10	21.400	10.40	5.09	1.880	0.776	0.519	0.406	0.147
61		2	1	1	0	0.000	0.567	1.720	3.020	6.610	10.500	15.700	16.60	14.700	11.50	7.00	3.780	1.600	0.932	0.683	0.120
62		2	2	1	0	0.179	0.470	1.210	1.990	4.260	7.390	10.200	13.90	13.900	11.70	9.67	6.040	2.080	0.985	0.387	0.150
63		2	1	1	0	0.615	3.610	7.200	9.790	11.400	14.400	19.700	20.80	14.400	8.52	7.97	5.430	3.810	1.930	2.360	1.410
64		2	2	1	0	0.000	0.000	0.871	2.190	3.470	13.300	28.900	32.20	15.900	11.60	9.18	6.950	3.110	1.940	1.850	0.979

1	0.000	0.000	0.000	0	0	15	22	2
2	0.000	0.000	0.000	0	0	15	22	1
3	0.104	0.000	0.000	0	0	15	22	2
4	0.000	0.000	0.000	0	0	15	22	1
5	0.000	0.000	0.000	0	0	15	22	1
6	0.000	0.000	0.000	0	0	15	22	2
7	0.300	0.000	0.000	0	0	15	22	1
8	0.283	0.116	0.000	0	0	15	22	2
9	0.106	0.000	0.000	0	0	15	22	2
10	0.000	0.000	0.000	0	0	15	22	1
11	0.000	0.000	0.000	0	0	15	22	1
12	0.000	0.000	0.000	0	0	15	22	2
13	1.040	0.361	0.000	0	0	15	22	1
14	0.238	0.000	0.000	0	.	15	22	2
15	0.000	0.000	0.000	0	0	15	22	1
16	0.000	0.000	0.000	0	0	15	22	2
17	0.104	0.000	0.000	0	0	15	22	2
18	0.000	0.000	0.000	0	0	15	22	1
19	0.000	0.000	0.000	0	0	15	22	1
20	0.000	0.000	0.000	0	0	15	22	2

21	0.000	0.000	0.000	0	0	15	22	2
22	0.000	0.000	0.000	0	0	15	22	1
23	0.219	0.147	0.000	0	0	15	22	2
24	0.000	0.000	0.000	0	0	15	22	1
25	0.000	0.000	0.000	0	0	15	22	1
26	0.000	0.000	0.000	0	0	15	22	2
27	0.000	0.000	0.000	0	0	15	22	1
28	0.000	0.000	0.512	0	0	15	22	2
29	0.000	0.000	0.000	0	0	15	22	2
30	0.288	0.000	0.000	0	0	15	22	1
31	0.124	0.000	0.000	0	0	15	22	2
32	0.000	0.000	0.000	0	0	15	22	1
33	0.266	0.000	0.000	0	0	15	22	1
34	0.132	0.000	0.000	0	0	15	22	2
35	0.365	0.000	0.000	0	0	15	22	2
36	0.161	0.000	0.000	0	0	15	22	1
37	0.801	0.000	0.000	0	0	15	22	2
38	0.211	0.000	0.000	0	0	15	22	1
39	0.109	0.000	0.000	0	0	15	22	1
40	0.000	0.000	0.000	0	0	15	22	2
41	0.000	0.000	0.000	0	0	15	22	2
42	0.000	0.000	0.000	0	0	15	22	1
43	0.000	0.000	0.000	0	0	15	22	1
44	0.000	0.000	0.000	0	0	15	22	2
45	0.000	0.000	0.000	0	0	15	22	1
46	0.000	0.000	0.000	0	0	15	22	2

47	0.000	0.000	0.000	0	0	15	22	1
48	0.000	0.000	0.000	0	0	15	22	2
49	0.000	0.000	0.000	0	0	15	22	2
50	0.000	0.000	0.000	0	0	15	22	1
51	0.000	0.000	0.000	0	0	15	22	1
52	0.000	0.000	0.000	0	0	15	22	2
53	0.408	0.000	0.000	0	0	15	22	1
54	0.000	0.000	0.000	0	0	15	22	2
55	0.000	0.000	0.000	0	0	15	22	2
56	0.000	0.000	0.000	0	0	15	22	1
57	0.139	0.000	0.000	0	0	15	22	1
58	0.176	0.000	0.000	0	0	15	22	2
59	0.118	0.000	0.000	0	0	15	22	1
60	0.000	0.000	0.000	0	0	15	22	2
61	0.000	0.000	0.000	0	0	15	22	2
62	0.000	0.000	0.000	0	0	15	22	1
63	0.867	0.476	0.231	0	0	15	22	2
64	0.668	0.270	0.168	0	0	15	22	1

FED PHARMACOKINETIC DATASET

Obs	sub	seq	per	GRP	AUCT	AUCI	CMAX	TMAX	KE	THALF	TRT
1	(b) (6)	2	1	1	51.0174	53.0217	15.70	2.51667	0.19708	3.51707	2
2		2	2	1	43.2031	.	19.70	3.00000	.	.	1
3		2	1	1	51.0534	51.2573	21.90	3.00000	0.50986	1.35949	2
4		2	2	1	37.4547	38.3153	18.00	3.00000	0.35556	1.94945	1
5		1	1	1	37.8076	38.0307	15.00	1.50000	0.77567	0.89361	1
6		1	2	1	27.8025	.	9.14	3.50000	.	.	2
7		1	1	1	46.5285	47.7008	18.30	3.50000	0.25591	2.70853	1
8		1	2	1	47.3895	.	15.40	4.00000	.	.	2
9		2	1	1	53.8994	54.1011	12.20	3.00000	0.52545	1.31915	2
10		2	2	1	48.6777	48.9509	24.90	3.50000	0.53808	1.28819	1
11		1	1	1	46.6550	46.9473	27.40	2.50000	0.43108	1.60793	1
12		1	2	1	31.9385	32.8472	14.10	3.00000	0.24762	2.79929	2
13		1	1	1	52.5475	53.6666	7.61	5.00000	0.32257	2.14880	1
14		1	2	1	52.5685	.	12.10	1.50000	.	.	2
15		1	1	1	72.3662	72.6766	29.50	3.50000	0.68293	1.01495	1
16		1	2	1	49.6353	49.8913	20.40	3.00000	0.48820	1.41981	2
17		2	1	1	30.4708	.	10.30	2.50000	.	.	2
18		2	2	1	32.3432	32.8508	18.50	2.00000	0.39792	1.74194	1
19		1	1	1	42.7239	42.9916	20.80	3.50000	0.64992	1.06652	1
20		1	2	1	31.4965	31.6299	16.30	2.50000	1.01217	0.68481	2
21		2	1	1	36.2595	36.3826	13.30	3.50000	0.86952	0.79716	2
22		2	2	1	43.0163	43.1730	16.90	3.00000	0.70862	0.97816	1
23		2	1	1	54.1328	.	16.80	3.50000	.	.	2
24		2	2	1	58.6538	.	27.90	3.00000	.	.	1
25		1	1	1	35.6315	35.8193	12.40	1.50000	0.95855	0.72312	1
26		1	2	1	30.8473	31.9219	10.00	5.00000	0.47457	1.46058	2
27		1	1	1	37.6528	38.0067	24.30	2.50000	0.51422	1.34796	1
28		1	2	1	41.8300	.	16.40	2.00000	.	.	2
29		2	1	1	56.8983	57.3799	28.10	2.50000	0.60216	1.15110	2
30		2	2	1	53.6389	54.3205	16.60	3.01667	0.42252	1.64049	1
31		2	1	1	82.8240	83.1441	32.90	2.50000	0.38740	1.78921	2
32		2	2	1	82.2064	82.5806	31.90	2.00000	0.48105	1.44090	1
33		1	1	1	48.3995	49.4181	17.00	3.50000	0.26114	2.65435	1
34		1	2	1	46.9951	47.3508	17.00	3.00000	0.37109	1.86787	2
35		2	1	1	63.6626	64.4541	22.90	3.50000	0.46118	1.50298	2
36		2	2	1	55.5818	55.8399	15.10	3.50000	0.62373	1.11130	1

Obs	sub	seq	per	GRP	AUCT	AUCI	CMAX	TMAX	KE	THALF	TRT
37	(b) (6)	2	1	1	66.4865	.	16.20	3.00000	.	.	2
38		2	2	1	71.4175	.	18.80	3.50000	.	.	1
39		1	1	1	61.6143	61.8657	22.80	3.00000	0.43354	1.59881	1
40		1	2	1	70.1968	70.7306	26.50	2.50000	0.40835	1.69745	2
41		2	1	1	76.7270	77.0435	34.60	2.50000	0.51499	1.34596	2
42		2	2	1	64.9285	65.4386	26.30	2.50000	0.50191	1.38103	1
43		1	1	1	28.8805	29.1315	7.67	3.50000	0.60555	1.14465	1
44		1	2	1	29.7514	30.1794	12.30	2.50000	0.37147	1.86594	2
45		1	1	1	31.0550	31.4626	13.90	2.50000	0.59870	1.15776	1
46		1	2	1	49.1523	49.2929	33.00	1.25000	0.88139	0.78642	2
47		1	1	1	45.4953	45.8007	22.90	2.50000	0.56305	1.23105	1
48		1	2	1	48.1119	48.2833	24.30	2.50000	0.68236	1.01581	2
49		2	1	1	44.6040	44.8267	21.90	5.00000	0.96981	0.71473	2
50		2	2	1	43.8555	44.0764	14.60	3.50000	1.13153	0.61258	1
51		1	1	1	38.3088	38.6006	17.00	2.00000	0.91157	0.76039	1
52		1	2	1	44.8843	45.0473	16.30	2.00000	0.69907	0.99153	2
53		1	1	1	60.7703	.	34.30	2.50000	.	.	1
54		1	2	1	54.6964	55.1908	29.60	2.50000	0.78891	0.87861	2
55		2	1	1	36.4658	36.7471	15.10	2.50000	0.77128	0.89869	2
56		2	2	1	36.8150	37.2733	12.80	2.00000	0.52366	1.32366	1
57		1	1	1	42.8346	43.0991	24.00	5.00000	0.52552	1.31897	1
58		1	2	1	43.4958	44.0819	17.30	2.00000	0.30028	2.30832	2
59		1	1	1	61.8590	.	28.60	1.00000	.	.	1
60		1	2	1	79.1137	.	44.10	2.50000	.	.	2
61		2	1	1	45.5983	45.7810	16.60	2.50000	0.65656	1.05573	2
62		2	2	1	44.5601	44.7874	13.90	2.50000	0.66013	1.05001	1
63		2	1	1	70.9912	73.1423	20.80	2.50000	0.10738	6.45487	2
64		2	2	1	73.3478	.	32.20	2.51667	.	.	1

4.6.5 Fed Study Codes

Same as in fasting study

4.6.6 Fed Study Output

FED STATISTICAL OUTPUT

The GLM Procedure

Class Level Information		
Class	**Levels**	**Values**
sub	32	201 202 203 204 205 206 208 209 210 211 212 213 214 215 216 217 218 219 220 221 222 223 224 225 226 228 229 230 232 233 234 235
trt	2	1 2
per	2	1 2
seq	2	1 2

Data for Analysis of AUCT CMAX LAUCT LCMAX	
Number of Observations Read	64
Number of Observations Used	64

Data for Analysis of AUCI LAUCI	
Number of Observations Read	64
Number of Observations Used	50

Note: Variables in each group are consistent with respect to the presence or absence of missing values.

FED STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	33	4.50371835	0.13647631	7.92	<.0001
Error	30	0.51662967	0.01722099		
Corrected Total	63	5.02034802			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.897093	3.393440	0.131229	3.867131

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.35438126	0.35438126	20.58	<.0001
sub(seq)	30	4.13339214	0.13777974	8.00	<.0001
per	1	0.01534114	0.01534114	0.89	0.3528
trt	1	0.00060381	0.00060381	0.04	0.8527

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.35438126	0.35438126	20.58	<.0001
sub(seq)	30	4.13339214	0.13777974	8.00	<.0001
per	1	0.01566327	0.01566327	0.91	0.3479
trt	1	0.00060381	0.00060381	0.04	0.8527

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	**DF**	**Type III SS**	**Mean Square**	**F Value**	**Pr > F**
seq	1	0.35438126	0.35438126	2.57	0.1192

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.00615515	0.03287146	-0.19	0.8527

FED STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	33	6.61934190	0.20058612	2.50	0.0065
Error	30	2.40492095	0.08016403		
Corrected Total	63	9.02426286			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.733505	9.661150	0.283133	2.930630

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.03844672	0.03844672	0.48	0.4939
sub(seq)	30	6.55454618	0.21848487	2.73	0.0038
per	1	0.00002473	0.00002473	0.00	0.9861
trt	1	0.02632428	0.02632428	0.33	0.5709

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.03844672	0.03844672	0.48	0.4939
sub(seq)	30	6.55454618	0.21848487	2.73	0.0038
per	1	0.00022812	0.00022812	0.00	0.9578
trt	1	0.02632428	0.02632428	0.33	0.5709

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	**DF**	**Type III SS**	**Mean Square**	**F Value**	**Pr > F**
seq	1	0.03844672	0.03844672	0.18	0.6778

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	0.04064135	0.07092179	0.57	0.5709

FED STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	30	3.14712489	0.10490416	5.30	0.0002
Error	19	0.37639788	0.01981041		
Corrected Total	49	3.52352277			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.893176	3.655526	0.140749	3.850321

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.33873326	0.33873326	17.10	0.0006
sub(seq)	27	2.78404007	0.10311260	5.20	0.0002
per	1	0.02207964	0.02207964	1.11	0.3043
trt	1	0.00227191	0.00227191	0.11	0.7386

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.26661951	0.26661951	13.46	0.0016
sub(seq)	27	2.71676551	0.10062094	5.08	0.0003
per	1	0.02270849	0.02270849	1.15	0.2977
trt	1	0.00227191	0.00227191	0.11	0.7386

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	**DF**	**Type III SS**	**Mean Square**	**F Value**	**Pr > F**
seq	1	0.26661951	0.26661951	2.65	0.1152

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.01472632	0.04348556	-0.34	0.7386

AUCT/AUCI RATIO FOR INDIVIDUAL SUBJECTS

Obs	sub	trt	AUCRATIO
1	(b) (6)	1	.
2		1	0.98
3		1	0.99
4		1	0.98
5		1	0.99
6		1	0.99
7		1	0.98
8		1	1.00
9		1	0.98
10		1	0.99
11		1	1.00
12		1	.
13		1	0.99
14		1	0.99
15		1	0.99
16		1	1.00
17		1	0.98
18		1	1.00
19		1	.
20		1	1.00
21		1	0.99
22		1	0.99
23		1	0.99
24		1	0.99
25		1	0.99
26		1	0.99
27		1	.
28		1	0.99
29		1	0.99
30		1	.
31		1	0.99
32		1	.
33		2	0.96
34		2	1.00
35		2	.
36		2	.

Obs	sub	trt	AUCRATIO
37	(b) (6)	2	1.00
38		2	0.97
39		2	.
40		2	0.99
41		2	.
42		2	1.00
43		2	1.00
44		2	.
45		2	0.97
46		2	.
47		2	0.99
48		2	1.00
49		2	0.99
50		2	0.99
51		2	.
52		2	0.99
53		2	1.00
54		2	0.99
55		2	1.00
56		2	1.00
57		2	1.00
58		2	1.00
59		2	0.99
60		2	0.99
61		2	0.99
62		2	.
63		2	1.00
64		2	0.97

TEST PRODUCT/REFERENCE PRODUCT RATIOS FOR INDIVIDUAL SUBJECTS

(b) (6)	2	0.85	.	1.25	1.19	.	.
	2	0.73	0.75	0.82	1.00	0.70	1.43
	1	1.36	.	1.64	0.43	.	.
	1	0.98	.	1.19	0.88	.	.
	2	0.90	0.90	2.04	1.17	1.02	0.98
	1	1.46	1.43	1.94	0.83	1.74	0.57
	1	1.00	.	0.63	3.33	.	.
	1	1.46	1.46	1.45	1.17	1.40	0.71
	2	1.06	.	1.80	0.80	.	.
	1	1.36	1.36	1.28	1.40	0.64	1.56
	2	1.19	1.19	1.27	0.86	0.81	1.23
	2	1.08	.	1.66	0.86	.	.
	1	1.16	1.12	1.24	0.30	2.02	0.50
	1	0.90	.	1.48	1.25	.	.
	2	0.94	0.95	0.59	1.21	0.70	1.43
	2	0.99	0.99	0.97	0.80	1.24	0.81
	1	1.03	1.04	1.00	1.17	0.70	1.42
	2	0.87	0.87	0.66	1.00	1.35	0.74
	2	1.07	.	1.16	1.17	.	.
	1	0.88	0.87	0.86	1.20	1.06	0.94
	2	0.85	0.85	0.76	1.00	0.97	1.03
	1	0.97	0.97	0.62	1.40	1.63	0.61
	1	0.63	0.64	0.42	2.00	0.68	1.47
	1	0.95	0.95	0.94	1.00	0.83	1.21
	2	0.98	0.98	0.67	0.70	1.17	0.86
	1	0.85	0.86	1.04	1.00	1.30	0.77
	1	1.11	.	1.16	1.00	.	.
	2	1.01	1.01	0.85	0.80	0.68	1.47
	1	0.98	0.98	1.39	2.50	1.75	0.57
	1	0.78	.	0.65	0.40	.	.
	2	0.98	0.98	0.84	1.00	1.01	0.99
	2	1.03	.	1.55	1.01	.	.

RATIO OF SPONSOR/REVIEWER CALCULATED PARAMETERS

Obs	sub	seq	per	trt	AUCTO_N	AUCIO_N	CMAXO_N	TMAXO_N
1	(b) (6)	2	2	1	1.00	.	1	1.00
2		2	2	1	1.00	1.00	1	1.00
3		1	1	1	1.00	1.00	1	1.00
4		1	1	1	1.00	1.00	1	1.00

Obs	sub	seq	per	trt	AUCTO_N	AUCIO_N	CMAXO_N	TMAXO_N
5	(b) (6)	2	2	1	1.00	1.00	1	1.00
6		1	1	1	1.00	1.00	1	1.00
7		1	1	1	1.00	1.00	1	1.00
8		1	1	1	1.00	1.00	1	1.00
9		2	2	1	1.00	1.00	1	1.00
10		1	1	1	1.00	1.00	1	1.00
11		2	2	1	1.00	1.00	1	1.00
12		2	2	1	1.00	.	1	1.00
13		1	1	1	1.00	1.00	1	1.00
14		1	1	1	1.00	1.00	1	1.00
15		2	2	1	1.00	1.00	1	1.01
16		2	2	1	1.00	1.00	1	1.00
17		1	1	1	1.00	1.00	1	1.00
18		2	2	1	1.00	1.00	1	1.00
19		2	2	1	1.00	.	1	1.00
20		1	1	1	1.00	1.00	1	1.00
21		2	2	1	1.00	1.00	1	1.00
22		1	1	1	1.00	1.00	1	1.00
23		1	1	1	1.00	1.00	1	1.00
24		1	1	1	1.00	1.00	1	1.00
25		2	2	1	1.00	1.00	1	1.00
26		1	1	1	1.00	1.00	1	1.00
27		1	1	1	1.00	.	1	1.00
28		2	2	1	1.00	1.00	1	1.00
29		1	1	1	1.00	1.00	1	1.00
30		1	1	1	1.00	.	1	1.00
31		2	2	1	1.00	1.00	1	0.83
32		2	2	1	1.00	.	1	1.01
33		2	1	2	1.00	1.00	1	1.01
34		2	1	2	1.00	1.00	1	1.00
35		1	2	2	1.00	.	1	1.00
36		1	2	2	1.00	.	1	1.00
37		2	1	2	1.02	1.02	1	1.00
38		1	2	2	1.00	1.00	1	1.00
39		1	2	2	1.00	.	1	1.00
40		1	2	2	1.01	1.01	1	1.00
41		2	1	2	1.00	.	1	1.00
42		1	2	2	1.00	1.00	1	1.00
43		2	1	2	1.00	1.00	1	1.00
44		2	1	2	1.00	.	1	1.00

Obs	sub	seq	per	trt	AUCTO_N	AUCIO_N	CMAXO_N	TMAXO_N
45	(b) (6)	1	2	2	1.00	1.00	1	1.00
46		1	2	2	1.08	.	1	1.00
47		2	1	2	1.00	1.00	1	1.00
48		2	1	2	1.00	1.00	1	1.00
49		1	2	2	1.00	1.00	1	1.00
50		2	1	2	1.00	1.00	1	1.00
51		2	1	2	1.00	.	1	1.00
52		1	2	2	1.00	1.00	1	1.00
53		2	1	2	1.00	1.00	1	1.00
54		1	2	2	0.99	0.99	1	1.00
55		1	2	2	1.00	1.00	1	1.00
56		1	2	2	1.00	1.00	1	1.00
57		2	1	2	1.00	1.00	1	1.00
58		1	2	2	1.00	1.00	1	1.00
59		1	2	2	1.00	1.00	1	1.00
60		2	1	2	1.00	1.00	1	1.00
61		1	2	2	1.00	1.00	1	1.00
62		1	2	2	1.00	.	1	1.00
63		2	1	2	1.00	1.00	1	1.00
64		2	1	2	1.00	1.00	1	1.00

4.7 Additional Attachments

None

BIOEQUIVALENCE DEFICIENCIES

ANDA: 202827

APPLICANT: Roxane Laboratories, Inc.

DRUG PRODUCT: Lisdexamfetamine Dimesylate Capsules, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg

The Division of Bioequivalence II (DB II) has completed its review and the following deficiencies have been identified:

1. For Lisdexamfetamine, you re-assayed a total of 319 samples due to unacceptable internal standard response (i.e., 134 samples in the fasting BE study No. LISD-C70-PVFS-1 and 185 samples in the fed BE study No. LISD-C70-PVFD-1). Please investigate and justify the high number of samples repeated due to internal standard response.

2. In the Tables 2A and 2B (Reassayed Samples) of the analytical reports (Project AFUB) for both the fasting and fed BE studies, you did not provide the original values for the reassayed samples, instead citing NRR (No Recorded Result). Please provide original values and chromatograms for all repeated samples.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

4.8 Outcome Page

ANDA: 202827

5 *COMPLETED ASSIGNMENT FOR 202827 ID: 15572*

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
15572	2/23/2011	Bioequivalence Study	Fasting Study	1	1
15572	2/23/2011	Bioequivalence Study	Fed Study	1	1
15572	11/8/2011	Other	Dissolution Waiver	1	1
15572	11/8/2011	Other	Dissolution Waiver	1	1
15572	11/8/2011	Other	Dissolution Waiver	1	1
15572	11/8/2011	Other	Dissolution Waiver	1	1
15572	11/8/2011	Other	Dissolution Waiver	1	1
				Bean Total:	7

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY

BE Study Fasting	
Clinical (Common to all APIs)	1
Bioanalytical (API 1)	1
Statistical Analysis (API 1)	1
Metabolite	1
Fasting Study Total	*4*
BE Study Fed	
Clinical (Common to all APIs)	1
Bioanalytical (API 1)	1
Statistical Analysis (API 1)	1
Metabolite	1
Fed Study Total	*4*
Dissolution Study/ Dissolution Waiver(s)	
Strength 5 (DIW)	2.5
Dissolution Study/Waiver Total	*2.5*

Grand Total	**10.5**

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SVETLANA A CHERSTNIAKOVA
11/30/2011

MOHEB H MAKARY
11/30/2011

ETHAN M STIER on behalf of BARBARA M DAVIT
11/30/2011

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	202827		
Drug Product Name	Lisdexamfetamine Dimesylate Capsule		
Strength (s)	20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg		
Applicant Name	Roxane Laboratories, Inc.		
Address	1809 Wilson Road Columbus, OH 43228		
Applicant's Point of Contact	Elizabeth Ernst		
Contact's Phone Number	(614) 272-4785		
Contact's Fax Number	(614) 276-2470		
Submission Date(s)	02/23/2011		
First Generic	No		
Reviewer	Huong Huynh, Ph.D.		
Study Number (s)	LISD-C70-PVFS-1	LISD-C70-PVFD-1	
Study Type (s)	Fasting	Fed	
Strength(s)	70 mg	70 mg	
Clinical Site	Novum Pharmaceutical Research Services		
Clinical Site Address	3760 Pecos McLeod Las Vegas, NV 89121		
Analytical Site	(b) (4)		
Analytical Address			
OVERALL REVIEW RESULT	**INADEQUATE**		

BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1	FASTING	70 mg	PENDING
1	FED	70 mg	PENDING
1	DISSOLUTION	20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg	INADEQUATE

I. EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

There is no USP method for this product, however there is an FDA-recommended method: 900 mL 0.1 N Hydrochloric acid using USP Apparatus II (paddle) at 50 rpm. The firm conducted dissolution testing using the FDA-recommended method and used sinker. The firm's dissolution method is acceptable. However, its proposed specification of NLT 80% (Q) in 20 minutes is unacceptable. Based on data submitted, the Division of Bioequivalence (DB) II recommends the following specification:

NLT (b) (4) (Q) of the labeled amount of drug is dissolved in 15 minutes.

The firm should indicate if it accepts the FDA-recommended specification

The firm conducted long-term storage stability (LTSS) testing data demonstrating stability of Lisdexamfetamine, and its metabolite dextroamphetamine in human plasma with K_2EDTA for 42 days at -20^{o}C, which is sufficient to cover the maximum storage period of study samples in the fasting and fed bioequivalence studies.

The firm provided all the SAS data files for the fasting (#LISD-C70-PVFS-1) and fed (#LISD-C70-PVFD-1) BE studies in the correct format (xpt).

The firm submitted all the requested summary bio-tables in both PDF and MSWord format.

The DB II will review the fasting and fed BE studies and waiver requests at a later date.

The dissolution testing is **incomplete** pending firm's acknowledgment of the FDA-recommended specification.

Table 1: SUBMISSION CONTENT CHECKLIST

Information			YES	NO	N/A
Did the firm use the FDA-recommended dissolution method			☒	☐	☐
Did the firm use the USP dissolution method			☐	☐	☒
Did the firm use 12 units of both test and reference in dissolution testing			☒	☐	☐
Did the firm provide complete dissolution data (all raw data, range, mean, % CV, dates of dissolution testing)			☒	☐	☐
Did the firm conduct dissolution testing with its own proposed method			☐	☒	☐
Is FDA method in the public dissolution database (on the web)			☒	☐	☐
SAS datasets submitted to the electronic document room (edr)	Fasting BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Fed BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Other study	PK parameters	☐	☐	☒
		Plasma concentrations	☐	☐	☒
Are the DBE Summary Tables present an in either PDF and/or MS Word Format?			☒	☐	☐
If any of the tables are missing or incomplete please indicate that in the comments and request the firm to provide the complete DBE Summary Tables 1-16.					
Is the Long Term Storage Stability (LTSS) sufficient to cover the maximum storage time of the study samples?			☒	☐	☐
If the LTSS is NOT sufficient please request the firm to provide the necessary data.					

External Dissolution Database

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Lisdexamfetamine Dimesylate	Capsule	II (Paddle)	50	0.1 N HCl	900	5, 10, 15 and 20	10/06/2008

Specification from Internal Dissolution database: NLT (b) (4) % (Q) in 15 minutes.

Table 2: SUMMARY OF IN VITRO DISSOLUTION DATA

Dissolution Conditions			Apparatus:		USP Apparatus II (Paddles) with sinkers					
			Speed of Rotation:		50 rpm					
			Medium:		0.1 N HCl					
			Volume:		900 mL					
			Temperature		37.0º +/- 0.5º C					
Firm's Proposed Specifications			NLT (b)(4)% (Q) of the labeled amount dissolves in 20 minutes							
Dissolution Testing Site (Name, Address)			(b) (4)							
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference - Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)				Study Report Location
						5	10	15	20	COA Attached to 5.3.1.3
Study Report #: NA	10/4/2010	Vyvanse® (Lisdexamfetamine dimesylate) Capsules, 20 mg Shire US Inc. Lot No. 8001432A Expiration Date 5/2011	20 mg Capsules	12	Average	85	97	98	99	
					Range	(b) (4)				
					%RSD	16.5	5.6	3.1	2.4	
Study Report #: NA	10/4/2010	Lisdexamfetamine dimesylate Capsules, 20 mg Roxane Laboratories Lot No. 4000480 Manufacture Date: 9/14/2010	20 mg Capsules	12	Average	61	95	99	99	
					Range	(b) (4)				
					%RSD	52.1	7.6	3.5	2.2	

Dissolution Conditions			Apparatus:	USP Apparatus II (Paddles) with sinkers						
			Speed of Rotation:	50 rpm						
			Medium:	0.1 N HCl						
			Volume:	900 mL						
			Temperature	37.0º +/- 0.5º C						
Firm's Proposed Specifications			NLT (b)(4)% (Q) of the labeled amount dissolves in 20 minutes							
Dissolution Testing Site (Name, Address)			(b) (4)							
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference - Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)				Study Report Location
						5	10	15	20	COA Attached to 5.3.1.3
Study Report #: NA	10/5/2010	Vyvanse® (Lisdexamfetamine dimesylate) Capsules, 30 mg Shire US Inc. Lot No. 3073098 Expiration Date 5/2011	30 mg Capsules	12	Average	70	95	98	99	
					Range	(b) (4)				
					%RSD	20.4	6.1	3.5	2.9	
Study Report #: NA	10/5/2010	Lisdexamfetamine dimesylate Capsules, 30 mg Roxane Laboratories Lot No. 4000481 Manufacture Date: 9/15/2010	30 mg Capsules	12	Average	73	91	96	97	
					Range	(b) (4)				
					%RSD	21.9	9.9	5.5	3.9	

Dissolution Conditions			Apparatus:		USP Apparatus II (Paddles) with sinkers					
			Speed of Rotation:		50 rpm					
			Medium:		0.1 N HCl					
			Volume:		900 mL					
			Temperature		37.0º +/- 0.5º C					
Firm's Proposed Specifications			NLT (b) (4) (Q) of the labeled amount dissolves in 20 minutes							
Dissolution Testing Site (Name, Address)			[redacted] (b) (4)							
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference - Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)				Study Report Location
						5	10	15	20	COA Attached to 5.3.1.3
Study Report #: NA	10/4/2010	Vyvanse® (Lisdexamfetamine dimesylate) Capsules, 40 mg Shire US Inc. Lot No. 80014909A Expiration Date 6/2011	40 mg Capsules	12	Average	66	100	101	101	
					Range	[redacted] (b) (4)				
					%RSD	31.6	1.5	1.2	1.4	
Study Report #: NA	10/5/2010	Lisdexamfetamine dimesylate Capsules, 40 mg Roxane Laboratories Lot No. 4000482 Manufacture Date: 9/16/2010	40 mg Capsules	12	Average	74	100	101	101	
					Range	[redacted] (b) (4)				
					%RSD	19.2	1.9	1.6	1.2	

Dissolution Conditions			Apparatus:		USP Apparatus II (Paddles) with sinkers					
			Speed of Rotation:		50 rpm					
			Medium:		0.1 N HCl					
			Volume:		900 mL					
			Temperature		37.0º +/- 0.5º C					
Firm's Proposed Specifications			NLT (b) (4) % (Q) of the labeled amount dissolves in 20 minutes							
Dissolution Testing Site (Name, Address)			(b) (4)							
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference - Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)				Study Report Location
						5	10	15	20	COA Attached to 5.3.13
Study Report #: NA	10/6/2010	Vyvanse® (Lisdexamfetamine dimesylate) Capsules, 50 mg Shire US Inc. Lot No. 3073103 Expiration Date 6/2011	50 mg Capsules	12	Average	41	82	93	96	
					Range	17-65	62-99	84-102	89-102	
					%RSD	41.3	14.8	6.5	4.1	
Study Report #: NA	10/6/2010	Lisdexamfetamine dimesylate Capsules, 50 mg Roxane Laboratories Lot No. 4000483 Manufacture Date: 9/16/2010	50 mg Capsules	12	Average	66	97	99	99	
					Range	20-89	91-101	96-100	96-100	
					%RSD	32.1	3.0	1.6	1.6	

Dissolution Conditions			Apparatus:	USP Apparatus II (Paddles) with sinkers						
			Speed of Rotation:	50 rpm						
			Medium:	0.1 N HCl						
			Volume:	900 mL						
			Temperature	37.0º +/- 0.5º C						
Firm's Proposed Specifications			NLT (b) (4)% (Q) of the labeled amount dissolves in 20 minutes							
Dissolution Testing Site (Name, Address)			(b) (4)							
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference - Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)				Study Report Location
						5	10	15	20	COA Attached to 5.3.1.3
Study Report #: NA	10/7/2010	Vyvanse® (Lisdexamfetamine dimesylate) Capsules, 60 mg Shire US Inc. Lot No. 3074084 Expiration Date 6/2011	60 mg Capsules	12	Average	42	86	95	98	
					Range	(b) (4)				
					%RSD	43.5	9.0	3.4	2.1	
Study Report #: NA	10/8/2010	Lisdexamfetamine dimesylate Capsules, 60 mg Roxane Laboratories Lot No. 4000484 Manufacture Date: 9/17/2010	60 mg Capsules	12	Average	58	97	98	98	
					Range	(b) (4)				
					%RSD	29.6	3.2	2.0	1.7	

Dissolution Conditions			Apparatus:		USP Apparatus II (Paddles) with sinkers					
			Speed of Rotation:		50 rpm					
			Medium:		0.1 N HCl					
			Volume:		900 mL					
			Temperature		37.0º +/- 0.5º C					
Firm's Proposed Specifications			NLT (b) (4)% (Q) of the labeled amount dissolves in 20 minutes							
Dissolution Testing Site (Name, Address)			(b) (4)							
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference - Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes)				Study Report Location
						5	10	15	20	COA Attached to 5.3.1.3
Study Report #: NA	6/6/2010	Vyvanse® (Lisdexamfetamine dimesylate) Capsules, 70 mg Shire US Inc. Lot No. 3074098 Expiration Date 7/2011	70 mg Capsules	12	Average	74	97	100	100	
					Range	(b) (4)				
					%RSD	22.0	6.7	2.8	1.4	
Study Report #: NA	6/16/2010	Lisdexamfetamine dimesylate Capsules, 70 mg Roxane Laboratories Lot No. 4000324 Manufacture Date: 6/24/2010	70 mg Capsules	12	Average	38	94	97	98	
					Range	(b) (4)				
					%RSD	32.0	4.2	2.3	1.6	

II. COMMENTS

1. The firm conducted dissolution testing for Lisdexamfetamine Dimesylate Capsules, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg, comparing it to Shire Development's Vyvanse® (lisdexamfetamine dimesylate) Capsules, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg using the FDA-recommended method. The firm also used sinker. The firm's dissolution method is acceptable. However, its proposed specification of NLT (b) (4)% (Q) in 20 minutes is unacceptable. Based on data submitted, the Division of Bioequivalence II (DB II) recommends the following specification:

   NLT (b) (4)% (Q) of the labeled amount of drug is dissolved in 15 minutes.

   The firm should indicate if it accepts the FDA-recommended specification.

2. The firm conducted long-term storage stability (LTSS) testing data demonstrating stability of Lisdexamfetamine, and its metabolite dextroamphetamine in human plasma with K_2EDTA for 42 days at -20^{o}C, which is sufficient to cover the maximum storage period of study samples in the fasting (#LISD-C70-PVFS-1) and fed (#LISD-C70-PVFD-1) BE studies.

3. The firm submitted electronic SAS transport files (*.xpt) in Module 5.3.1.2.25 Individual Subject Data Listing.

4. The DB II summary tables are located in Module 2.7 Clinical Summary.

5. The DB II will review the fasting and fed BE studies and waiver requests at a later date.

6. The dissolution testing is **incomplete** pending firm's acknowledgment of the FDA-recommended specification.

III. DEFICIENCY COMMENTS

The firm submitted the dissolution testing data using a modification of the FDA-recommended method: 900 mL 0.1 N Hydrochloric acid using USP Apparatus II (paddle) with sinker at 50 rpm. The firm's dissolution method is acceptable however, its proposed specification of NLT (b) (4)% (Q) in 20 minutes is unacceptable. Based on data submitted, the DB II recommends the following specification:

NLT 80% (Q) of the labeled amount of drug is dissolved in 15 minutes.

The firm should indicate if it accepts the FDA-recommended specification.

IV. RECOMMENDATIONS

The firm submitted the dissolution testing data using a modification of the FDA-recommended method: 900 mL 0.1 N Hydrochloric acid using USP Apparatus II (paddle) with sinker at 50 rpm. The firm's dissolution method is acceptable however, its proposed specification of NLT (b) (4)% (Q) in 20 minutes is unacceptable. Based on data submitted, the DB II recommends the following specification:

NLT (b) (4)% (Q) of the labeled amount of drug is dissolved in 15 minutes.

The firm should indicate if it accepts the FDA-recommended specification.

(b) (4)

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BIOEQUIVALENCE DEFICIENCY

ANDA: 202827

APPLICANT: Roxane Laboratories, Inc.

DRUG PRODUCT: Lisdexamfetamine Dimesylate Capsules
20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg

The Division of Bioequivalence II (DB II) has completed its review of only the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the fasting and fed bioequivalence studies and waiver requests will be conducted later. The following deficiency has been identified:

We agree with the use of the following dissolution method:

Medium: 900 mL 0.1 N Hydrochloric acid
Apparatus: USP Apparatus II (paddle) with sinker
Speed: 50 rpm

However, your proposed specification of NLT (b)(4)% (Q) in 20 minutes is unacceptable. Based on data submitted, the DB II recommends the following specification:

NLT 80% (Q) of the labeled amount of drug is dissolved in 15 minutes.

Please indicate if you accept the above FDA-recommended specification.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

VI. OUTCOME

ANDA 202827

Completed Assignment for 202830 ID: 14879

Reviewer: Huynh, Huong **Date Completed:**

Verifier: **Date Verified:**

Division: Division of Bioequivalence

Description: Lisdexamfetamine Dimesylate Capsules, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg

---

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
14879	2/23/2011	Dissolution Data	Dissolution Review	1	1
				Bean Total:	1

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY POINTS ANDA 202827		
Dissolution Study/Dissolution Waiver		
Dissolution Review	1	
	TOTAL	**1**

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/s/

HUONG T HUYNH
09/08/2011

KULDEEP R DHARIWAL
09/08/2011

ETHAN M STIER on behalf of BARBARA M DAVIT
09/23/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202827Orig1s000

CHEMISTRY REVIEW(S)

Recommendation | Adequate

Notes:

- **API and DP** are not still USP Compendial
- **DMF 022442 –** Adequate (Previous 6/17/2022)
- **DMF 022442 –** Adequate per Current Panorama dated *4/10/2023*.
- **Labeling -** Adequate per Current Panorama dated 6/21/2023.

ANDA 202827

Lisdexamfetamine Dimesylate Capsules
20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg

Mohmmed K Ahmed

DIMRP1 | OLDP | CDER | OPQ| FDA

Hikma Pharmaceuticals USA Inc.

Table of Contents

Table of Contents ..... **i**

Chemistry Review Data Sheet **1**

1. ANDA 202827 1
2. REVIEW # 6 1
3. REVIEW DATE: 1
4. REVIEWER: 1
5. PREVIOUS DOCUMENTS: 1
6. SUBMISSION(S) BEING REVIEWED: 1
7. NAME & ADDRESS OF APPLICANT: 2
8. DRUG PRODUCT NAME/CODE/TYPE: 2
9. LEGAL BASIS FOR SUBMISSION: 2
10. PHARMACOL. CATEGORY: 3
11. DOSAGE FORM: 3
12. STRENGTH/POTENCY: 4
13. ROUTE OF ADMINISTRATION: 4
14. Rx/OTC DISPENSED: _X_Rx ___OTC 4
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): 4
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: 4
17. RELATED/SUPPORTING DOCUMENTS: 4
18. STATUS 5
19. ORDER OF REVIEW 6

Executive Summary **7**

I. Recommendations 7

A. Recommendation and Conclusion on Approvability 7

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 7

II. Summary of Chemistry Assessments 7

A. Description of the Drug Product(s) and Drug Substance(s) 7

B. Description of How the Drug Product is Intended to be Used 8

Basis for Approvability or Not-Approval Recommendation 8

Chemistry Assessment 9

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body of Data based on QbR-QOS 9

2.3 Introduction to the Quality Overall Summary 9

2.3.S DRUG SUBSTANCE 9
2.3.S.1 General Information 9
2.3.S.2 Manufacture 12
2.3.S.3 Characterization 14
2.3.S.4 Control of Drug Substance 15
2.3.S.5 Reference Standards or Materials 43
2.3.S.6 Container Closure System 46
2.3.S.7 Stability 47

2.3.P DRUG PRODUCT 47
2.3.P.1 Description and Composition of the Drug Product 47
2.3.P.2 Pharmaceutical Development 55
2.3.P.3 Manufacture 71
2.3.P.4 Control of Excipients 111
2.3.P.5 Control of Drug Product 112
2.3.P.6 Reference Standards or Materials 129
2.3.P.7 Container Closure System 130
2.3.P.8 Stability 132

A APPENDICES 137
A.1 Facilities and Equipment (biotech only) 137
A.2 Adventitious Agents Safety Evaluation 137
A.3 Novel Excipients 137

R REGIONAL INFORMATION 138
R.1 Executed Batch Records 138
R.2 Comparability Protocols 138
R.3 Methods Validation Package 138

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 138

A. Labeling & Package Insert 138

B. Environmental Assessment or Claim of Categorical Exclusion 139

III. List Of Deficiencies To Be Communicated 139

Chemistry Review Data

1. **ANDA: 202827**
2. **REVIEW #: 6**
3. **REVIEW DATE: 7/17/2023**
4. **REVIEWERS: Ying Zhang / Mohammed K Ahmed**
5. **PREVIOUS DOCUMENTS:**

Previous Document(s)	Document Date
Original Submission	2/23/2011
Amendment	4/8/2011
Amendment	4/22/2011
Chemistry Review #1	8/30/2012
Amendment	2/6/2013
General Correspondence	7/25/2013
Chemistry Review #2	10/18/2013
General Correspondence	10/18/2013
Amendment	2/13/2014
Amendment	4/4/2014
Amendment	5/22/2014
Amendment	5/23/2014

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Labeling-Response to Discipline Review Letter	6/9/2023
Response to Information Request - Quality - Minor	6/6/2023
Resubmission – Minor – Complete Response Amendment – Product Quality / Labeling	3/29/2023
Labeling Minor	11/23/2022
Minor Amendment – Final Approval Requested Amendment 29	9/19/2022
Administrative Amendment	4/19/2016

7. NAME & ADDRESS OF APPLICANT (356h):

Name: Hikma Pharmaceuticals USA Inc. (Former: Roxane Laboratories Inc.)
Address: 1809 Wilson Road Columbus, OH 43228
US Agent: N/A
Email Address: dra-columbus@Hikma.com

Contact Person: George E. Prestash IV, Associate Director, RA / Shane Shupe, Director, RA

Telephone: 614-241-4145 (GP) / (b) (6)) Fax: 614-276-2470

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: None
Non-Proprietary Name (USAN): Lisdexamfetamine Dimesylate Capsules

9. LEGAL BASIS FOR SUBMISSION:

The basis of Roxane Laboratories Inc. proposed ANDA for Lisdexamfetamine Dimesylate Capsules, is the RLD, Vyvanse 70 mg (NDA 21977) manufactured by Shire Development. According to information published in Approved Drug Products with Therapeutic equivalence Evaluation (Electronic Orange Book), Vyvanse is covered by several patents and exclusivities, which are listed below:

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N021977	003	7105486	Jun 29, 2023			U - 727	
N021977	003	7223735	Jun 29, 2023		Y		
N021977	003	7655630	Feb 24, 2023	Y			
N021977	003	7659253	Feb 24, 2023	Y	Y	U - 727	
N021977	003	7659254	Feb 24, 2023			U - 1034	
N021977	003	7662787	Feb 24, 2023	Y			
N021977	003	7662788	Feb 24, 2023			U - 727	
N021977	003	7671030	Feb 24, 2023		Y	U - 727	
N021977	003	7671031	Feb 28, 2023			U - 727	
N021977	003	7674774	Mar 18, 2023		Y	U - 842	
N021977	003	7678770	Mar 25, 2023			U - 842	
N021977	003	7678771	Mar 25, 2023		Y	U - 842	
N021977	003	7687466	Feb 24, 2023		Y		
N021977	003	7687467	Apr 8, 2023		Y	U - 842	
N021977	003	7700561	Jun 29, 2023		Y		
N021977	003	7713936	Feb 24, 2023			U - 727	
N021977	003	7718619	Feb 24, 2023		Y	U - 842	
N021977	003	7723305	Feb 24, 2023		Y	U - 842	

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
N021977	003	NCE	Feb 23, 2012
N021977	003	I - 645	Jan 31, 2015
N021977	003	M - 82	Apr 5, 2013
N021977	003	NPP	Nov 10, 2013
N021977	003	NPP	Apr 23, 2011

The applicant provided a Paragraph IV patent certification in module 1.3.5.2, and they stated they will not market the product until the exclusivity expires and upon approval of this ANDA.

10. **PHARMACOL. CATEGORY:** Indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in adults and pediatric patients 6 years and older.

11. **DOSAGE FORM:** Capsule

12. **STRENGTH/POTENCY:** 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg.

13. **ROUTE OF ADMINISTRATION:** Oral

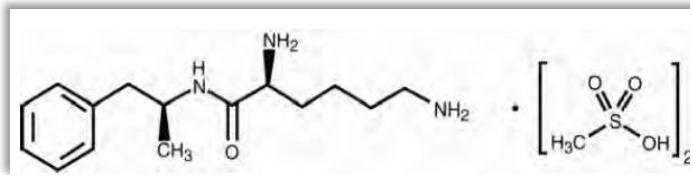
14. **Rx/OTC DISPENSED:** _X_ **Rx** ___ **OTC**

15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):**

_____SPOTS product – Form Completed

__X___Not a SPOTS product

16. **CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

USAN	Lisdexamfetamine Dimesylate
Chemical name	(2S)-2,6-diamino-N-[(1S)-1-methyl-2-phenylethyl]hexanamide Dimethylsulfonate.
Molecular Formula	$C_{15}H_{25}N_3O \cdot (CH_4O_3S)_2$
Molecular Weight	455.60
CAS number	608137-33-3
Chemical Structure	

17. **RELATED/SUPPORTING DOCUMENTS:**

A. DMFs:

Chemistry Review Data Sheet

(b) (4)

Updated as per Form 356h dated 6/6/2023:

DMFs	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS2	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Lisdexamfetamine Dimesylate	3	Adequate	6/17/2022/ 4/10/2023	By DMF Team
	III		(b) (4)				
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

[1] Action codes for DMF Table: 1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available

7 – Other (explain under "Comments") Chemistry Review Data Sheet

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS as Panorama (Current):

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology ECD / IR and Consults	Complete	3/30/2023	Not Indicated.
EES	Acceptable	As of 3/6/2014*	

Methods Validation	N/A		
Labeling	In-Adequate Minor→ Adequate	10/31/2022→ 6/21/2023	Alison Park
Bioequivalence	Acceptable	9/20/2022	Bio. Coordinator
Biopharmaceutics	No Action indicated		
EA	Categorical exclusion claimed		
Radiopharmaceutical	N/A		

*** Overall Re-eval date: 6/29/2014**

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ___No If no, explain reason(s) below:

20. RLD Information as per Form 356h:

20. If an ANDA, or 505(b)(2), identify the listed drug product that is/are the basis for the submission.

Name of Drug: VYVANSE® (lisdexamfetamine dimesylate) Capsules Application Number of Relied Upon Product: 021977

Indicate Patent Certification: ☐ P1 ☐ P2 ☐ P3 ☑ P4 ☐ Section viii - MOU ☐ Statement of no relevant patents

Chemistry Review for ANDA 202827:

Executive Summary:

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable per CMC perspective. DMF is adequate.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

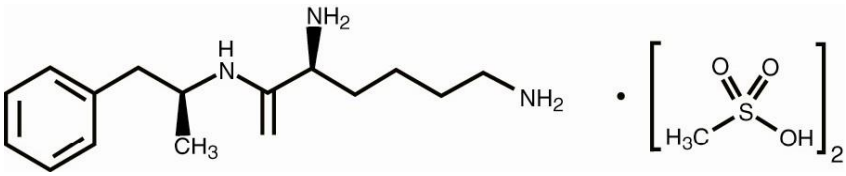
None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Lisdexamfetamine Dimesylate Capsules are designed as a capsule for once-a-day oral administration. The chemical designation for Lisdexamfetamine Dimesylate is (2S)-2,6-diamino-*N*-[(1*S*)-1-methyl-2-phenylethyl] hexanamide dimethanesulfonate. The molecular formula is C15H25N3O•(CH4O3S)2, which corresponds to a molecular weight of 455.60.

The chemical structure is:



Lisdexamfetamine dimesylate is a white to off-white powder that is soluble in water (792 mg/mL). Lisdexamfetamine dimesylate capsules contain 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg of Lisdexamfetamine dimesylate and the following inactive ingredients: ammonium hydroxide, calcium phosphate, gelatin, iron oxide black, isopropyl alcohol, magnesium stearate, microcrystalline cellulose, n-butyl alcohol, propylene glycol, shellac glaze, sodium starch glycolate, and titanium dioxide. In addition, the 20 mg capsule also contains yellow iron oxide. The 30 mg capsule also contains FD&C yellow #6. The 40 mg capsule also contains FD&C blue #1 and FD&C green #3. The 50 mg and 60 mg capsules also contain D&C red #28 and FD&C blue #1. The 70 mg capsule also contains D&C red #28, FD&C blue #1, and FD&C yellow #6.

B. Description of How the Drug Product is Intended to be Used

Lisdexamfetamine is a prodrug of dextroamphetamine. After oral administration, Lisdexamfetamine is rapidly absorbed from the gastrointestinal tract and converted to dextroamphetamine, which is responsible for the drug's activity. Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known. Amphetamines are thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. The parent drug, Lisdexamfetamine, does not bind to the sites responsible for the reuptake of norepinephrine and dopamine *in vitro*.

The maximum recommended daily dose is 70 mg / day, according to the label.

C. Basis for Approvability or Not-Approval Recommendation

Approvable

Chemistry Assessment

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body of Data based on QbR-QOS

2.3 Introduction to the Quality Overall Summary

Proprietary Name of Drug Product	N/A
Non-Proprietary Name of Drug Product	Lisdexamfetamine Dimesylate Capsules, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg.
Non-Proprietary Name of Drug Substance	Lisdexamfetamine Dimesylate.
Company Name	Hikma Pharmaceuticals USA Inc. (Former Roxane Laboratories Inc.)
Dosage Form	Capsule
Strength (s)	20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg.
Route of Administration	Oral
Proposed Indication(s)	Indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in adults and pediatric patients 6 years and older.

2.3.S - DRUG SUBSTANCE | Adequate

2.3.S.1 – General Information | Adequate

Firm's Response: Following data belongs to Tentative Approval dated 6/23/2014.

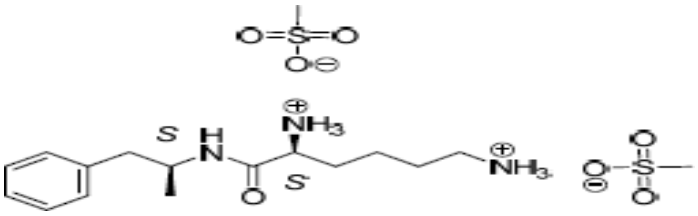
What are the nomenclature, molecular structure, molecular formula, and molecular weight?

Nomenclature:

(2S)-2,6-diamino-N-[(1S)-1-methyl-2-phenylethyl] hexanamide dimethyl sulfonate.

Synonym: Hexanamide, 2,6-diamino-N-[(1S)-1-methyl-2-phenylethyl] – (2S)-,dimethyl sulfonate

Molecular Structure:



Molecular formula: $C_{15}H_{25}N_3O \cdot (CH_4O_3S)_2$; Molecular Weight: 455.60; CAS #: 608137-33-3.

Reviewer's Assessment: Remains SATISFACTORY as per current submission dated 9/19/2022.

The drug substance does not have a monograph in current USP. The information provided by the sponsor has been verified by the reviewer with Merck Index.

What are the physicochemical properties including physical description, pKa, polymorphism, aqueous solubility (as function of pH), hygroscopicity, melting points, and partition coefficient?

Firm's Response: Following data belongs to Tentative Approval dated 6/23/2014.

Physical Description: Lisdexamfetamine Dimesylate is a white to off white crystalline powder.

pKa: not available

Polymorphism: No information is available in literature suggesting the existence of polymorphism for Lisdexamfetamine Dimesylate. However, a control of the crystalline form at time of the API release is performed.

Solubility Characteristics:
Solubility in water is 792 mg/mL. Solubility in 95% aqueous ethanol is 1 part per 5 parts.

Chemistry Assessment Section

(b) (4)

Hygroscopicity: Lisdexamfetamine Dimesylate, (b) (4) is not hygroscopic.

(b) (4)

Melting Point: approximately 193°C as performed by the supplier.

Chirality: Lisdexamfetamine Dimesylate has two asymmetric carbon centers. They are both in the S configuration. (b) (4)

Reviewer's Comment: ~~NOT~~ SATISFACTORY

The information regarding the properties of the drug substance provided by the ANDA sponsor is more detailed than what is contained in the DMF (b) (4) 2). The data for physical description and solubility match the information in Merck Index. According to Merck Index, the melting point should be 120 - 122°C, (b) (4)

therefore, we will not comment.

The firm did not provide the solubility information for different pH values.

Deficiency:

Provide solubility data across the physiological pH range. If such data is not available in the literature, then you should determine it experimentally.

Chemistry Assessment Section

Response: ACCEPTABLE

Requested information was provided and has been incorporated into the text above.

2.3.S.2 – Manufacture | Adequate

Who manufactures the drug substance?

How do the manufacturing processes and controls ensure consistent production of drug substance?

Following Information as per Amendment for Final approval dated 9/19/2022.

Cover Letter Notes:

Drug Substance

The drug substance section has been revised to provide for recent updates received from the drug substance manufacturer (b) (4) Please refer to Section 3.2.S.2.1 for a detailed list of changes and an updated Manufacturer document. Additionally, a summary of the changes that were made to the Drug Substance Specification (20001632R-01) to comply with current compendia and Hikma site requirements are further detailed in Section 3.2.S.4.1.

(b) (4)

181 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

ADMINISTRATIVE:

A. Reviewer's Signature

B. Endorsement Block

Mohammed K Ahmed, Review Chemist/ 11/20/2022, 11/22/2022, 11/23/2022; 6/1/2023, 6/2/2023; 7/19/2023; 7/21/2023.

Vijay Sharma, Ph.D./ATL/ November 24, 2022; June 02, 2023; July 21, 2023

Kevin Ninan / OPQ RBPM /

TYPE OF LETTER: CMC Acceptable.

Mohammed Ahmed

Digitally signed by Mohammed Ahmed
Date: 7/31/2023 10:05:31AM
GUID: 508da705000289d2784a9f95c27536e8

Vijay Sharma

Digitally signed by Vijay Sharma
Date: 7/31/2023 08:14:27AM
GUID: 558186220030c277f07ae3f71171ed7c

Recommendation | Inadequate-CR-Minor

Notes:

- **API and DP are not USP Compendial**
- **DMF (b) (4) – Adequate (*June 17, 2022*)**

ANDA 202827

Lisdexamfetamine Dimesylate Capsules
20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg

Mohmmed K Ahmed

DIMRP1 | OLDP | CDER | OPQ| FDA

Hikma Pharmaceuticals

USA Inc.

Table of Contents

Table of Contents ..... **i**

Chemistry Review Data Sheet **1**

1. ANDA 202827 1
2. REVIEW # 4 1
3. REVIEW DATE: 1
4. REVIEWER: 1
5. PREVIOUS DOCUMENTS: 1
6. SUBMISSION(S) BEING REVIEWED: 1
7. NAME & ADDRESS OF APPLICANT: 2
8. DRUG PRODUCT NAME/CODE/TYPE: 2
9. LEGAL BASIS FOR SUBMISSION: 2
10. PHARMACOL. CATEGORY: 3
11. DOSAGE FORM: 3
12. STRENGTH/POTENCY: 4
13. ROUTE OF ADMINISTRATION: 4
14. Rx/OTC DISPENSED: _X_Rx ___OTC 4
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): 4
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: 4
17. RELATED/SUPPORTING DOCUMENTS: 4
18. STATUS 5
19. ORDER OF REVIEW 6

Executive Summary **7**

I. Recommendations 7

A. Recommendation and Conclusion on Approvability 7

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 7

II. Summary of Chemistry Assessments 7

A. Description of the Drug Product(s) and Drug Substance(s) 7

B. Description of How the Drug Product is Intended to be Used 8

Basis for Approvability or Not-Approval Recommendation 8

Chemistry Assessment 9

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body of Data based on QbR-QOS 9

2.3 Introduction to the Quality Overall Summary 9

2.3.S DRUG SUBSTANCE 9
2.3.S.1 General Information 9
2.3.S.2 Manufacture 12
2.3.S.3 Characterization 14
2.3.S.4 Control of Drug Substance 15
2.3.S.5 Reference Standards or Materials 43
2.3.S.6 Container Closure System 46
2.3.S.7 Stability 47

2.3.P DRUG PRODUCT 47
2.3.P.1 Description and Composition of the Drug Product 47
2.3.P.2 Pharmaceutical Development 55
2.3.P.3 Manufacture 71
2.3.P.4 Control of Excipients 111
2.3.P.5 Control of Drug Product 112
2.3.P.6 Reference Standards or Materials 129
2.3.P.7 Container Closure System 130
2.3.P.8 Stability 132

A APPENDICES 137
A.1 Facilities and Equipment (biotech only) 137
A.2 Adventitious Agents Safety Evaluation 137
A.3 Novel Excipients 137

R REGIONAL INFORMATION 138
R.1 Executed Batch Records 138
R.2 Comparability Protocols 138
R.3 Methods Validation Package 138

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 138

A. Labeling & Package Insert 138

B. Environmental Assessment or Claim of Categorical Exclusion 139

III. List Of Deficiencies To Be Communicated 139

Chemistry Review Data

1. **ANDA: 202827**

2. **REVIEW #: 4**

3. **REVIEW DATE: 11/8/2022**

4. **REVIEWERS: Ying Zhang / Mohammed K Ahme**

5. **PREVIOUS DOCUMENTS:**

Previous Document(s)	Document Date
Original Submission	2/23/2011
Amendment	4/8/2011
Amendment	4/22/2011
Chemistry Review #1	8/30/2012
Amendment	2/6/2013
General Correspondence	7/25/2013
Chemistry Review #2	10/18/2013
General Correspondence	10/18/2013
Amendment	2/13/2014
Amendment	4/4/2014
Amendment	5/22/2014
Amendment	5/23/2014

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	Document Date
Minor Amendment – Final Approval Requested Amendment 29	9/19/2022
Administrative Amendment	4/19/2016

7. NAME & ADDRESS OF APPLICANT:

Name: Hikma Pharmaceuticals USA Inc. (Former: Roxane Laboratories Inc.)
Address: 1809 Wilson Road
Columbus, OH
43228
US Agent: N/A
Email Address: dra-columbus@Hikma.com
Contact Person: George E. Prestash IV, Associate Director, RA / Shane Shupe, Director, RA

Telephone: 614-241-4145 (GP)
/ (b) (4)
Fax: 614-276-2470

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: None
Non-Proprietary Name (USAN): Lisdexamfetamine Dimesylate Capsules

9. LEGAL BASIS FOR SUBMISSION:

The basis of Roxane Laboratories Inc. proposed ANDA for Lisdexamfetamine Dimesylate Capsules, is the RLD, Vyvanse 70 mg (NDA 21977) manufactured by Shire Development. According to information published in Approved Drug Products with Therapeutic equivalence Evaluation (Electronic Orange Book), Vyvanse is covered by several patents and exclusivities, which are listed below:

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N021977	003	7105486	Jun 29, 2023			U - 727	
N021977	003	7223735	Jun 29, 2023		Y		
N021977	003	7655630	Feb 24, 2023	Y			
N021977	003	7659253	Feb 24, 2023	Y	Y	U - 727	
N021977	003	7659254	Feb 24, 2023			U - 1034	
N021977	003	7662787	Feb 24, 2023	Y			
N021977	003	7662788	Feb 24, 2023			U - 727	
N021977	003	7671030	Feb 24, 2023		Y	U - 727	
N021977	003	7671031	Feb 28, 2023			U - 727	
N021977	003	7674774	Mar 18, 2023		Y	U - 842	
N021977	003	7678770	Mar 25, 2023			U - 842	
N021977	003	7678771	Mar 25, 2023		Y	U - 842	
N021977	003	7687466	Feb 24, 2023		Y		
N021977	003	7687467	Apr 8, 2023		Y	U - 842	
N021977	003	7700561	Jun 29, 2023		Y		
N021977	003	7713936	Feb 24, 2023			U - 727	
N021977	003	7718619	Feb 24, 2023		Y	U - 842	
N021977	003	7723305	Feb 24, 2023		Y	U - 842	

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
N021977	003	NCE	Feb 23, 2012
N021977	003	I - 645	Jan 31, 2015
N021977	003	M - 82	Apr 5, 2013
N021977	003	NPP	Nov 10, 2013
N021977	003	NPP	Apr 23, 2011

The applicant provided a Paragraph IV patent certification in module 1.3.5.2, and they stated they will not market the product until the exclusivity expires and upon approval of this ANDA.

10. PHARMACOL. CATEGORY: Indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in adults and pediatric patients 6 years and older.

11. DOSAGE FORM: Capsule

12. STRENGTH/POTENCY: 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg

13. ROUTE OF ADMINISTRATION: Oral

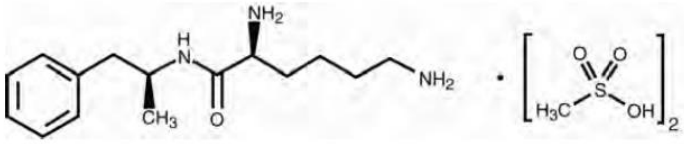
14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

USAN	Lisdexamfetamine Dimesylate
Chemical name	(2S)-2,6-diamino-N-[(1S)-1-methyl-2-phenylethyl]hexanamide Dimethylsulfonate.
Molecular Formula	$C_{15}H_{25}N_3O \cdot (CH_4O_3S)_2$
Molecular Weight	455.60
CAS number	608137-33-3
Chemical Structure	

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Lisdexamfetamine Dimesylate	3	Adequate	6/17/2022	By DMF Team
	III		(b) (4)	4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	As of 3/6/2014*	
Methods Validation	N/A		
Labeling	In-Adequate Minor	10/31/2022	Alison Park
Bioequivalence	Acceptable	9/20/2022	Bio. Coordinator
Biopharmaceutics	Pending		
EA	Categorical exclusion claimed		
Radiopharmaceutical	N/A		

*** Overall Re-eval date: 6/29/2014**

19.ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes _____No If no, explain reason(s) below:

Chemistry Review for ANDA 202827:

Executive Summary:

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable per CMC perspective. DMF is adequate.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

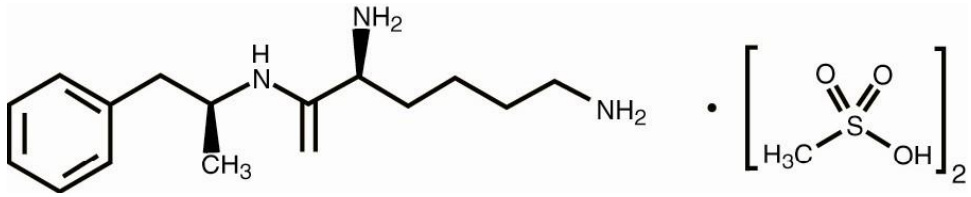
None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Lisdexamfetamine Dimesylate Capsules are designed as a capsule for once-a-day oral administration. The chemical designation for Lisdexamfetamine Dimesylate is (2S)-2,6-diamino-*N*-[(1*S*)-1-methyl-2-phenylethyl] hexanamide dimethanesulfonate. The molecular formula is C15H25N3O•(CH4O3S)2, which corresponds to a molecular weight of 455.60.

The chemical structure is:



Lisdexamfetamine dimesylate is a white to off-white powder that is soluble in water (792 mg/mL). Lisdexamfetamine dimesylate capsules contain 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg of Lisdexamfetamine dimesylate and the following inactive ingredients: ammonium hydroxide, calcium phosphate, gelatin, iron oxide black, isopropyl alcohol, magnesium stearate, microcrystalline cellulose, n-butyl alcohol, propylene glycol, shellac glaze, sodium starch glycolate, and titanium dioxide. In addition, the 20 mg capsule also contains yellow iron oxide. The 30 mg capsule also contains FD&C yellow #6. The 40 mg capsule also contains FD&C blue #1 and FD&C green #3. The 50 mg and 60 mg capsules also contain D&C red #28 and FD&C blue

#1. The 70 mg capsule also contains D&C red #28, FD&C blue #1, and FD&C yellow #6.

B. Description of How the Drug Product is Intended to be Used

Lisdexamfetamine is a prodrug of dextroamphetamine. After oral administration, Lisdexamfetamine is rapidly absorbed from the gastrointestinal tract and converted to dextroamphetamine, which is responsible for the drug's activity. Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known. Amphetamines are thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. The parent drug, Lisdexamfetamine, does not bind to the sites responsible for the reuptake of norepinephrine and dopamine *in vitro*.

The maximum recommended daily dose is 70mg/day, according to the label.

C. Basis for Approvability or Not-Approval Recommendation

Not Approvable.

Chemistry Assessment

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body of Data based on QbR-QOS

2.3 Introduction to the Quality Overall Summary

Proprietary Name of Drug Product	None
Non-Proprietary Name of Drug Product	Lisdexamfetamine Dimesylate Capsules, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg.
Non-Proprietary Name of Drug Substance	Lisdexamfetamine Dimesylate.
Company Name	Hikma Pharmaceuticals USA Inc. (Former Roxane Laboratories Inc.)
Dosage Form	Capsule
Strength (s)	20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg.
Route of Administration	Oral
Proposed Indication(s)	Indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in adults and pediatric patients 6 years and older.

2.3.S - DRUG SUBSTANCE | Adequate

2.3.S.1 – General Information | Adequate

What are the nomenclature, molecular structure, molecular formula, and molecular weight?

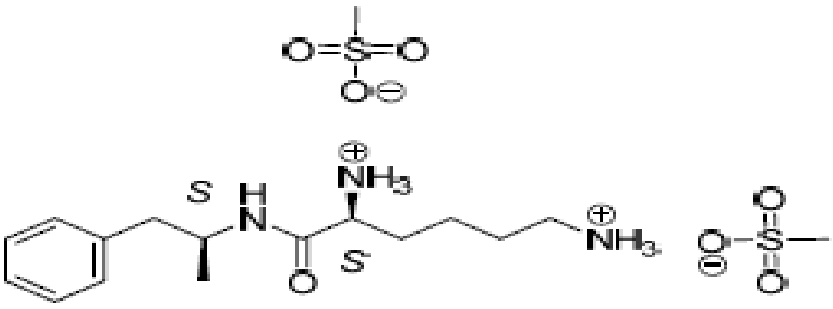
Firm's Response: Following data belongs to Tentative Approval dated 6/23/2014.

Nomenclature:

(2S)-2,6-diamino-N-[(1S)-1-methyl-2-phenylethyl] hexanamide dimethyl sulfonate.

Synonym: Hexanamide, 2,6-diamino-N-[(1S)-1-methyl-2-phenylethyl] – (2S)-,dimethyl sulfonate

Molecular Structure:



Molecular formula: $C_{15}H_{25}N_3O \cdot (CH_4O_3S)_2$; Molecular Weight: 455.60; CAS #: 608137-33-3.

Reviewer's Assessment: Remains SATISFACTORY as per current submission dated 9/19/2022.
The drug substance does not have a monograph in current USP. The information provided by the sponsor has been verified by the reviewer with Merck Index.

What are the physicochemical properties including physical description, pKa, polymorphism, aqueous solubility (as function of pH), hygroscopicity, melting points, and partition coefficient?

Firm's Response: Following data belongs to Tentative Approval dated 6/23/2014.

Physical Description: Lisdexamfetamine Dimesylate is a white to off white crystalline powder.

pKa: not available

Polymorphism: No information is available in literature suggesting the existence of polymorphism for Lisdexamfetamine Dimesylate. (b) (4)

Solubility Characteristics:
Solubility in water is 792 mg/mL. Solubility in 95% aqueous ethanol is 1 part per 5 parts.

(b) (4)

Hygroscopicity: Lisdexamfetamine Dimesylate, (b) (4) (b) (4) is not hygroscopic.

Melting Point: approximately 193°C as performed by the supplier.

Chirality: Lisdexamfetamine Dimesylate has two asymmetric carbon centers. They are both in

the S configuration. [redacted] (b) (4)

Reviewer's Comment: ~~NOT~~ SATISFACTORY

The information regarding the properties of the drug substance provided by the ANDA sponsor is more detailed than what is contained in the DMF [redacted] (b) (4)

The data for physical description and solubility match the information in Merck Index. According to Merck Index, the melting point should be 120 - 122°C, [redacted] (b) (4)

therefore, we will not comment.

The firm did not provide the solubility information for different pH values.

Deficiency:

Provide solubility data across the physiological pH range. If such data is not available in the literature, then you should determine it experimentally.

Chemistry Assessment Section

Response: ACCEPTABLE

Requested information was provided and has been incorporated into the text above.

2.3.S.2 – Manufacture | Adequate

Who manufactures the drug substance?

How do the manufacturing processes and controls ensure consistent production of drug substance?

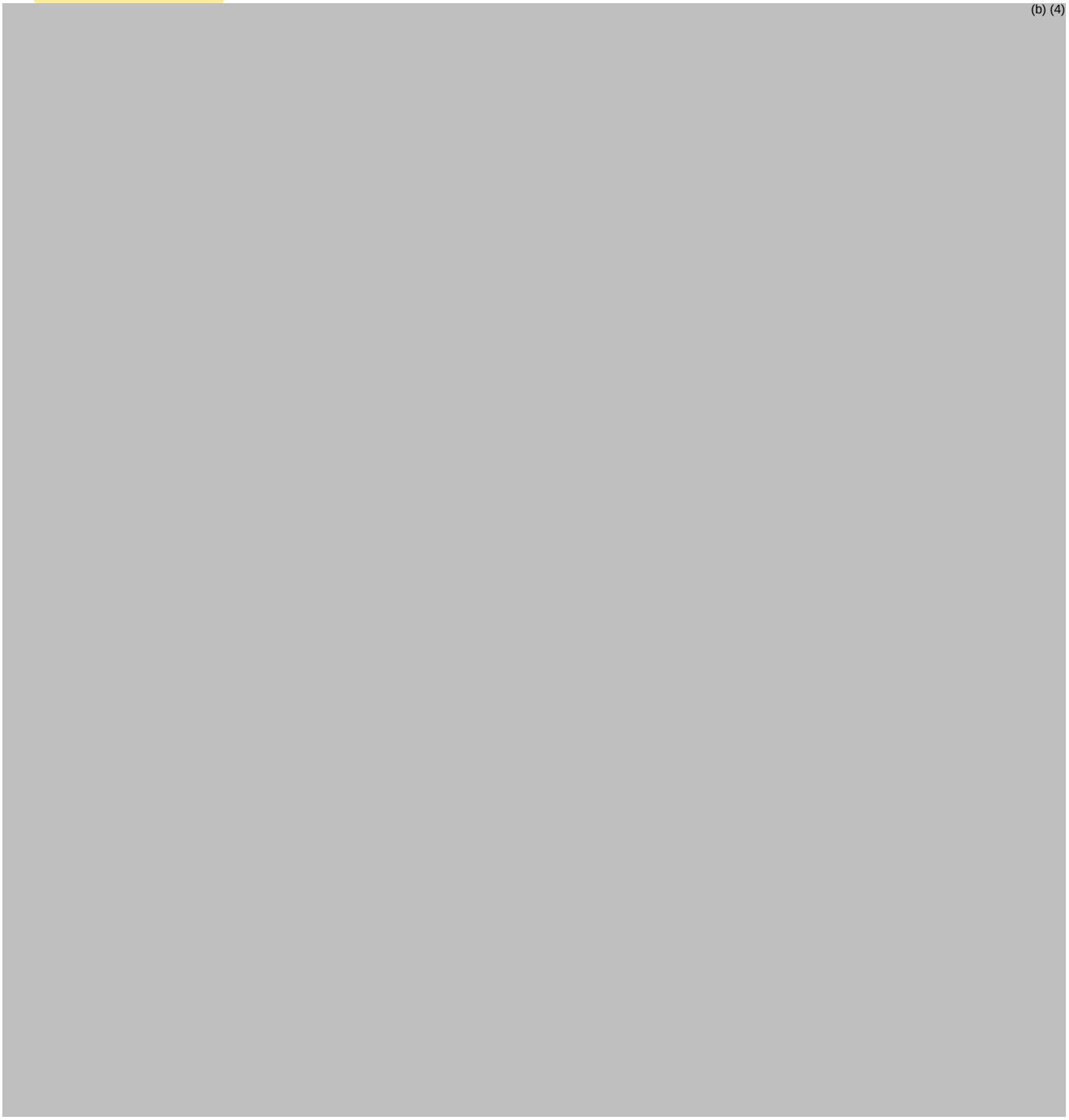
Following Information as per Amendment for Final approval dated 9/19/2022.

Cover Letter Notes:

Drug Substance

The drug substance section has been revised to provide for recent updates received from the drug substance manufacturer [redacted] (b) (4) Please refer to Section 3.2.S.2.1 for a detailed list of changes and an updated Manufacturer document. Additionally, a summary of the changes that were made to the Drug Substance Specification (20001632R-01) to comply with current compendia and Hikma site requirements are further detailed in Section 3.2.S.4.1.

(b) (4)



ADMINISTRATIVE:

A. Reviewer's Signature

B. Endorsement Block

Mohammed K Ahmed, Review Chemist/ 11/20/2022, 11/22/2022, 11/23/2022.

Vijay Sharma, Ph.D./ATL/ November 24, 2022

DeWayne Johnson / OPQ RBPM /

TYPE OF LETTER: CMC Not Acceptable (CR-Minor)

Mohammed Ahmed

Digitally signed by Mohammed Ahmed
Date: 12/02/2022 12:59:18PM
GUID: 508da705000289d2784a9f95c27536e8

Vijay Sharma

Digitally signed by Vijay Sharma
Date: 12/02/2022 02:03:24PM
GUID: 558186220030c277f07ae3f71171ed7c

J. Nguyen 6/11/14
First Generic Drug
No further comment from chemistry perspective.

ANDA 202827

Lisdexamfetamine Dimesylate Capsules
20mg, 30mg, 40mg, 50mg, 60mg and 70mg

Roxane Laboratories, Inc.

Ying Zhang, Ph.D.
Chemistry Division IV
Office of Generic Drugs
Center for Drug Evaluation and Research

Table of Contents

Table of Contents i

Chemistry Review Data Sheet 1

1. ANDA 202-827: 1
2. REVIEW #3: 1
3. REVIEW DATE: 1
4. REVIEWER: 1
5. PREVIOUS DOCUMENTS: 1
6. SUBMISSION(S) BEING REVIEWED: 1
7. NAME & ADDRESS OF APPLICANT: 2
8. DRUG PRODUCT NAME/CODE/TYPE: 2
9. LEGAL BASIS FOR SUBMISSION: 2
10. PHARMACOL. CATEGORY: 3
11. DOSAGE FORM: 3
12. STRENGTH/POTENCY: 4
13. ROUTE OF ADMINISTRATION: 4
14. Rx/OTC DISPENSED: _X_Rx ___OTC 4
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): 4
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: 4
17. RELATED/SUPPORTING DOCUMENTS: 4
18. STATUS 5
19. ORDER OF REVIEW 6

Executive Summary 7

I. Recommendations 7

A. Recommendation and Conclusion on Approvability 7

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 7

II. Summary of Chemistry Assessments 7

A. Description of the Drug Product(s) and Drug Substance(s) 7

B. Description of How the Drug Product is Intended to be Used 8

Basis for Approvability or Not-Approval Recommendation 8

Chemistry Assessment 9

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data based on QbR-QOS 9

2.3 Introduction to the Quality Overall Summary 9

2.3.S DRUG SUBSTANCE 9
2.3.S.1 General Information 9
2.3.S.2 Manufacture 12
2.3.S.3 Characterization 14
2.3.S.4 Control of Drug Substance 15
2.3.S.5 Reference Standards or Materials 43
2.3.S.6 Container Closure System 46
2.3.S.7 Stability 47

2.3.P DRUG PRODUCT 47
2.3.P.1 Description and Composition of the Drug Product 47
2.3.P.2 Pharmaceutical Development 55
2.3.P.3 Manufacture 71
2.3.P.4 Control of Excipients 111
2.3.P.5 Control of Drug Product 112
2.3.P.6 Reference Standards or Materials 129
2.3.P.7 Container Closure System 130
2.3.P.8 Stability 132

A APPENDICES 137
A.1 Facilities and Equipment (biotech only) 137
A.2 Adventitious Agents Safety Evaluation 137
A.3 Novel Excipients 137

R REGIONAL INFORMATION 138
R.1 Executed Batch Records 138
R.2 Comparability Protocols 138
R.3 Methods Validation Package 138

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 138

A. Labeling & Package Insert 138

B. Environmental Assessment Or Claim Of Categorical Exclusion 139

III. List Of Deficiencies To Be Communicated 139

Chemistry Review Data Sheet

1. ANDA: 202-827

2. REVIEW #: 3

3. REVIEW DATE: March 14, 2014

4. REVIEWER: Ying Zhang, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Document(s)	Document Date
Original Submission	2/23/2011
Amendment	4/8/2011
Amendment	4/22/2011
Chemistry Review #1	8/30/2012
Amendment	2/6/2013
General Correspondence	7/25/2013
Chemistry Review #2	10/18/2013

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
General Correspondence	10/18/2013
Amendment	2/13/2014
Amendment	4/4/2014
Amendment	5/22/2014
Amendment	5/23/2014

7. NAME & ADDRESS OF APPLICANT:

Name:	Roxane Laboratories Inc.
Address:	1809 Wilson Road Columbus, OH 43228
US Agent:	N/A
Contact Person:	**Anton (Tony) Amann, Executive Director, Drug Regulatory Affairs and Medical Affairs**
Telephone:	614-272-4785
Fax:	614-276-2470

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: None
Non-Proprietary Name (USAN): Lisdexamfetamine Dimesylate Capsules

9. LEGAL BASIS FOR SUBMISSION:

The basis of Roxane Laboratories Inc. proposed ANDA for Lisdexamfetamine Dimesylate Capsules, is the RLD, Vyvanse 70 mg (NDA 21977) manufactured by Shire Development. According to information published in Approved Drug Products with Therapeutic equivalence Evaluation (Electronic Orange Book), Vyvanse is covered by several patents and exclusivities, which are listed below:

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N021977	003	7105486	Jun 29, 2023			U - 727	
N021977	003	7223735	Jun 29, 2023		Y		
N021977	003	7655630	Feb 24, 2023	Y			
N021977	003	7659253	Feb 24, 2023	Y	Y	U - 727	
N021977	003	7659254	Feb 24, 2023			U - 1034	
N021977	003	7662787	Feb 24, 2023	Y			
N021977	003	7662788	Feb 24, 2023			U - 727	
N021977	003	7671030	Feb 24, 2023		Y	U - 727	
N021977	003	7671031	Feb 28, 2023			U - 727	
N021977	003	7674774	Mar 18, 2023		Y	U - 842	
N021977	003	7678770	Mar 25, 2023			U - 842	
N021977	003	7678771	Mar 25, 2023		Y	U - 842	
N021977	003	7687466	Feb 24, 2023		Y		
N021977	003	7687467	Apr 8, 2023		Y	U - 842	
N021977	003	7700561	Jun 29, 2023		Y		
N021977	003	7713936	Feb 24, 2023			U - 727	
N021977	003	7718619	Feb 24, 2023		Y	U - 842	
N021977	003	7723305	Feb 24, 2023		Y	U - 842	

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
N021977	003	NCE	Feb 23, 2012
N021977	003	I - 645	Jan 31, 2015
N021977	003	M - 82	Apr 5, 2013
N021977	003	NPP	Nov 10, 2013
N021977	003	NPP	Apr 23, 2011

The applicant provided a Paragraph IV patent certification in module 1.3.5.2, and they stated they will not market the product until the exclusivity expires and upon approval of this ANDA.

10. PHARMACOL. CATEGORY: for treatment of ADHD

11. DOSAGE FORM: Capsule

12. STRENGTH/POTENCY: 20mg, 30mg, 40mg, 50mg, 60mg and 70mg

13. ROUTE OF ADMINISTRATION: Oral

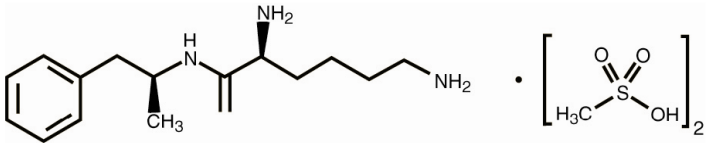
14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

USAN	Lisdexamfetamine Dimesylate
Chemical name	(2S)-2,6-diamino-N-[(1S)-1-methyl-2-phenylethyl]hexanamide dimethylsulfonate Hexanamide, 2,6-diamino-N-[(1S)-1-methyl-2-phenylethyl] – (2S)-,dimethylsulfonate
Molecular Formula	$C_{15}H_{25}N_3O \cdot (CH_4O_3S)_2$
Molecular Weight	455.60
CAS number	608137-33-3
Chemical Structure	

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Lisdexamfetamine Dimesylate	3	adequate	4/14/2014	By Hong Wen
	III		(b) (4)	4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	As of 3/6/2014*	

Methods Validation	N/A		
Labeling	Acceptable	2/25/2014	Alison Park
Bioequivalence	Acceptable	2/28/2012	S. Cherstniakova
EA	Categorical exclusion claimed		
Radiopharmaceutical	N/A		

*** Overall Re-eval date: 6/29/2014**

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X_ Yes ____ No If no, explain reason(s) below:

Chemistry Review for ANDA 202-827

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable per CMC perspective. DMF is adequate.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

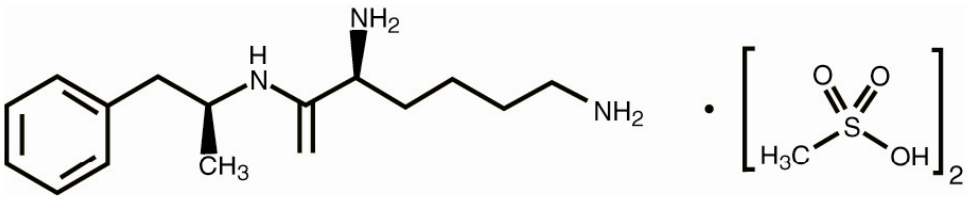
None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Lisdexamfetamine Dimesylate Capsules are designed as a capsule for once-a-day oral administration. The chemical designation for lisdexamfetamine dimesylate is (2S)-2,6-diamino-*N*-[(1*S*)-1-methyl-2-phenylethyl] hexanamide dimethanesulfonate. The molecular formula is C15H25N3O•(CH4O3S)2, which corresponds to a molecular weight of 455.60.

The chemical structure is:



Lisdexamfetamine dimesylate is a white to off-white powder that is soluble in water (792 mg/mL). Lisdexamfetamine dimesylate capsules contain 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg of lisdexamfetamine dimesylate and the following inactive ingredients: ammonium hydroxide, calcium phosphate, gelatin, iron oxide black, isopropyl alcohol, magnesium stearate, microcrystalline cellulose, n-butyl alcohol, propylene glycol, shellac glaze, sodium starch glycolate, and titanium dioxide. In addition, the 20 mg capsule also contains yellow iron oxide. The 30 mg capsule also contains FD&C yellow #6. The 40 mg capsule also contains FD&C blue #1 and FD&C green #3. The 50 mg and 60 mg capsules also contain D&C red #28 and FD&C blue

#1. The 70 mg capsule also contains D&C red #28, FD&C blue #1, and FD&C yellow #6.

B. Description of How the Drug Product is Intended to be Used

Lisdexamfetamine is a prodrug of dextroamphetamine. After oral administration, lisdexamfetamine is rapidly absorbed from the gastrointestinal tract and converted to dextroamphetamine, which is responsible for the drug's activity. Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known. Amphetamines are thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. The parent drug, lisdexamfetamine, does not bind to the sites responsible for the reuptake of norepinephrine and dopamine *in vitro*.

The maximum recommended daily dose is 70mg/day, according to the label.

C. Basis for Approvability or Not-Approval Recommendation

Approvable.

Note: This is a QbD submission, and the firm requested us for feedback in their amendment dated 4/22/2011. The QbD information was reviewed and our comments were returned to the firm on 9/17/2012. The firm did not respond to our QbD comments. In this review we only cover their response to our chemistry deficiency letter, and the previous QbD related review is deleted unless it causes quality concerns.

Chemistry Assessment

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data based on QbR-QOS

2.3 Introduction to the Quality Overall Summary

Proprietary Name of Drug Product	None
Non-Proprietary Name of Drug Product	Lisdexamfetamine Dimesylate Capsules, 20, 30, 40, 50, 60 and 70mg
Non-Proprietary Name of Drug Substance	Lisdexamfetamine Dimesylate
Company Name	Roxane Laboratories Inc
Dosage Form	capsule
Strength(s)	20mg, 30mg, 40mg, 50mg, 60mg and 70mg
Route of Administration	Oral
Proposed Indication(s)	Lisdexamfetamine Dimesylate Capsules is a prodrug of the CNS stimulant dextroamphetamine and is indicated for the treatment of ADHD.

2.3.S DRUG SUBSTANCE

2.3.S.1 General Information

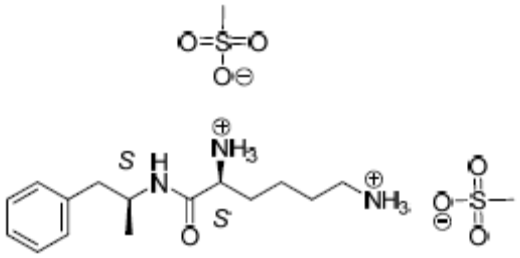
What are the nomenclature, molecular structure, molecular formula, and molecular weight?

Firm's Response:

Nomenclature:
(2S)-2,6-diamino-N-[(1S)-1-methyl-2-phenylethyl]hexanamide dimethylsulfonate

Synonyms:
Hexanamide, 2,6-diamino-N-[(1S)-1-methyl-2-phenylethyl] – (2S)-,dimethylsulfonate

Molecular Structure:



Molecular formula: $C_{15}H_{25}N_3O \cdot (CH_4O_3S)_2$

Molecular Weight: 455.60

CAS#: 608137-33-3

Reviewer's Comment: SATISFACTORY

The drug substance does not have a monograph in USP. The information provided by the sponsor has been verified by the reviewer with Merck Index.

What are the physicochemical properties including physical description, pKa, polymorphism, aqueous solubility (as function of pH), hygroscopicity, melting points, and partition coefficient?

Firm's Response:

Physical Description: Lisdexamfetamine Dimesylate is a white to off white crystalline powder.

pKa: not available

Polymorphism: No information is available in literature suggesting the existence of polymorphism for Lisdexamfetamine Dimesylate. (b) (4)

Solubility Characteristics:
Solubility in water is 792 mg/mL. Solubility in 95% aqueous ethanol is 1 part per 5 parts.

(b) (4)

[redacted]

Hygroscopicity: Lisdexamfetamine Dimesylate, [redacted] (b) (4) , is not hygroscopic.

Melting Point: approximately 193°C as performed by the supplier.

Chirality: Lisdexamfetamine Dimesylate has two asymmetric carbon centers. They are both in the S configuration. [redacted] (b) (4)

Reviewer's Comment: ~~NOT~~ SATISFACTORY

The information regarding the properties of the drug substance provided by the ANDA sponsor is more detailed than what is contained in the DMF [redacted] (b) (4)).

The data for physical description and solubility match the information in Merck Index. According to Merck Index, the melting point should be 120 - 122°C, [redacted] (b) (4)

therefore we will not comment.

The firm did not provide the solubility information for different pH values.

Deficiency:

Provide solubility data across the physiological pH range. If such data is not available in the literature, then you should determine it experimentally.

Response: ACCEPTABLE

Requested information was provided and has been incorporated into the text above.

2.3.S.2 Manufacture

Who manufactures the drug substance?

How do the manufacturing processes and controls ensure consistent production of drug substance?

(b) (4)

127 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YING ZHANG
06/11/2014

JENNIFER H NGUYEN
06/11/2014

ZHIGANG SUN
06/11/2014

NAIQI YA on behalf of ROBERT L ISER
06/11/2014

MINOR
C. Olele, 10/16/13

ANDA 202827

Lisdexamfetamine Dimesylate Capsules
20mg, 30mg, 40mg, 50mg, 60mg and 70mg

Roxane Laboratories, Inc.

Ying Zhang, Ph.D.
Chemistry Division IV
Office of Generic Drugs
Center for Drug Evaluation and Research

Table of Contents

Table of Contents i

Chemistry Review Data Sheet 1

1. ANDA 202-827: 1
2. REVIEW #2: 1
3. REVIEW DATE: 1
4. REVIEWER: 1
5. PREVIOUS DOCUMENTS: 1
6. SUBMISSION(S) BEING REVIEWED: 1
7. NAME & ADDRESS OF APPLICANT: 1
8. DRUG PRODUCT NAME/CODE/TYPE: 2
9. LEGAL BASIS FOR SUBMISSION: 2
10. PHARMACOL. CATEGORY: 3
11. DOSAGE FORM: 3
12. STRENGTH/POTENCY: 4
13. ROUTE OF ADMINISTRATION: 4
14. Rx/OTC DISPENSED: _X_Rx ___OTC 4
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): 4
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: 4
17. RELATED/SUPPORTING DOCUMENTS: 4
18. STATUS 5
19. ORDER OF REVIEW 6

Executive Summary 7

I. Recommendations 7

A. Recommendation and Conclusion on Approvability 7

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 7

II. Summary of Chemistry Assessments 7

A. Description of the Drug Product(s) and Drug Substance(s) 7

B. Description of How the Drug Product is Intended to be Used 8

Basis for Approvability or Not-Approval Recommendation 8

Chemistry Assessment 9

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data based on QbR-QOS 9

2.3 Introduction to the Quality Overall Summary 9

2.3.S DRUG SUBSTANCE 9
2.3.S.1 General Information 9
2.3.S.2 Manufacture 12
2.3.S.3 Characterization 14
2.3.S.4 Control of Drug Substance 15
2.3.S.5 Reference Standards or Materials 41
2.3.S.6 Container Closure System 43
2.3.S.7 Stability 43

2.3.P DRUG PRODUCT 43
2.3.P.1 Description and Composition of the Drug Product 43
2.3.P.2 Pharmaceutical Development 51
2.3.P.3 Manufacture 67
2.3.P.4 Control of Excipients 105
2.3.P.5 Control of Drug Product 106
2.3.P.6 Reference Standards or Materials 121
2.3.P.7 Container Closure System 121
2.3.P.8 Stability 123

A APPENDICES 129
A.1 Facilities and Equipment (biotech only) 129
A.2 Adventitious Agents Safety Evaluation 129
A.3 Novel Excipients 129

R REGIONAL INFORMATION 130
R.1 Executed Batch Records 130
R.2 Comparability Protocols 130
R.3 Methods Validation Package 130

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 130

A. Labeling & Package Insert 130

B. Environmental Assessment Or Claim Of Categorical Exclusion 131

III. List Of Deficiencies To Be Communicated 131

Chemistry Review Data Sheet

1. ANDA: 202-827

2. REVIEW #: 2

3. REVIEW DATE: July 18, 2013

4. REVIEWER: Ying Zhang, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Document(s)	Document Date
Original Submission	2/23/2011
Amendment	4/8/2011
Amendment	4/22/2011
Chemistry Review #1	8/30/2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	2/6/2013
General Correspondence	7/25/2013

7. NAME & ADDRESS OF APPLICANT:

Name: Roxane Laboratories Inc.
Address: 1809 Wilson Road
Columbus, OH
43228
US Agent: N/A

Contact Person: **Anton (Tony) Amann, Executive Director, Drug Regulatory Affairs and Medical Affairs**
Telephone: 614-272-4785
Fax: 614-276-2470

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: None
Non-Proprietary Name (USAN): Lisdexamfetamine Dimesylate Capsules

9. LEGAL BASIS FOR SUBMISSION:

The basis of Roxane Laboratories Inc. proposed ANDA for Lisdexamfetamine Dimesylate Capsules, is the RLD, Vyvanse 70 mg (NDA 21977) manufactured by Shire Development. According to information published in Approved Drug Products with Therapeutic equivalence Evaluation (Electronic Orange Book), Vyvanse is covered by several patents and exclusivities, which are listed below:

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N021977	003	7105486	Jun 29, 2023			U - 727	
N021977	003	7223735	Jun 29, 2023		Y		
N021977	003	7655630	Feb 24, 2023	Y			
N021977	003	7659253	Feb 24, 2023	Y	Y	U - 727	
N021977	003	7659254	Feb 24, 2023			U - 1034	
N021977	003	7662787	Feb 24, 2023	Y			
N021977	003	7662788	Feb 24, 2023			U - 727	
N021977	003	7671030	Feb 24, 2023		Y	U - 727	
N021977	003	7671031	Feb 28, 2023			U - 727	
N021977	003	7674774	Mar 18, 2023		Y	U - 842	
N021977	003	7678770	Mar 25, 2023			U - 842	
N021977	003	7678771	Mar 25, 2023		Y	U - 842	
N021977	003	7687466	Feb 24, 2023		Y		
N021977	003	7687467	Apr 8, 2023		Y	U - 842	
N021977	003	7700561	Jun 29, 2023		Y		
N021977	003	7713936	Feb 24, 2023			U - 727	
N021977	003	7718619	Feb 24, 2023		Y	U - 842	
N021977	003	7723305	Feb 24, 2023		Y	U - 842	

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
N021977	003	NCE	Feb 23, 2012
N021977	003	I - 645	Jan 31, 2015
N021977	003	M - 82	Apr 5, 2013
N021977	003	NPP	Nov 10, 2013
N021977	003	NPP	Apr 23, 2011

The applicant provided a Paragraph IV patent certification in module 1.3.5.2, and they stated they will not market the product until the exclusivity expires and upon approval of this ANDA.

10. PHARMACOL. CATEGORY: for treatment of ADHD

11. DOSAGE FORM: Capsule

12. STRENGTH/POTENCY: 20mg, 30mg, 40mg, 50mg, 60mg and 70mg

13. ROUTE OF ADMINISTRATION: Oral

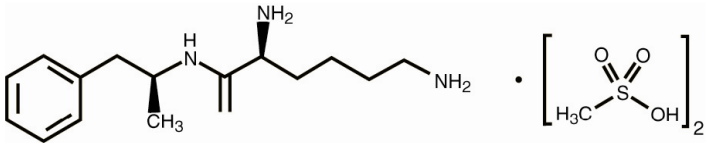
14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

USAN	Lisdexamfetamine Dimesylate
Chemical name	(2S)-2,6-diamino-N-[(1S)-1-methyl-2-phenylethyl]hexanamide dimethylsulfonate Hexanamide, 2,6-diamino-N-[(1S)-1-methyl-2-phenylethyl] – (2S)-,dimethylsulfonate
Molecular Formula	$C_{15}H_{25}N_3O \cdot (CH_4O_3S)_2$
Molecular Weight	455.60
CAS number	608137-33-3
Chemical Structure	

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Lisdexamfetamine Dimesylate	3	Inadequate	1/23/2013	By B. Scott
	III		(b) (4)	4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	11/1/2012	

Methods Validation	N/A		
Labeling	ECD Pending	As of 7/18/2013	Alison Park
Bioequivalence	Acceptable	2/28/2012	S. Cherstniakova
EA	Categorical exclusion claimed		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X_ Yes ____ No If no, explain reason(s) below:

Chemistry Review for ANDA 202-827

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not approvable due to MINOR deficiencies.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

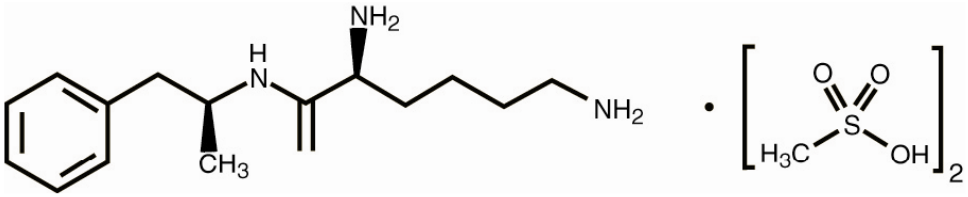
None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Lisdexamfetamine Dimesylate Capsules are designed as a capsule for once-a-day oral administration. The chemical designation for lisdexamfetamine dimesylate is (2S)-2,6-diamino-*N*-[(1*S*)-1-methyl-2-phenylethyl] hexanamide dimethanesulfonate. The molecular formula is C15H25N3O•(CH4O3S)2, which corresponds to a molecular weight of 455.60.

The chemical structure is:



Lisdexamfetamine dimesylate is a white to off-white powder that is soluble in water (792 mg/mL). Lisdexamfetamine dimesylate capsules contain 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg of lisdexamfetamine dimesylate and the following inactive ingredients: ammonium hydroxide, calcium phosphate, gelatin, iron oxide black, isopropyl alcohol, magnesium stearate, microcrystalline cellulose, n-butyl alcohol, propylene glycol, shellac glaze, sodium starch glycolate, and titanium dioxide. In addition, the 20 mg capsule also contains yellow iron oxide. The 30 mg capsule also contains FD&C yellow #6. The 40 mg capsule also contains FD&C blue #1 and FD&C green #3. The 50 mg and 60 mg capsules also contain D&C red #28 and FD&C blue

#1. The 70 mg capsule also contains D&C red #28, FD&C blue #1, and FD&C yellow #6.

B. Description of How the Drug Product is Intended to be Used

Lisdexamfetamine is a prodrug of dextroamphetamine. After oral administration, lisdexamfetamine is rapidly absorbed from the gastrointestinal tract and converted to dextroamphetamine, which is responsible for the drug's activity. Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known. Amphetamines are thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. The parent drug, lisdexamfetamine, does not bind to the sites responsible for the reuptake of norepinephrine and dopamine *in vitro*.

The maximum recommended daily dose is 70mg/day, according to the label.

C. Basis for Approvability or Not-Approval Recommendation

Not approval is recommended for MINOR CMC deficiencies. DMF is deficient.

Note: This is a QbD submission, and the firm requested us for feedback in their amendment dated 4/22/2011. The QbD information was reviewed and our comments were returned to the firm on 9/17/2012. The firm did not respond to our QbD comments. In this review we only cover their response to our chemistry deficiency letter, and the previous QbD related review is deleted unless it causes quality concerns.

Chemistry Assessment

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data based on QbR-QOS

2.3 Introduction to the Quality Overall Summary

Proprietary Name of Drug Product	None
Non-Proprietary Name of Drug Product	Lisdexamfetamine Dimesylate Capsules, 20, 30, 40, 50, 60 and 70mg
Non-Proprietary Name of Drug Substance	Lisdexamfetamine Dimesylate
Company Name	Roxane Laboratories Inc
Dosage Form	capsule
Strength(s)	20mg, 30mg, 40mg, 50mg, 60mg and 70mg
Route of Administration	Oral
Proposed Indication(s)	Lisdexamfetamine Dimesylate Capsules is a prodrug of the CNS stimulant dextroamphetamine and is indicated for the treatment of ADHD.

2.3.S DRUG SUBSTANCE

2.3.S.1 General Information

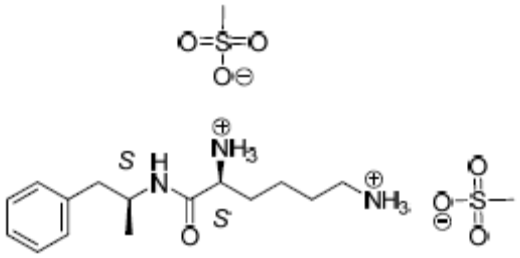
What are the nomenclature, molecular structure, molecular formula, and molecular weight?

Firm's Response:

Nomenclature:
(2S)-2,6-diamino-N-[(1S)-1-methyl-2-phenylethyl]hexanamide dimethylsulfonate

Synonyms:
Hexanamide, 2,6-diamino-N-[(1S)-1-methyl-2-phenylethyl] – (2S)-,dimethylsulfonate

Molecular Structure:



Molecular formula: $C_{15}H_{25}N_3O \cdot (CH_4O_3S)_2$

Molecular Weight: 455.60

CAS#: 608137-33-3

Reviewer's Comment: SATISFACTORY

The drug substance does not have a monograph in USP. The information provided by the sponsor has been verified by the reviewer with Merck Index.

What are the physicochemical properties including physical description, pKa, polymorphism, aqueous solubility (as function of pH), hygroscopicity, melting points, and partition coefficient?

Firm's Response:

Physical Description: Lisdexamfetamine Dimesylate is a white to off white crystalline powder.

pKa: not available

Polymorphism: No information is available in literature suggesting the existence of polymorphism for Lisdexamfetamine Dimesylate. (b) (4)

Solubility Characteristics:
Solubility in water is 792 mg/mL. Solubility in 95% aqueous ethanol is 1 part per 5 parts.

(b) (4)

Hygroscopicity: Lisdexamfetamine Dimesylate, (b) (4) (b) (4) is not hygroscopic.

Melting Point: approximately 193°C as performed by the supplier.

Chirality: Lisdexamfetamine Dimesylate has two asymmetric carbon centers. They are both in the S configuration. (b) (4)

Reviewer's Comment: ~~NOT~~ SATISFACTORY

The information regarding the properties of the drug substance provided by the ANDA sponsor is more detailed than what is contained in the DMF (b) (4). The data for physical description and solubility match the information in Merck Index. According to Merck Index, the melting point should be 120 - 122°C, while the

(b) (4)

The firm did not provide the solubility information for different pH values.

Deficiency:

Provide solubility data across the physiological pH range. If such data is not available in the literature, then you should determine it experimentally.

Response: ACCEPTABLE

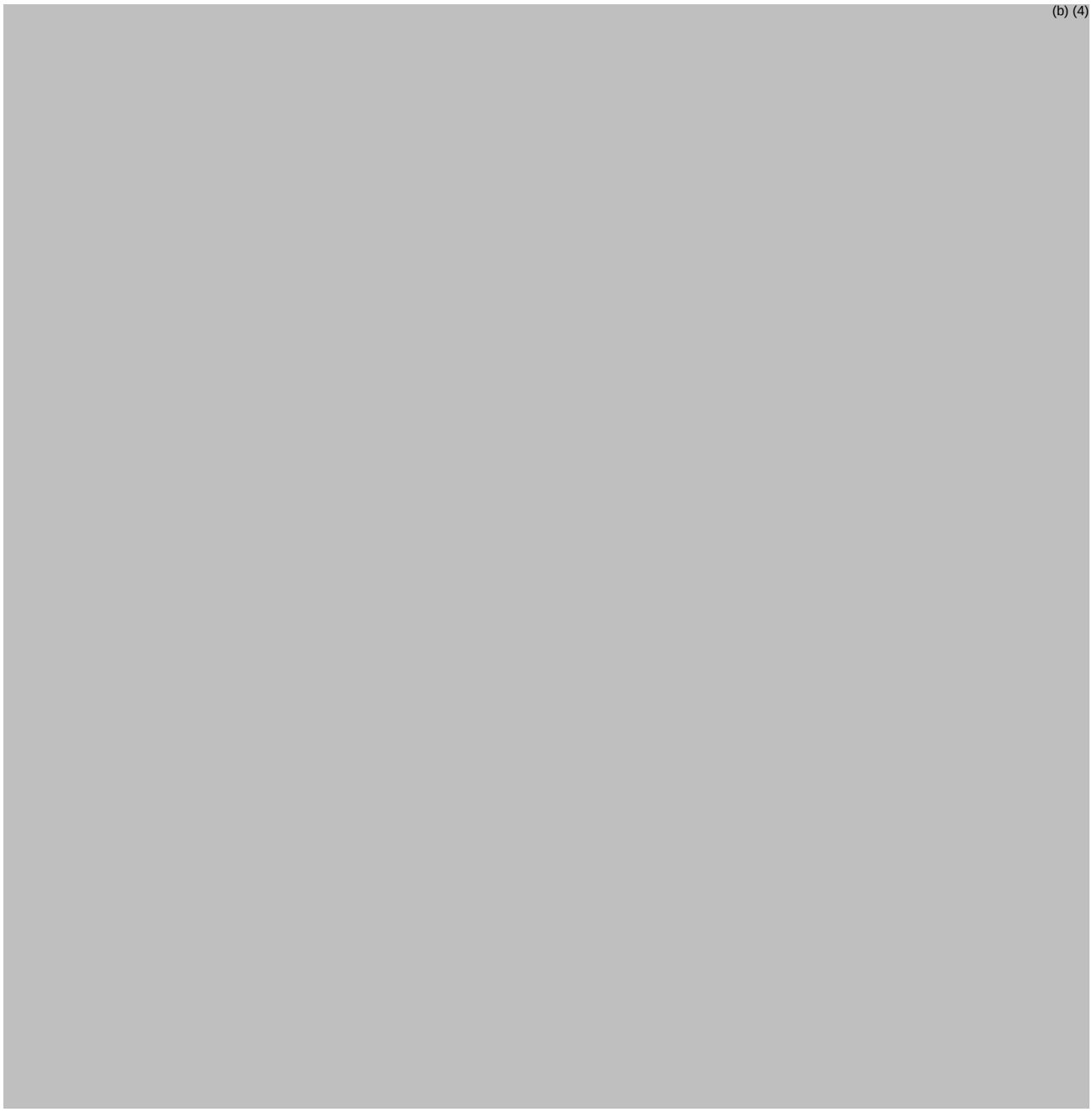
Requested information was provided and has been incorporated into the text above.

2.3.S.2 Manufacture

Who manufactures the drug substance?

How do the manufacturing processes and controls ensure consistent production of drug substance?

(b) (4)



121 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

Sincerely yours,

{See appended electronic signature page}

Robert L. Iser
Director
Division of Chemistry IV
Office of Generic Drugs
Center for Drug Evaluation and Research

Y. Zhang 9/13/2013
A. Jung 9/13/2013
R. Iser 10/15/2013
C. Olele 10/16/13

Minor

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YING ZHANG
10/16/2013

CHINYELUM A OLELE
10/18/2013

HUIJEONG A JUNG
10/18/2013

ROBERT L ISER
10/18/2013

MAJOR, QbD

ANDA 202-827

Lisdexamfetamine Dimesylate Capsules
20mg, 30mg, 40mg, 50mg, 60mg and 70mg

Roxane Laboratories, Inc.

Ying Zhang, Ph.D.
Chemistry Division IV
Office of Generic Drugs
Center for Drug Evaluation and Research

Table of Contents

Table of Contents ..... **i**

Chemistry Review Data Sheet **1**

1. ANDA 202-827: 1
2. REVIEW #1: 1
3. REVIEW DATE: 1
4. REVIEWER: 1
5. PREVIOUS DOCUMENTS: 1
6. SUBMISSION(S) BEING REVIEWED: 1
7. NAME & ADDRESS OF APPLICANT: 1
8. DRUG PRODUCT NAME/CODE/TYPE: 2
9. LEGAL BASIS FOR SUBMISSION: 2
10. PHARMACOL. CATEGORY: 3
11. DOSAGE FORM: 3
12. STRENGTH/POTENCY: 3
13. ROUTE OF ADMINISTRATION: 3
14. Rx/OTC DISPENSED: _X_Rx ___OTC 3
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): 3
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: 3
17. RELATED/SUPPORTING DOCUMENTS: 4
18. STATUS 5
19. ORDER OF REVIEW 5

Executive Summary **6**

I. Recommendations 6

A. Recommendation and Conclusion on Approvability 6

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 6

II. Summary of Chemistry Assessments 6

A. Description of the Drug Product(s) and Drug Substance(s) 6

B. Description of How the Drug Product is Intended to be Used 7

Basis for Approvability or Not-Approval Recommendation 7

Chemistry Assessment 8

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data based on QbR-QOS 8

2.3 Introduction to the Quality Overall Summary 8

2.3.S DRUG SUBSTANCE 8
2.3.S.1 General Information 8
2.3.S.2 Manufacture 10
2.3.S.3 Characterization 12
2.3.S.4 Control of Drug Substance 13
2.3.S.5 Reference Standards or Materials 36
2.3.S.6 Container Closure System 36
2.3.S.7 Stability 37

2.3.P DRUG PRODUCT 37
2.3.P.1 Description and Composition of the Drug Product 37
2.3.P.2 Pharmaceutical Development 43
2.3.P.3 Manufacture 59
2.3.P.4 Control of Excipients 97
2.3.P.5 Control of Drug Product 98
2.3.P.6 Reference Standards or Materials 111
2.3.P.7 Container Closure System 111
2.3.P.8 Stability 113

A APPENDICES 118
A.1 Facilities and Equipment (biotech only) 118
A.2 Adventitious Agents Safety Evaluation 118
A.3 Novel Excipients 118

R REGIONAL INFORMATION 119
R.1 Executed Batch Records 119
R.2 Comparability Protocols 119
R.3 Methods Validation Package 119

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 119

A. Labeling & Package Insert 119

B. Environmental Assessment Or Claim Of Categorical Exclusion 120

III. List Of Deficiencies To Be Communicated 120

Chemistry Review Data Sheet

1. ANDA: 202-827

2. REVIEW #: 1

3. REVIEW DATE: June 20, 2012

4. REVIEWER: Ying Zhang, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Document(s)	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	2/23/2011
Amendment	4/8/2011
Amendment	4/22/2011

7. NAME & ADDRESS OF APPLICANT:

Name:	Roxane Laboratories Inc.
Address:	1809 Wilson Road Columbus, OH 43228
US Agent:	N/A
Contact Person:	Elizabeth Ernst, Executive Director, Drug Regulatory Affairs and Medical Affairs
Telephone:	614-272-4785
Fax:	614-276-2470

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: None
Non-Proprietary Name (USAN): Lisdexamfetamine Dimesylate Capsules

9. LEGAL BASIS FOR SUBMISSION:

The basis of Roxane Laboratories Inc. proposed ANDA for Lisdexamfetamine Dimesylate Capsules, is the RLD, Vyvanse 70 mg (NDA 21977) manufactured by Shire Development. According to information published in Approved Drug Products with Therapeutic equivalence Evaluation (Electronic Orange Book), Vyvanse is covered by several patents and exclusivities, which are listed below:

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N021977	003	7105486	Jun 29, 2023			U - 727	
N021977	003	7223735	Jun 29, 2023		Y		
N021977	003	7655630	Feb 24, 2023	Y			
N021977	003	7659253	Feb 24, 2023	Y	Y	U - 727	
N021977	003	7659254	Feb 24, 2023			U - 1034	
N021977	003	7662787	Feb 24, 2023	Y			
N021977	003	7662788	Feb 24, 2023			U - 727	
N021977	003	7671030	Feb 24, 2023		Y	U - 727	
N021977	003	7671031	Feb 28, 2023			U - 727	
N021977	003	7674774	Mar 18, 2023		Y	U - 842	
N021977	003	7678770	Mar 25, 2023			U - 842	
N021977	003	7678771	Mar 25, 2023		Y	U - 842	
N021977	003	7687466	Feb 24, 2023		Y		
N021977	003	7687467	Apr 8, 2023		Y	U - 842	
N021977	003	7700561	Jun 29, 2023		Y		
N021977	003	7713936	Feb 24, 2023			U - 727	
N021977	003	7718619	Feb 24, 2023		Y	U - 842	
N021977	003	7723305	Feb 24, 2023		Y	U - 842	

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
N021977	003	NCE	Feb 23, 2012
N021977	003	I - 645	Jan 31, 2015
N021977	003	M - 82	Apr 5, 2013
N021977	003	NPP	Nov 10, 2013
N021977	003	NPP	Apr 23, 2011

The applicant provided a Paragraph IV patent certification in module 1.3.5.2, and they stated they will not market the product until the exclusivity expires and upon approval of this ANDA.

10. PHARMACOL. CATEGORY: for treatment of ADHD

11. DOSAGE FORM: Capsule

12. STRENGTH/POTENCY: 20mg, 30mg, 40mg, 50mg, 60mg and 70mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

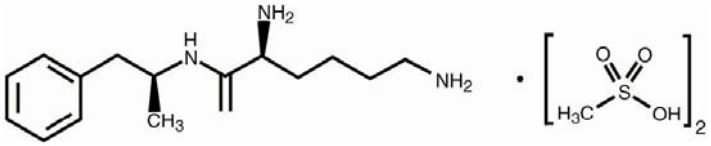
_____SPOTS product – Form Completed

__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

USAN	Lisdexamfetamine Dimesylate
Chemical name	(2S)-2,6-diamino-N-[(1S)-1-methyl-2-phenylethyl]hexanamide dimethylsulfonate
	Hexanamide, 2,6-diamino-N-[(1S)-1-methyl-2-phenylethyl] – (2S)-,dimethylsulfonate
Molecular Formula	$C_{15}H_{25}N_3O \cdot (CH_4O_3S)_2$

Molecular Weight 455.60
CAS number 608137-33-3
Chemical Structure



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Lisdexamfetamine Dimesylate	1	Inadequate	10/10/2011	By R. Maheswaran
	III		(b) (4)	4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

[1] Action codes for DMF Table:

1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending	As of 6/22/2012	
Methods Validation	N/A		
Labeling	Pending	As of 6/22/2012	
Bioequivalence	Acceptable	2/28/2012	S. Cherstniakova
EA	Categorical exclusion claimed		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X_ Yes ____ No If no, explain reason(s) below:

Chemistry Review for ANDA 202-827

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not approvable due to major deficiencies. The firm needs to re-develop the analytical methods for assay and related substance for the drug product.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

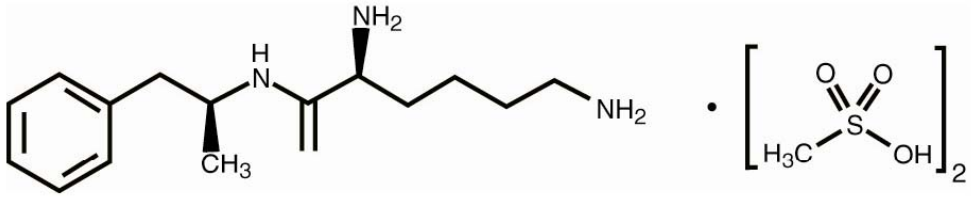
None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Lisdexamfetamine Dimesylate Capsules are designed as a capsule for once-a-day oral administration. The chemical designation for lisdexamfetamine dimesylate is (2S)-2,6-diamino-*N*-[(1*S*)-1-methyl-2-phenylethyl] hexanamide dimethanesulfonate. The molecular formula is C15H25N3O•(CH4O3S)2, which corresponds to a molecular weight of 455.60.

The chemical structure is:



Lisdexamfetamine dimesylate is a white to off-white powder that is soluble in water (792 mg/mL). Lisdexamfetamine dimesylate capsules contain 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg of lisdexamfetamine dimesylate and the following inactive ingredients: ammonium hydroxide, calcium phosphate, gelatin, iron oxide black, isopropyl alcohol, magnesium stearate, microcrystalline cellulose, n-butyl alcohol, propylene glycol, shellac glaze, sodium starch glycolate, and titanium dioxide. In addition, the 20 mg capsule also contains yellow iron oxide. The 30 mg capsule also contains FD&C yellow #6. The 40 mg capsule also contains FD&C blue #1 and FD&C green

#3. The 50 mg and 60 mg capsules also contain D&C red #28 and FD&C blue #1. The 70 mg capsule also contains D&C red #28, FD&C blue #1, and FD&C yellow #6.

B. Description of How the Drug Product is Intended to be Used

Lisdexamfetamine is a prodrug of dextroamphetamine. After oral administration, lisdexamfetamine is rapidly absorbed from the gastrointestinal tract and converted to dextroamphetamine, which is responsible for the drug's activity. Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known. Amphetamines are thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. The parent drug, lisdexamfetamine, does not bind to the sites responsible for the reuptake of norepinephrine and dopamine *in vitro*.

The maximum recommended daily dose is 70mg/day, according to the label.

C. Basis for Approvability or Not-Approval Recommendation

Not approval is recommended for major CMC deficiencies.

Note: This is a QbD submission, and the firm requested us for feedback in their amendment dated April 22, 2011. The QbD information as well as the assessment from this reviewer is addressed in this review. However, the QbD related recommendations for the firm are not included.

Chemistry Assessment

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data based on QbR-QOS

2.3 Introduction to the Quality Overall Summary

Proprietary Name of Drug Product	None
Non-Proprietary Name of Drug Product	Lisdexamfetamine Dimesylate Capsules, 20, 30, 40, 50, 60 and 70mg
Non-Proprietary Name of Drug Substance	Lisdexamfetamine Dimesylate
Company Name	Roxane Laboratories Inc
Dosage Form	capsule
Strength(s)	20mg, 30mg, 40mg, 50mg, 60mg and 70mg
Route of Administration	Oral
Proposed Indication(s)	Lisdexamfetamine Dimesylate Capsules is a prodrug of the CNS stimulant dextroamphetamine and is indicated for the treatment of ADHD.

2.3.S DRUG SUBSTANCE

2.3.S.1 General Information

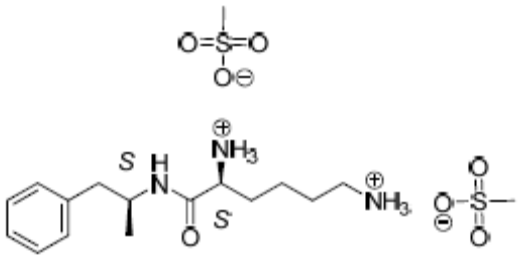
What are the nomenclature, molecular structure, molecular formula, and molecular weight?

Firm's Response:

Nomenclature:
(2S)-2,6-diamino-N-[(1S)-1-methyl-2-phenylethyl]hexanamide dimethylsulfonate

Synonyms:
Hexanamide, 2,6-diamino-N-[(1S)-1-methyl-2-phenylethyl] – (2S)-,dimethylsulfonate

Molecular Structure:



Molecular formula: $C_{15}H_{25}N_3O \cdot (CH_4O_3S)_2$

Molecular Weight: 455.60

CAS#: 608137-33-3

Reviewer's Comment: SATISFACTORY

The drug substance does not have a monograph in USP. The information provided by the sponsor has been verified by the reviewer with Merck Index.

What are the physicochemical properties including physical description, pKa, polymorphism, aqueous solubility (as function of pH), hygroscopicity, melting points, and partition coefficient?

Firm's Response:

Physical Description: Lisdexamfetamine Dimesylate is a white to off white crystalline powder.

pKa: not available

Polymorphism: No information is available in literature suggesting the existence of polymorphism for Lisdexamfetamine Dimesylate. (b) (4)

Solubility Characteristics: Solubility in water is 792 mg/mL. Solubility in 95% aqueous ethanol is 1 part per 5 parts.

Hygroscopicity: Lisdexamfetamine Dimesylate, (b) (4) is not hygroscopic.

Melting Point: approximately 193°C as performed by the supplier.

Chirality: Lisdexamfetamine Dimesylate has two asymmetric carbon centers. They are both in the S configuration. (b) (4)

Reviewer's Comment: NOT SATISFACTORY

The information regarding the properties of the drug substance provided by the ANDA sponsor is more detailed than what is contained in the DMF (b) (4). The data for physical description and solubility match the information in Merck Index. According to Merck Index, the melting point should be 120 - 122°C, (b) (4) therefore we will not comment.

The firm did not provide the solubility information for different pH values.

Deficiency:

Provide solubility data across the physiological pH range. If such data is not available in the literature, then you should determine it experimentally.

2.3.S.2 Manufacture

Who manufactures the drug substance?

How do the manufacturing processes and controls ensure consistent production of drug substance?

(b) (4)

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/s/

YING ZHANG
08/29/2012

SIMON S ENG
08/29/2012

HUIJEONG A JUNG
08/30/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202827Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ANDA 202827

INFORMATION REQUEST
QUALITY

Hikma Pharmaceuticals USA Inc
1809 Wilson Road
Columbus, OH 43228
Attention: George Prestash Iv
Associate Director, Ra

Dear George Prestash Iv:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on March 29, 2023, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Lisdexamfetamine Dimesylate Capsules, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg.

Reference is also made to any amendments submitted prior to the issuance of this letter.

We are reviewing the Quality section of your submission and request the following additional information/clarification and/or have the following comments:

QUALITY

(b) (4)

(b) (4)

We request a complete written response, no later than June 8, 2023 in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. If you are responding to a late cycle information request[1], the goal date may be extended based upon the major or minor deficiencies included upon receipt of the response. The goal date assigned to the amendment may extend the review goal date for your current submission.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
QUALITY
MINOR

If you do not submit a complete written response by June 8, 2023, the listed information requests may be incorporated in a discipline review letter or complete response letter.

As described in FDA's draft guidance for industry *Cover Letter Attachments for Controlled Correspondences and ANDA Submissions*, FDA recommends that you include the appropriate attachment(s) along with the cover letter for your submission to help FDA ensure that your submission is properly triaged and assigned to the appropriate assessors. This will also ensure that submissions are effectively managed by FDA and acted upon within the performance review goal dates set by the Generic Drug User Fee Amendments.

If you have any questions, please contact Kevin Ninan, Regulatory Business Process Manager, at kevin.ninan@fda.hhs.gov or (240) 402 - 8732.

Sincerely,

{See appended electronic signature page}

Kevin Ninan
Regulatory Business Process Manager
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

[1] Late cycle defined as IRs or DRLs issued after the mid-cycle of an original ANDA or less than 90 days from the goal date for any ANDA amendment.

Kevin
Ninan

Digitally signed by Kevin Ninan
Date: 6/05/2023 08:15:25AM
GUID: 5130b7c1000123364dc4c595d0d94f5f

ANDA 202827

DISCIPLINE REVIEW LETTER
LABELING

Hikma Pharmaceuticals USA Inc.
1809 Wilson Road
Columbus, OH 43228
Attention: George E. Prestash IV
Associate Director, RA

Dear Sir:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on February 23, 2011, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Lisdexamfetamine Dimesylate Capsules, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg.

Reference is also made to any amendments submitted prior to the issuance of this letter.

The following comments have been identified by the Division of Labeling Review (DLR) based on your submission(s) on November 23, 2022. Prior to final approval, the proposed labeling should be clear and precise (grammar, spelling, and formatting) for end users, and accurately reflect the Reference Listed Drug (RLD) information to comply with FDA policies, laws, regulations (i.e., 21 CFR 314.94(a)(8)), official compendia, and relevant guidance.

PRESCRIBING INFORMATION

a. Comment on the pregnancy registry information in your labeling. The labeling for the reference listed drug (RLD) contains third party pregnancy registry information in its labeling. Your proposed labeling may retain the information once you have verified with the third party that the data for your generic drug product will be accepted as part of their pregnancy registry. If it is determined that the data for your generic drug product will not be accepted by the third party, remove the pregnancy registry information in your labeling.
b. Highlights of Prescribing Information, Limitation statement: Revise both instances of the established name from "**LISDEXAMFETAMINE DIMESYLATE capsules**" to read, "**LISDEXAMFETAMINE DIMESYLATE CAPSULES**".
c. **1 INDICATIONS AND USAGE**, Limitations of Use heading, 2nd bullet, 1st sentence: Revise the sentence from "Lisdexamfetamine dimesylate capsules are not indicated for weight loss" to read, "Lisdexamfetamine

dimesylate capsules are not indicated or recommended for weight loss." in accordance with the RLD.

d. **11 DESCRIPTION**: Add an equivalency statement (e.g., “Lisdexamfetamine dimesylate capsules contain 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg of lisdexamfetamine dimesylate (equivalent to X.X mg, XX.X mg... of lisdexamfetamine)") per USP, General Chapter <7> Labeling and the RLD labeling.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the Electronic Orange Book are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

If you would like to respond to these possible deficiencies before the end of this review cycle, we request a complete written response to this discipline review letter (DRL) no later than June 16, 2023. If you submit a written response during this review cycle, depending on the timing and/or the information contained in your response, we may not be able to consider your response before taking action on your application. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

DISCIPLINE REVIEW LETTER
LABELING
MINOR

Please note that we are providing these preliminary thoughts on possible deficiencies to you before a complete review of your entire application. As contemplated in the

Generic Drug User Fee Amendments of 2022 (GDUFA III)[1], these possible deficiencies do not reflect a complete review of your application and should not be construed as such. In addition, these possible deficiencies do not necessarily reflect input from supervisory levels. You should be aware that these deficiencies may be modified or additional deficiencies may be identified as we complete our review of your entire application.

Deficiencies addressed by applicants in a response to a DRL may appear in a Complete Response Letter (CRL) if FDA's review of the response has been deferred or if FDA has outstanding concerns after review of the response. The CRL will include all deficiencies that must be satisfactorily addressed before the ANDA can be approved.

If the applicant receives a CRL, but has already responded to some (or all) identified deficiencies in a DRL response, the applicant does not need to re-submit previously submitted information in a CRL amendment. However, the applicant should still submit a CRL amendment and should clearly identify the previously provided DRL response that renders its CRL amendment complete.

Additionally, please take note of the following if you choose to respond to these possible deficiencies before the end of this review cycle:

1. If your submission is a response to a Major DRL received by the due date (or any agreed-upon extension), FDA may classify the response as Major and assign an appropriate goal date for that amendment.
2. If you do not respond by the requested due date, FDA may defer review of your response.
3. FDA will strive to review your response during the review cycle in which it is received if such review can be completed during such review cycle. However, if the Agency determines that it cannot review the response before a goal date or if a complete response letter is otherwise ready to be issued, the review of your response may be deferred. When FDA defers review of your response, it will be reviewed during the next review cycle for the application.
4. If you are responding to a late cycle DRL[2], the goal date may be extended based upon the major or minor deficiencies included upon receipt of the response.
5. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as a major or minor amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

[1] GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2023-2027 (available at https://www.fda.gov/media/153631/download).
[2] Late cycle defined as IRs or DRLs issued after the mid-cycle of an original ANDA or IRs or DRLs issued less than 90 days from the goal date of an ANDA amendment

As described in FDA's draft guidance for industry *Cover Letter Attachments for Controlled Correspondences and ANDA Submissions*, FDA recommends that you include the appropriate attachment(s) along with the cover letter for your submission to help FDA ensure that your submission is properly triaged and assigned to the appropriate assessors. This will also ensure that submissions are effectively managed by FDA and acted upon within the performance review goal dates set by the Generic Drug User Fee Amendments.

If you have any questions, please contact Julie Call, Labeling Project Manager, at julie.call@fda.hhs.gov or 240-402-8598.

Sincerely,

{See appended electronic signature page}

Julie Call, PharmD, PMP
Labeling Project Manager
Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

Julie Call

Digitally signed by Julie Call
Date: 6/02/2023 04:08:29PM
GUID: 525d9e9d00038c406bce70608a211ab1

ANDA 202827

COMPLETE RESPONSE

Hikma Pharmaceuticals USA Inc.
1809 Wilson Road
Columbus, OH 43228
Attention: George E. Prestash IV
Associate Director, Regulatory Affairs

Dear George E. Prestash IV:

This is in reference to your abbreviated new drug application (ANDA) received for review on February 23, 2011, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Lisdexamfetamine Dimesylate Capsules, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg.

Reference is also made to the tentative approval letter issued by this office on June 23, 2014, and to any amendments thereafter.

We also acknowledge receipt of your amendment received on November 23, 2022, which was deferred and not reviewed for this action. You may incorporate applicable sections of the deferred amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this ANDA, as amended, and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

(b) (4)

[redacted]

(b) (4)

LABELING

1. PRESCRIBING INFORMATION

   a. CONTENTS*: Delete (b) (4)" from the end of the table of contents (below "**17 PATIENT COUNSELING INFORMATION**").

   b. **2.1 Pre-treatment Screening**, 1st sentence: Replace "children, adolescents, and adults" with "patients" and add "including lisdexamfetamine dimesylate capsules," after "CNS stimulants," in accordance with the RLD.

   c. **2.2 General Instructions for Use**: Retain the heading "*Information for lisdexamfetamine dimesylate capsules:*" in accordance with the RLD.

d. **2.5** subsection heading: Add "in" for clarity as such:
2.5 Dosage in Patients with Renal Impairment.

e. **5.2 Serious Cardiovascular Reactions**, 2nd sentence: Replace "children and adolescents" with "pediatric patients" in accordance with the RLD.

f. **6.1 Clinical Trials Experience**, 2nd heading: Add "ADHD" in the heading as such: *Adverse Reactions Associated with Discontinuation of Treatment in ADHD Clinical Trials*:

g. **Table 1** title: Revise in accordance with the RLD as such:
Table 1 Adverse Reactions Reported by 2% or More of Pediatric Patients Ages 6 to 12 Years with ADHD Taking Lisdexamfetamine Dimesylate and Greater than or Equal to Twice the Incidence in Patients Taking Placebo in a 4-Week Clinical Trial (Study 1)

h. **Table 1**, Insomnia row: Revise (b) (4)% to "22%" in accordance with the RLD.

i. **Table 2** title: Revise in accordance with the RLD as such:
Table 2 Adverse Reactions Reported by 2% or More of Pediatric Patients Ages 13 to 17 Years with ADHD Taking Lisdexamfetamine Dimesylate and Greater than or Equal to Twice the Incidence in Patients Taking Placebo in a 4-Week Clinical Trial (Study 4)

j. **Table 3** title: Add "with ADHD" in accordance with the RLD.

k. **8.5 Geriatric Use**, 2nd sentence: Revise beginning of the sentence to read, "Other reported clinical experience and pharmacokinetic data [*see Clinical Pharmacology (12.3)*] have not identified..." in accordance with the RLD.

l. **Figure 4** title: Replace "Children" with "Pediatric Patients" in accordance with the RLD.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the Electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

BIOEQUIVALENCE / DISSOLUTION / FACILITY INSPECTIONS/EVALUATIONS

There are no further questions for the above listed disciplines at this time. The comments provided in this communication are comprehensive as of the date the discipline review was completed. However, these comments are subject to revision if any scientific or regulatory division identifies additional concerns, as well as any concerns due to inspection results that may arise in the future. Additionally, the compliance status of each facility named in the application may be reevaluated upon resubmission.

FDA publishes new and revised product-specific guidances describing the Agency's current recommendations on demonstrating bioequivalence and certain other approval requirements. To ensure you are aware of FDA's recommendations for the most accurate, sensitive, and reproducible methodology to demonstrate bioequivalence (21 CFR 320.24(a)), please continue to monitor for the availability of new and revised product-specific guidances in the *Federal Register* and on the FDA Web site at the following address:
https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm.

OTHER

The resubmission to this CR letter will be considered to represent a **MINOR** AMENDMENT, given that the deficiencies have been classified as **MINOR**.

Provided that the amendment contains no additional information that requires a substantial expenditure of resources to review, prominently identify the submission with the following wording in bold, capital letters at the top of the first page of the submission. If your submission includes gratuitous information in addition to the category or categories below, clearly identify the type of information submitted immediately following the wording below:

RESUBMISSION
MINOR
COMPLETE RESPONSE AMENDMENT
PRODUCT QUALITY / LABELING

Upon review of your amendment, FDA may identify information in the amendment that may require a change in classification and an adjustment to the goal date.

Within one year after the date of this letter, you are required to respond by taking one of the actions available under 21 CFR 314.110(b). If you do not take one of these actions, we may consider your lack of response as a request to withdraw the ANDA under 21 CFR 314.110(c)(1). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter does not fulfill the requirements in 21 CFR 314.110(b)(1) and therefore will not be processed as a resubmission and will not start a new review cycle.

The drug product may not be marketed without final Agency approval under section 505(j) of the FD&C Act.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[1] with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts. All finished dosage forms or active pharmaceutical ingredients manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self-identification or fee payment.

GDUFA II provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including by fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should

ensure your application addresses any changes to the RLD that occur after submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure you stay up to date with the Agency's current thinking on topics through guidances for industry, including product-specific guidances.

If you have any questions, call Megan Tychinski, Regulatory Project Manager, Division of Project Management, at (240) 402 - 2717.

Sincerely yours,

{See appended electronic signature page}

For Denise P. Toyer McKan, PharmD
Director, Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

[1] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).

Aaron Sigler

Digitally signed by Aaron Sigler
Date: 12/15/2022 02:46:14PM
GUID: 508da6fa0002827f1a9f2526d1b2cc69

ANDA 202827

DISCIPLINE REVIEW LETTER
LABELING

Hikma Pharmaceuticals USA Inc.
1809 Wilson Road
Columbus, OH 43228
Attention: George E. Prestash IV
Associate Director, Regulatory Affairs

Dear Sir:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on February 23, 2011, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Lisdexamfetamine Dimesylate Capsules, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg.

Reference is also made to any amendments submitted prior to the issuance of this letter.

The following comments have been identified by the Division of Labeling Review (DLR) based on your submission(s) on September 19, 2022. Prior to final approval, the proposed labeling should be clear and precise (grammar, spelling, and formatting) for end users, and accurately reflect the Reference Listed Drug (RLD) information to comply with FDA policies, laws, regulations (i.e., 21 CFR 314.94(a)(8)), official compendia, and relevant guidance.

PRESCRIBING INFORMATION

a. CONTENTS*: Delete (b) (4) the end of the table of contents (below "**17 PATIENT COUNSELING INFORMATION**").
b. **2.1 Pre-treatment Screening**, 1st sentence: Replace "children, adolescents, and adults" with "patients" and add "including lisdexamfetamine dimesylate capsules," after "CNS stimulants," in accordance with the RLD.
c. **2.2 General Instructions for Use**: Retain the heading "*Information for lisdexamfetamine dimesylate capsules:*" in accordance with the RLD.
d. **2.5** subsection heading: Add "in" for clarity as such:
   2.5 Dosage in Patients with Renal Impairment.
e. **5.2 Serious Cardiovascular Reactions**, 2nd sentence: Replace "children and adolescents" with "pediatric patients" in accordance with the RLD.
f. **6.1 Clinical Trials Experience**, 2nd heading: Add "ADHD" in the heading as such:

Adverse Reactions Associated with Discontinuation of Treatment in ADHD Clinical Trials:

g. **Table 1** title: Revise in accordance with the RLD as such:
Table 1 Adverse Reactions Reported by 2% or More of Pediatric Patients Ages 6 to 12 Years with ADHD Taking Lisdexamfetamine Dimesylate and Greater than or Equal to Twice the Incidence in Patients Taking Placebo in a 4-Week Clinical Trial (Study 1)
h. **Table 1**, Insomnia row: Revise (b) (4)% to "22%" in accordance with the RLD.
i. **Table 2** title: Revise in accordance with the RLD as such:
Table 2 Adverse Reactions Reported by 2% or More of Pediatric Patients Ages 13 to 17 Years with ADHD Taking Lisdexamfetamine Dimesylate and Greater than or Equal to Twice the Incidence in Patients Taking Placebo in a 4-Week Clinical Trial (Study 4)
j. **Table 3** title: Add "with ADHD" in accordance with the RLD.
k. **8.5 Geriatric Use**, 2nd sentence: Revise beginning of the sentence to read, "Other reported clinical experience and pharmacokinetic data *[see Clinical Pharmacology (12.3)]* have not identified..." in accordance with the RLD.
l. **Figure 4** title: Replace "Children" with "Pediatric Patients" in accordance with the RLD.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the Electronic Orange Book are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

If you would like to respond to these possible deficiencies before the end of this review cycle, we request a complete written response to this discipline review letter (DRL) no later than November 28, 2022. If you submit a written response during this review cycle, depending on the timing and/or the information contained in your response, we may not be able to consider your response before taking action on your application. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

DISCIPLINE REVIEW LETTER
LABELING
MINOR

Please note that we are providing these preliminary thoughts on possible deficiencies to you before a complete review of your entire application. As contemplated in the Generic Drug User Fee Amendments of 2022 (GDUFA III)[1], these possible deficiencies do not reflect a complete review of your application and should not be construed as such. In addition, these possible deficiencies do not necessarily reflect input from supervisory levels. You should be aware that these deficiencies may be modified or additional deficiencies may be identified as we complete our review of your entire application.

Deficiencies addressed by applicants in a response to a DRL may appear in a Complete Response Letter (CRL) if FDA's review of the response has been deferred or if FDA has outstanding concerns after review of the response. The CRL will include all deficiencies that must be satisfactorily addressed before the ANDA can be approved.

If the applicant receives a CRL, but has already responded to some (or all) identified deficiencies in a DRL response, the applicant does not need to re-submit previously submitted information in a CRL amendment. However, the applicant should still submit a CRL amendment and should clearly identify the previously provided DRL response that renders its CRL amendment complete.

Additionally, please take note of the following if you choose to respond to these possible deficiencies before the end of this review cycle:

1. If your submission is a response to a Major DRL received by the due date (or any agreed-upon extension), FDA may classify the response as Major and assign an appropriate goal date for that amendment.
2. If you do not respond by the requested due date, FDA may defer review of your response.
3. FDA will strive to review your response during the review cycle in which it is received if such review can be completed during such review cycle. However, if

[1] GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2023-2027 (available at https://www.fda.gov/media/153631/download).

the Agency determines that it cannot review the response before a goal date or if a complete response letter is otherwise ready to be issued, the review of your response may be deferred. When FDA defers review of your response, it will be reviewed during the next review cycle for the application.

4. If you are responding to a late cycle DRL[2], the goal date may be extended based upon the major or minor deficiencies included upon receipt of the response.
5. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as a major or minor amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

As described in FDA's draft guidance for industry *Cover Letter Attachments for Controlled Correspondences and ANDA Submissions*, FDA recommends that you include the appropriate attachment(s) along with the cover letter for your submission to help FDA ensure that your submission is properly triaged and assigned to the appropriate assessors. This will also ensure that submissions are effectively managed by FDA and acted upon within the performance review goal dates set by the Generic Drug User Fee Amendments.

If you have any questions, please contact Julie Call, Labeling Project Manager, at julie.call@fda.hhs.gov or 240-402-8598.

Sincerely,

{See appended electronic signature page}

Julie Call, PharmD, PMP
Labeling Project Manager
Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

[2] Late cycle defined as IRs or DRLs issued after the mid-cycle of an original ANDA or IRs or DRLs issued less than 90 days from the goal date of an ANDA amendment

Julie
Call

Digitally signed by Julie Call
Date: 11/18/2022 04:17:52PM
GUID: 525d9e9d00038c406bce70608a211ab1

EASILY CORRECTABLE DEFICIENCY FAX

ANDA 202827

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Roxane Laboratories, Inc. TEL: 614-272-4785

ATTN: Tony Amann FAX: 614-276-2470

FROM: Jennifer Nguyen FDA CONTACT PHONE: 240-402-8729

Dear Sir:

This communication is in reference to your abbreviated new drug application (ANDA) dated February 23, 2011 submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lisdexamfetamine Dimesylate Capsules 20, 30, 40, 50, 60, and 70 mg.

The deficiencies presented below represent *EASILY CORRECTABLE DEFICIENCIES* identified during the review and the current review cycle will remain open. You should provide a complete response to these deficiencies with an "*EASILY CORRECTABLE DEFICIENCY AMENDMENT*" within ten (10) business days.

If you do not submit a complete response within ten (10) business days, the review will be closed and the listed deficiencies will be incorporated in the next COMPLETE RESPONSE. Please provide your response after that complete response communication is received along with your response to any other issued comments. In addition, please notify the Regulatory Project Manager.

Please submit official archival copies of your response to the ANDA, facsimile or e-mail responses will not be accepted. A partial response to this communication will not be processed as an amendment and will not start a review. Please notify the Regulatory Project Manager when your amendment has been submitted.

If you have questions regarding these deficiencies please contact the Regulatory Project Manager, Andrew Kim at (240) 276-8438.

SPECIAL INSTRUCTIONS:

We have completed our review, as amended, and have the following comments:

(b) (4)

Sincerely yours,

{See appended electronic signature page}

Naiqi Ya, Ph.D.
Acting Director
Division of Chemistry IV
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ZHIGANG SUN
05/08/2014

EASILY CORRECTABLE DEFICIENCY FAX

ANDA 202827

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Roxane Laboratories, Inc. TEL: 614-272-4785

ATTN: Tony Amann FAX: 614-276-2470

FROM: Jennifer Nguyen FDA CONTACT PHONE: (240) 276-8707

Dear Sir:

This communication is in reference to your abbreviated new drug application (ANDA) dated February 23, 2011 submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lisdexamfetamine Dimesylate Capsules 20, 30, 40, 50, 60, and 70 mg.

The deficiencies presented below represent *EASILY CORRECTABLE DEFICIENCIES* identified during the review and the current review cycle will remain open. You should provide a complete response to these deficiencies with an "*EASILY CORRECTABLE DEFICIENCY AMENDMENT*" within ten (10) business days.

If you do not submit a complete response within ten (10) business days, the review will be closed and the listed deficiencies will be incorporated in the next COMPLETE RESPONSE. Please provide your response after that complete response communication is received along with your response to any other issued comments. In addition, please notify the Regulatory Project Manager.

Please submit official archival copies of your response to the ANDA, facsimile or e-mail responses will not be accepted. A partial response to this communication will not be processed as an amendment and will not start a review. Please notify the Regulatory Project Manager when your amendment has been submitted.

If you have questions regarding these deficiencies please contact the Regulatory Project Manager, Andrew Kim at (240) 276-8438.

SPECIAL INSTRUCTIONS:

We have completed our review, as amended, and have the following comments:

PRODUCT QUALITY

Sincerely yours,

{See appended electronic signature page}

Robert Iser, Ph.D.
Director
Division of Chemistry IV
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HUIJEONG A JUNG
03/24/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 202827

COMPLETE RESPONSE

Roxane Laboratories, Inc.
Attention: Anton Amann
Executive Director, Drug Regulatory Affairs and Medical Affairs
1809 Wilson Road
Columbus, OH 43228

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated February 23, 2011, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lisdexamfetamine Dimesylate Capsules 20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg.

We acknowledge receipt of your amendments dated February 6, and July 25, 2013.

The February 6, 2013 submission constituted a complete response to our January 7, 2013 action letter.

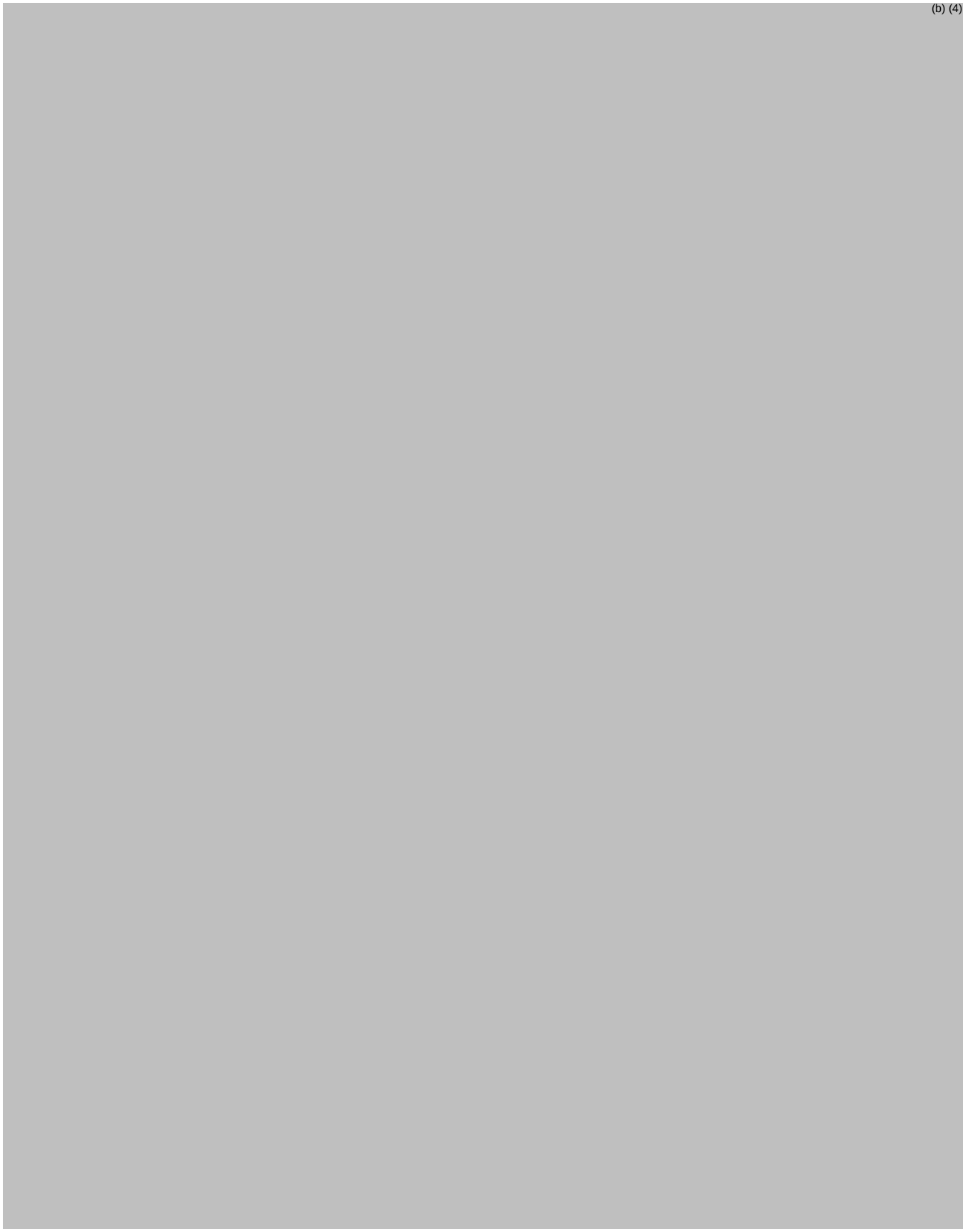
We also acknowledge receipt of your amendment dated October 18, 2013, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this ANDA, as amended, and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

(b) (4)

(b) (4)



(b) (4)

[redacted]

BIOEQUIVALENCE

The Division of Bioequivalence has completed its review and has no further questions at this time. The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

LABELING

Labeling Deficiencies determined on June 20, 2013 based on your submission dated February 6, 2013:

1. GENERAL COMMENT

   To assist in our review, we request that labeling be submitted in MS Word format. We note that the February 6, 2013 insert labeling submission in MS Word format did not match the February 6, 2013 FPL submission.

2. PRESCRIBING INFORMATION/PHYSICIAN INSERT

   Please revise your labeling in accordance to the most recently approved reference listed drug (RLD) labeling (NDA 021977/S-028, approved June 14, 2013). We refer you to the Drugs@FDA website for the RLD labeling.

3. MEDICATION GUIDE

   We refer you to PRESCRIBING INFORMATION/PHYSICIAN INSERT comment.

4. SPL

   The SPL provided does not contain the most recently approved language as found in the RLD labeling. Please revise.

Submit your revised labeling electronically in final print format.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained.

Prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the Electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

FACILITY INSPECTIONS

Office of Compliance has no further questions at this time. The compliance status of each facility named in the application may be re-evaluated upon re-submission.

OTHER

A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

RESUBMISSION
MINOR
COMPLETE RESPONSE AMENDMENT
CHEMISTRY / LABELING

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the ANDA under 21 CFR 314.65. You may also request an extension of time in which to resubmit the ANDA. A resubmission response must fully address all the deficiencies listed.

The drug product may not be legally marketed until you have been notified in writing that this ANDA is approved.

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of

an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self identification or fee payment.

Additionally, we note that the failure of any facility referenced in the application to self-identify and pay applicable fees means that FDA will not consider the GDUFA application review goal dates to apply to that application.

If you have any questions, call Andrew Kim, Regulatory Project Manager, at (240) 276-8438.

Sincerely yours,

{See appended electronic signature page}

Kathleen Uhl, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT L WEST

10/24/2013

Deputy Director, Office of Generic Drugs, for
Kathleen Uhl, M.D.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 202827

COMPLETE RESPONSE

Roxane Laboratories, Inc.
Attention: Randall S. Wilson
1809 Wilson Road
Columbus, OH 43228

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated February 23, 2011 submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lisdexamfetamine Dimesylate Capsules 20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg.

We acknowledge receipt of your amendments dated April 8, April 22, August 2, November 8, and December 22, 2011; August 14, August 20, September 21, November 8, 2012.

We have completed our review of this ANDA, as amended, and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

Please see the major deficiency letter issued by the Division of Chemistry on August 30, 2012.

BIOEQUIVALENCE

The Division of Bioequivalence II (DB II) has completed its review and has no further questions at this time.

We acknowledge that you will conduct dissolution testing using the following dissolution method and specification. The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37ºC ± 0.5ºC using USP apparatus 2 (paddle) with sinker at 50 rpm. The test product should meet the following specification:

NLT (b)(4)% (Q) in 15 minutes

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional

bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

LABELING

Labeling Deficiencies determined on November 12, 2012 based on your submission dated August 14, 2012:

1. **GENERAL COMMENT**
   To assist in our review, we request that labeling also be submitted in MS Word format.

2. **PRESCRIBING INFORMATION/PHYSICIAN INSERT:**
   a. FULL PRESCRIBING INFORMATION: CONTENTS: Please ensure that your section titles match the section titles in the approved labeling of the innovator. There are some slight inconsistencies. For example, the title for section 5.1 should read, "Serious Cardiovascular Reactions" not "Serious Cardiovascular Events".
   b. We believe the following information in 14 CLINICAL STUDIES to be protected under the I-645 exclusivity (MAINTENANCE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN ADULTS):

   Maintenance of Efficacy Study (Study 7): A double-blind, placebo-controlled, randomized withdrawal design study was conducted in adults ages 18 to 55 (N=123) who had a documented diagnosis of ADHD or met DSM-IV with adult prompts criteria for ADHD. At study entry, patients must have had documentation of treatment with lisdexamfetamine dimesylate for a minimum of 6 months and had to demonstrate treatment response as defined by CGI-S ≤3 and Total Score on the ADHD-RS with adult prompts <22. ADHD-RS Total Score is a measure of core symptoms of ADHD. Patients that maintained treatment response at week 3 of open label treatment phase (N=116) were eligible to be randomized to ongoing treatment with the same dose of lisdexamfetamine dimesylate (N=56) or switched to placebo (N=60) during the doubleblind phase. Patients were observed for relapse (treatment failure) during the 6 week double blind phase. Maintenance of efficacy for patients treated with lisdexamfetamine dimesylate was demonstrated by the significantly lower proportion of treatment failure (8.9%) compared to patients receiving placebo (75%) at endpoint during the double-blind randomized withdrawal phase (Figure 3). The endpoint measurement was defined as the last post-randomization treatment week at which a valid ADHD-RS with adult prompts total score and CGI-S were observed. Treatment failure was defined as a ≥50% increase (worsening) in the ADHD-RS with adult prompts Total Score and ≥2-point increase in the CGI-S score compared to scores at entry into the double-blind randomized withdrawal phase (Study 7, Figure 3).

   Revise to remove from your prescribing information.

   c. Please also remove, (b) (4)

3. SPL

The SPL provided does not contain the most recently approved language as found in the innovators labeling. Please revise

Submit your revised labeling electronically in final print format.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained.

Prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the Electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

OTHER

A partial response to this letter will not be processed as a resubmission and will not start a new review cycle. The resubmission to this will be considered to represent a **MAJOR** AMENDMENT. The designation as a **RESUBMISSION/AFTER ACTION MAJOR COMPLETE RESPONSE AMENDMENT** should appear prominently in your cover letter. In addition, please designate in bold on your cover letter each review discipline (Product Quality (CMC), Labeling, Bioequivalence, Microbiology, Clinical) you are providing responses to.

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the ANDA under 21 CFR 314.65. You may also request an extension of time in which to resubmit the ANDA. A resubmission response must fully address all the deficiencies listed.

The drug product may not be legally marketed until you have been notified in writing that this ANDA is approved.

If you have any questions, call, Andrew Kim, Regulatory Project Manager, at (240) 276-8438

Sincerely yours,

{See appended electronic signature page}

Gregory P. Geba, M.D., M.P.H.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT L WEST

01/07/2013

Deputy Director, Office of Generic Drugs, for
Gregory P. Geba, M.D., M.P.H.

QUALITY DEFICIENCY - MAJOR

ANDA 202827

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

TO: Roxane Laboratories, Inc.

TEL: (614) 272-4785

ATTN: Sarah Smith

FAX: (614) 276-2470

FROM: Simon Eng

FDA CONTACT PHONE: (240) 276-8529

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated February 23, 2011, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lisdexamfetamine Dimesylate Capsules, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg.

Reference is also made to your amendments dated April 8 and April 22, 2011.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached ____ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a ***QUALITY MAJOR AMENDMENT*** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

All ANDA documents will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

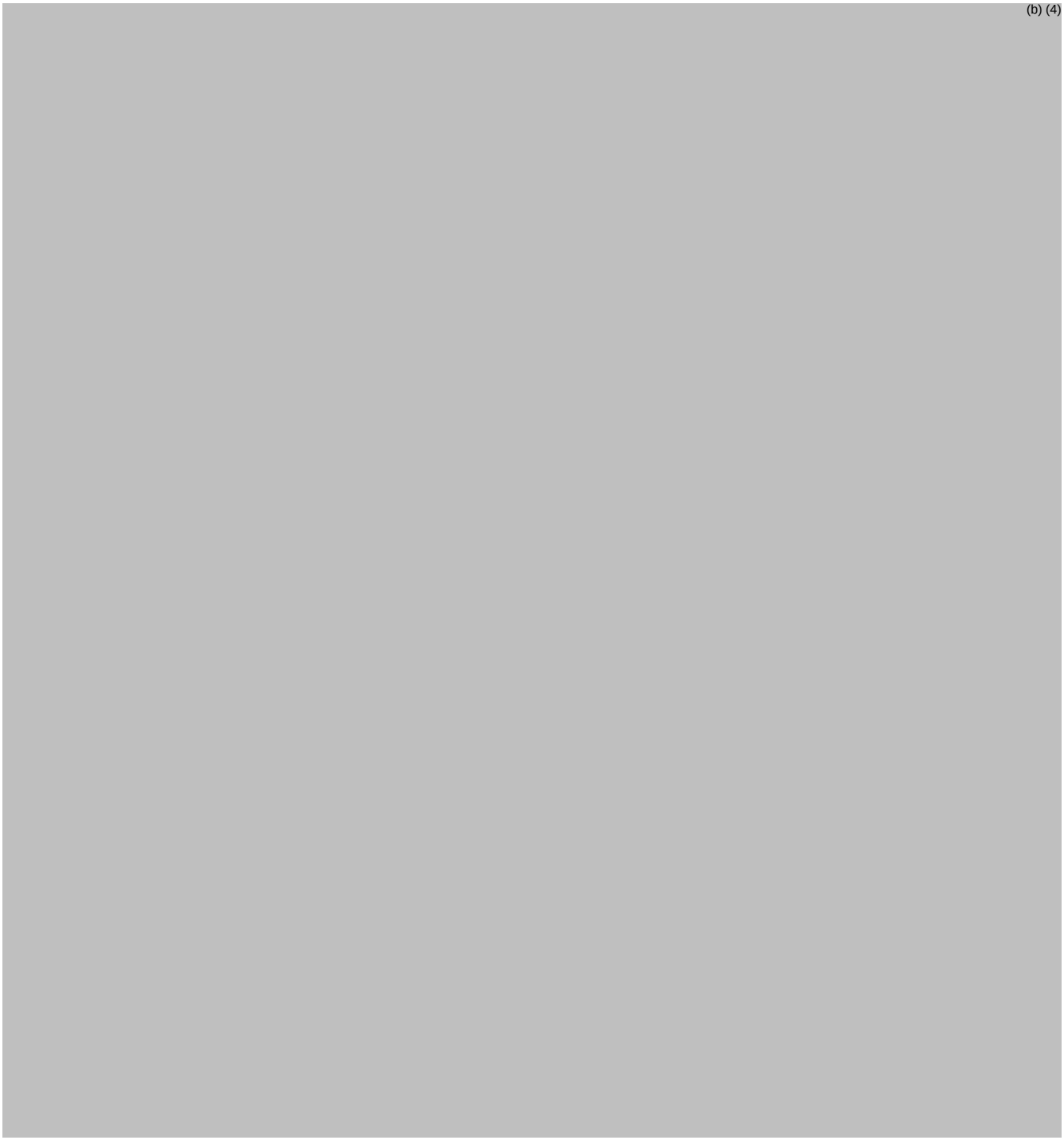
CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

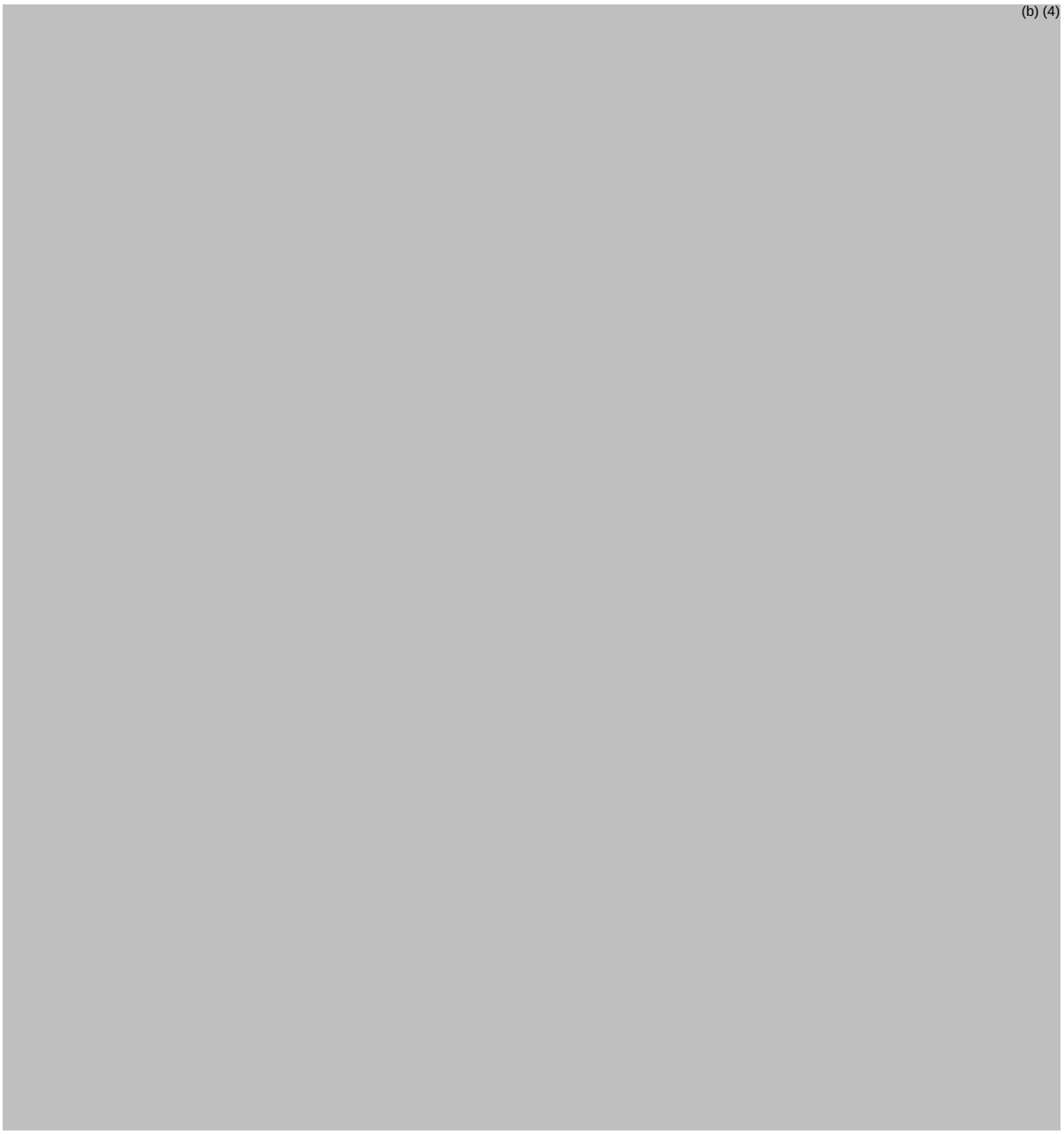
ANDA: 202-827 APPLICANT: Roxane Laboratories Inc.

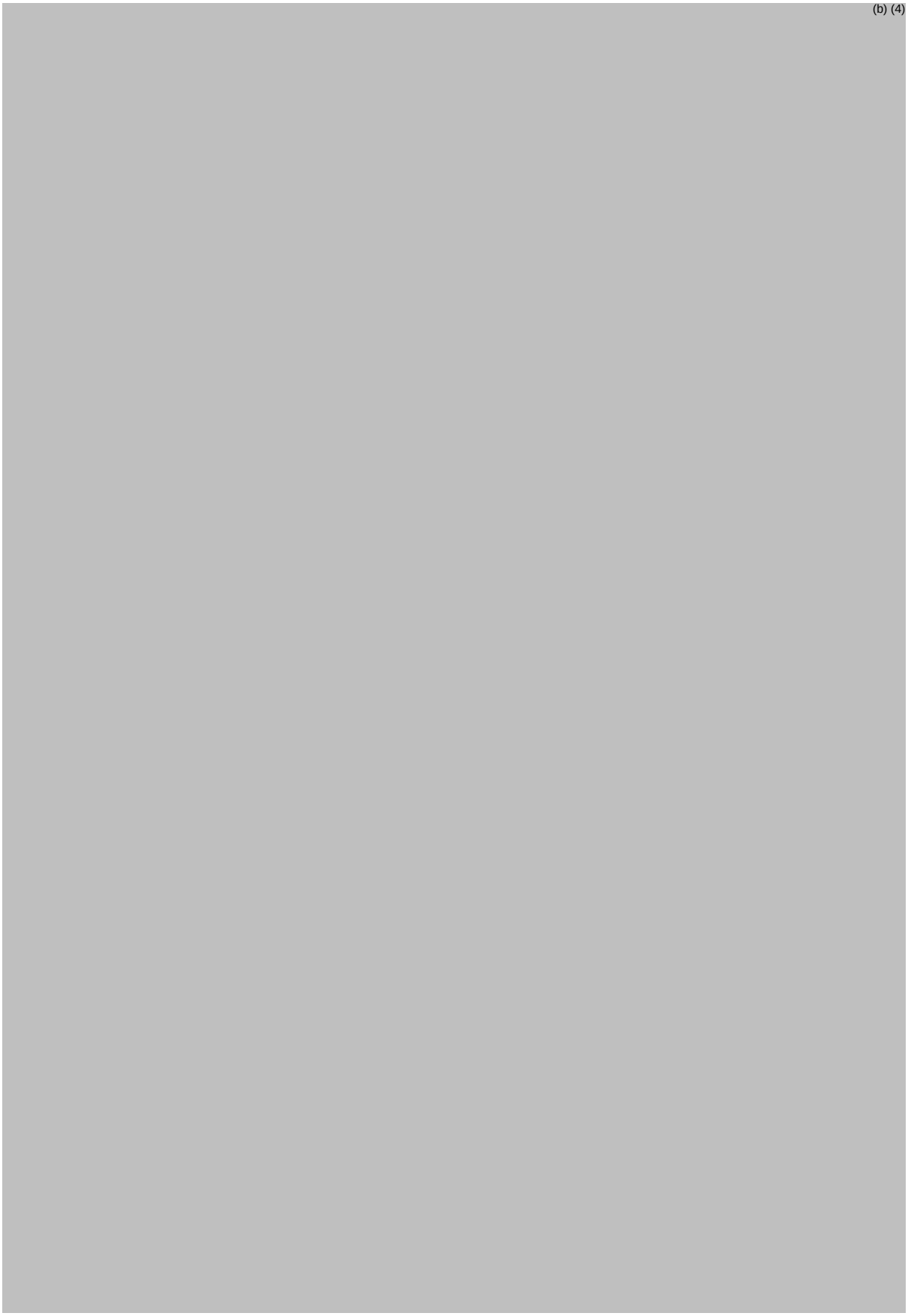
DRUG PRODUCT: Lisdexamfetamine Dimesylate Capsules, 20, 30, 40, 50, 60 and 70mg

The deficiencies presented below represent **MAJOR** deficiencies:

(b) (4)




(b) (4)


(b) (4)

Sincerely yours,

{See appended electronic signature page}

Robert Iser
Director
Division of Chemistry IV
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

HUIJEONG A JUNG
08/30/2012

BIOEQUIVALENCE AMENDMENT

ANDA 202827

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810

APPLICANT: Roxane Laboratories, Inc. TEL: (614) 272-4785

ATTN: Elizabeth Ernst FAX: (614) 276-2470

FROM: Scott Vehovic FDA CONTACT PHONE: (240) 276-8817

Dear Madam:

This facsimile is in reference to the bioequivalence data submitted on February 23, 2011, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lisdexamfetamine Dimesylate Capsules, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg.

Reference is also made to your amendment dated November 8, 2011.

The Division of Bioequivalence II has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **2** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Response to Information Request **Bioequivalence Other**

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response.**
Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence II, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents is:*

Office of Generic Drugs
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855-2810

ANDAs will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

Please submit your response in electronic format. This will improve document availability to review staff.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 202827

APPLICANT: Roxane Laboratories, Inc.

DRUG PRODUCT: Lisdexamfetamine Dimesylate Capsules, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, and 70 mg

The Division of Bioequivalence II (DB II) has completed its review and the following deficiencies have been identified:

1. For Lisdexamfetamine, you re-assayed a total of 319 samples due to unacceptable internal standard response (i.e., 134 samples in the fasting BE study No. LISD-C70-PVFS-1 and 185 samples in the fed BE study No. LISD-C70-PVFD-1). Please investigate and justify the high number of samples repeated due to internal standard response.

2. In the Tables 2A and 2B (Reassayed Samples) of the analytical reports (Project AFUB) for both the fasting and fed BE studies, you did not provide the original values for the reassayed samples, instead citing NRR (No Recorded Result). Please provide original values and chromatograms for all repeated samples.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ETHAN M STIER on behalf of BARBARA M DAVIT
12/13/2011