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***APPLICATION NUMBER:***

# 022063Orig1s000

# NON-CLINICAL REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**

# PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

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| Application number: | NDA 22063 |
| Supporting document/s: | Supporting Document Number 44, Applicant Serial number 22 |
| Applicant's letter date: | December 20, 2016 (Resubmission/Class 2) |
| CDER stamp date: | December 20, 2016 |
| Product: | SPD 465; Mydayis™ (Mixed salts of a single-entity Amphetamine) |
| Indication: | Attention Deficit Hyperactivity Disorder (ADHD) |
| Applicant: | Shire Development LLC |
| Review Division: | Division of Psychiatry Products |
| Reviewer: | Deepa B. Rao DVM, PhD |
| Supervisor/Team Leader: | Ikram Elayan, PhD |
| Division Director: | Mitchell V. Mathis MD |
| Project Manager: | Latrice Wilson, Pharm D |

## Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 22063 are owned by Shire Development LLC or are data for which Shire Development LLC has obtained a written right of reference.
Any information or data necessary for approval of NDA 22063 that Shire Development LLC does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 22063.

# TABLE OF CONTENTS

**Abbreviations**

| | |
|---|---|
| ADHD | Attention Deficit Hyperactivity Disorder |
| MAS | Mixed Amphetamine Salts |
| MRHD | Maximum Recommended Human Dose |

# 1 Executive Summary

## 1.1 Introduction

Shire Development LLC is seeking approval of SHP465 (under the trade name Mydayis™), for their once-daily new formulation, single-entity mixed amphetamine salt (MAS) drug product for oral administration in patients (b) (4) years old diagnosed with Attention Deficit Hyperactivity Disorder (ADHD). This new triple-bead formulation is based on the approved product Adderall® XR (NDA 21303), but allows relatively sustained-release delivery that extends up to 16 hours post-administration to provide ADHD patients with symptom control throughout the day following a convenient single morning dose.

This NDA 22063 is currently a Class 2/Resubmission by Shire Development LLC (filed under a 505(b)(1) application on 12 December, 2016). The original application was filed on 21 July 2006. An Approvable Letter was issued by FDA 18 May, 2007 under the trade name (b) (4) This current Class2/Resubmission aims to address all the deficiencies identified in the Approvable Letter.

## 1.2 Brief Discussion of Nonclinical Findings

From a nonclinical perspective, the original application was considered approvable pending the incorporation of the findings from additional nonclinical studies [pre- and postnatal developmental reproductive toxicology study and the juvenile animal study] into the drug's label.

Review of the pre- and postnatal reproductive toxicology study and the juvenile animal study were completed under the original application for this NDA 22063 by Dr.Ikram Elayan (dated May 10, 2007). Changes in activity, body weight, and reproductive performance were observed in the reproductive toxicology study as a result of treatment with amphetamine during pregnancy and lactation on the dams and the pups (F1 generation). Results from juvenile rat study indicated changes in activity, learning, and memory in pup rats treated with the MAS at a critical stage of their development (starting from post natal day 7 to maturation). Relevant changes from both studies are to be described in the labeling (see Section 1.3.3). Changes in the label (Sections 8 and 13) have been incorporated to include findings from these studies and to reflect consistency with the dose multiples based on the most sensitive and appropriate population age group of patients.

Information on nonclinical findings for carcinogenicity studies, genotoxicity studies, and fertility studies are minimally modified from the label for Adderall® XR to reflect dose multiples based on the most sensitive and appropriate population group of patients.

The new formulation includes an excipient (b) (4) Nonclinical studies for qualification of this excipient were reviewed under DMF (b) (4) (see Dr.Elayan's review dated May 10, 2007 under NDA 22063), and were considered adequate based on the results indicating that the excipient is not absorbed systemically in the rat and clinical data submitted by the sponsor (see Section 2.4).

Other nonclinical studies were reviewed under NDA 22063 (pharmacodynamics – effect on cytochrome P450 activities), or under NDA 21303 (genotoxicity). NDA 21303 is also owned by Shire Development LLC. A list of supporting nonclinical studies with corresponding reviews is documented under Section 3.3. The original NDA for Adderall® IR (NDA 11522) was approved by FDA on 19 January 1960.

## 1.3 Recommendations

### 1.3.1 Approvability

Based on the long history of clinical use of the active ingredients, supporting nonclinical studies that demonstrate the lack of systemic absorption of (b) (4) (b) (4) Mydayis™ appears to be reasonably safe for approval.

### 1.3.3 Labeling

Sections 8 and 13 have been excerpted from the sponsor's submission (Word file dated 12/2016 under Module 1.14.1.2). Proposed changes are underlined and italicized in blue below. It should be noted that the following label changes documented in this review are work-in- progress changes to the most updated version of the label, and may not reflect the finalized label (pending at this time) accurately.

**8 USE IN SPECIFIC POPULATIONS**

## 8.1 Pregnancy

Risk Summary

The limited available data from published literature and postmarketing reports on use of amphetamine 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 an embryofetal development study, amphetamine (*d*- to *l*- enantiomer ratio of 3:1, the same as in MYDAYIS) had no effects on embryofetal morphological development or survival when administered to pregnant rats and rabbits throughout the period of organogenesis *up to doses 10 times the maximum recommended human dose (MRHD).* However, in a pre- and post-natal development study, amphetamine (*d*- to *l*- ratio of 3:1) administered orally 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 MYDAYIS, 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*
Amphetamine (*d*- to *l*- enantiomer ratio of 3:1, the same as in MYDAYIS) had no apparent effects on embryofetal morphological development or survival when administered orally to pregnant rats and rabbits throughout the period of organogenesis at doses of up to 6 and 16 mg/kg/day, respectively. These doses are approximately (b) (4) 2 and 10 times, respectively, the ~~maximum recommended human dose~~ (MRHD) of 25 mg/day given to adolescents, on a mg/m$^2$ body surface area basis.
*Fetal malformations and death have been reported in mice following parenteral administration of d-amphetamine doses of 50 mg/kg/day (approximately 8 times the MRHD for adolescents on a mg/m$^2$ basis) or greater to pregnant animals. Administration of these doses was also associated with severe maternal toxicity.*

A pre- and postnatal development 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. These doses are approximately 0.6, (b) (4) 2, and 3 (b) (4) times the MRHD of amphetamine (*d*- to *l*- ratio of 3:1) for adolescents of 25 mg/day, on a mg/m$^2$ basis. 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

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 MYDAYIS.

## 8.4 Pediatric Use

Safety and effectiveness in pediatric patients with ADHD ages (b) (4) to 17 years has been established in two placebo-controlled clinical studies *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14)]*.

Safety and effectiveness in pediatric patients under (b) (4) years of age has not been established.

Growth Suppression

Growth should be monitored during treatment with stimulants, including MYDAYIS, and children who are not growing or gaining weight as expected may need to have their treatment interrupted *[see Warnings and Precautions (b) (4), Adverse Reactions (6.1)]*.

Juvenile Animal *Toxicity* Data

*Juvenile rats treated with mixed amphetamine salts (same as in MYDAYIS) early in the postnatal period through sexual maturation demonstrated transient changes in motor activity. Learning and memory was impaired at approximately 8 times the maximum recommended human dose (MRHD) given to children on a mg/m$^2$ basis. No recovery was seen following a drug free period. A delay in sexual maturation was observed at a dose approximately 8 times the MRHD in children on a mg/m2 basis, although there was no effect on fertility.*

In a juvenile developmental study rats received daily oral doses of amphetamine (*d* to *l* enantiomer ratio of 3:1, the same as in MYDAYIS) of 2, 6, or 20 mg/kg on days 7-13 of age; from day 14 to approximately day 60 of age these doses were given b.i.d. for total daily doses of 4, 12, or 40 mg/kg. The latter doses are approximately 0.8, 2 (b) (4) and (b) (4) 8 times the maximum recommended daily dose of (b) (4) 25 mg given to (b) (4) children on a mg/m$^2$ basis. Post-dosing hyperactivity was seen at all doses; motor activity measured prior to the daily dose was decreased during the dosing period but the decreased motor activity was largely absent after an 18 day drug-free recovery period. Performance in the Morris water maze test for learning and memory was impaired at the 40 mg/kg dose, and sporadically at the lower doses, when measured prior to the daily dose during the treatment period; no recovery was seen after a 19 day drug-free period. A delay in the developmental milestones of vaginal opening and preputial separation was seen at 40 mg/kg but there was no effect on fertility.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No evidence of carcinogenicity was found in studies in which *d, l*-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. These doses are approximately (b) (4) and 1 times, respectively, the maximum recommended human dose of 50 mg/day on a mg/m$^2$ body surface area basis in adults.

Mutagenesis

Amphetamine, in the enantiomer ratio present, *d*- to *l*- ratio of 3:1, was not clastogenic in the mouse bone marrow micronucleus test *in vivo* and was negative when tested in the E. coli component of the Ames test *in vitro*. *d, l*-Amphetamine (1:1 enantiomer ratio) has been reported to produce a positive response in the mouse bone marrow micronucleus test, an equivocal response in the Ames test, and negative responses in the *in vitro* sister chromatid exchange and chromosomal aberration assays.

Impairment of Fertility

Amphetamines, in the enantiomer ratio, *d*- to *l*- 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 (approximately (b) (4) 6 times the maximum recommended ~~human~~ (b) (4) dose of (b) (4) 25 mg/day on a mg/m$^2$ body surface area basis).

# 2 Drug Information

## 2.1 Drug

The active ingredients in Mydayis™ contain MAS. The MAS include equal amounts of the neutral sulfate salts of dextroamphetamine and amphetamine, the dextro isomer of amphetamine saccharate and d,l-amphetamine aspartate monohydrate, with the enantiomer ratio of d-amphetamine and l-amphetamine being in 3:1. The generic name, chemical name and corresponding CAS Number is tabulated below:

| Active Pharmaceutical Ingredient | Chemical Name | CAS Number |
|---|---|---|
| Amphetamine sulfate, USP | (±)-α-Methylphenylamine sulfate | 60-13-9 |
| Dextroamphetamine sulfate, USP | (+)-α-Methylphenylamine sulfate | 51-63-8 |
| Amphetamine aspartate monohydrate | (±)-α-Methylphenylamine aspartate monohydrate | 350708-35-9 |
| Dextroamphetamine saccharate | (+)-α-Methylphenylamine saccharate | 350708-40-6 |

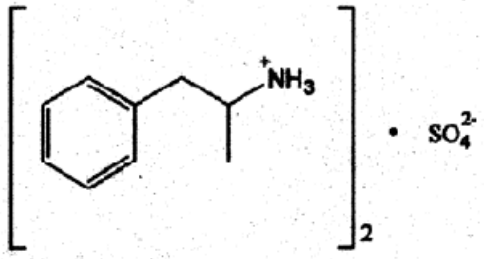
The molecular formula/molecular weight and structure for each active ingredient is depicted below:

**Amphetamine sulfate, USP**

**Molecular Formula:** $(C_9H_{13}N)_2 \cdot H_2SO_4$

**Molecular Weight:** 368.50

**CAS no. 60-13-9**

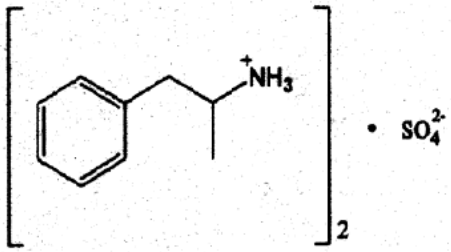


**Dextroamphetamine sulfate, USP**

**Molecular Formula:** $(C_9H_{13}N)_2 \cdot H_2SO_4$

**Molecular Weight:** 368.50

**CAS no. 51-63-8**

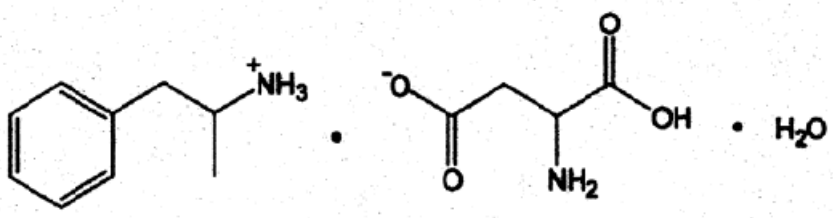


**Amphetamine aspartate monohydrate**

**Molecular Formula:** $C_9H_{13}N \cdot C_4H_7NO_4 \cdot H_2O$

**Molecular Weight:** 286.33

**CAS no.** 350708-35-9

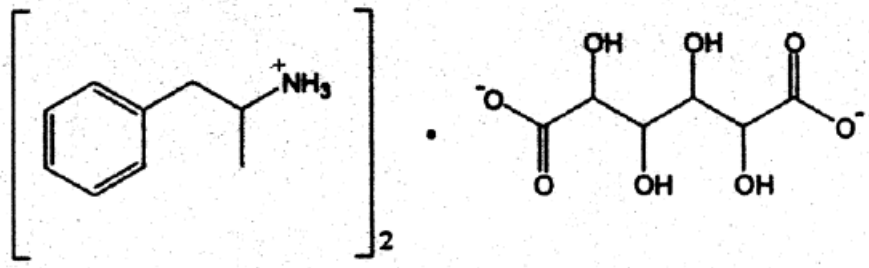


**Dextroamphetamine saccharate**

**Molecular Formula:** $(C_9H_{13}N)_2 \cdot C_6H_{10}O_8$

**Molecular Weight:** 480.56

**CAS no.** 350708-40-6



Generic Name
Mydayis™ (current resubmission)
(b) (4) (original application)

Code Name
SHP465
SPD465 (From Dr. Elayan's review dated May 10, 2007 under NDA 22063)

*Reviewer Note:*
*Nonclinical studies in Dr. Elayan's review refer to the drug product as SPD465, whereas this Class 2/Resubmission refers to the drug product as SHP465. Meeting Package dated 11 May, 2015 states that "The product was previously referred to as SPD465; however, it is now being studied under the code of SHP465".*

Pharmacologic Class
Central Nervous System (CNS) Stimulant

## 2.2 Relevant INDs, NDAs, and DMFs

IND 66329
Product Name: Mixed Salts of Single-Entity Amphetamine (SHP 465)
Sponsor: Shire Development Inc
Indication: ADHD
Status: Active since December 4, 2002

(b) (4)

NDA 21303
Product Name: Adderall® XR
Sponsor: Shire Development Inc
Indication: ADHD
Status: Approved on October 11, 2001

IND 58037
Product Name: Adderall® XR
Sponsor: Shire Development Inc
Indication: ADHD
Status: Active since March 25, 1999

NDA 11522
Product Name: Adderall® IR
Sponsor: Teva Womens Health Inc
Indication: Obesity
Status: Approved on January 19, 1960

## 2.3 Drug Formulation

Mydayis™ is a once-daily, triple-bead, sustained-release drug product formulation of MAS to be marketed as 12.5, 25, 37.5, and 50 mg strength capsules. A summary of the capsule components in tabled below:


The SL1381 IR and DR in the 12.5 mg capsules are from the approved Adderall XR® product. The composition of the beads (b) (4) are detailed in the Quality review. Individual inactive ingredients in the beads (b) (4) were considered to be within acceptable limits compared to the FDA inactive ingredients list.

## 2.4 Comments on Novel Excipients

The following is excerpted from Dr. Elayan's review dated May 10, 2007:
The nonclinical studies submitted for the qualification of the (b) (4) excipient (b) (4) are considered adequate for the purpose of the qualification and the results indicated that the excipient is not absorbed systemically in the rat, which is also believed to be true in humans based on the data submitted by the sponsor. All the studies demonstrated that the excipient at the doses used in these studies, did not result in any systemic toxicity. Therefore, it is considered that the levels of this excipient that humans will be exposed to will be safe and should not pose any systemic toxicity in response to oral administration. Moreover, the daily levels of the acrylate (b) (4) are considered to be acceptable as specified by the manufacturer of the excipient, and as expected from treatment with the high recommended dose. This is based on the fact that the levels of these (b) (4) in this drug product are much lower than levels found in other approved products containing similar (b) (4).

## 2.5 Comments on Impurities/Degradants of Concern

No nonclinical studies on impurities were conducted.
For a complete review, refer to the Quality review for this NDA.

## 2.6 Proposed Clinical Population and Dosing Regimen

Patients diagnosed with ADHD aged (b) (4) years.

## 2.7 Regulatory Background

NDA 22063 was originally submitted on 21 July 2006 (under the trade name (b) (4) and an Approvable Letter was issued to Shire on 18 May 2007.

# 3 Studies Submitted

No nonclinical studies have been submitted with this current Class 2/Resubmission.

## 3.3 Previous Reviews Referenced

Genotoxicity Studies:
The mouse micronucleus assay and the E.coli component of the Ames assay were reviewed under NDA 21303 by Dr. Edward Fisher (review dated August 7, 2001 in DARRTS)

Reproductive Toxicology Studies:
The fertility studies (Segment 1), and the embryo-fetal toxicity studies (Segment 2) were reviewed under NDA 21303 by Dr. Edward Fisher (review dated August 7, 2001 in DARRTS). The prenatal and postnatal toxicity studies (Segment 3), and the juvenile animal studies were submitted to NDA 21303 (DARRTS SDN 96, June 7, 2004), and reviewed under the current NDA 22063 by Dr. Ikram Elayan (review dated May 10, 2007).

Nonclinical studies to support the use of the excipient (b) (4) were submitted to DMF (b) (4) and have been reviewed under the current NDA 22063 by Dr. Ikram Elayan (review dated May 10, 2007).

Other reviews of literature and limited data are included under NDA 11522 (approved 19 January 1960).

# 4 Pharmacology

## 4.1 Primary Pharmacology

Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The exact mode of therapeutic action in ADHD is not known.

# 11 Integrated Summary and Safety Evaluation

Based on Shire Development LLC's original drug product Adderall® XR under NDA 21303 for ADHD (approved on October 11, 2001), the sponsor has pursued a new formulation that is longer acting extending up to 16 hours post-administration. This new formulation was originally filed on 21 July, 2006 under this NDA 22063. An Approvable Letter (18 May 2007) was issued by the FDA on 18 May 2007 for NDA 22063 (under the trade name (b) (4) Currently, this NDA 22063 is a Class 2 resubmission by Shire Development LLC filed on December 12, 2016 under a 505(b)(1) application that aims to address all the deficiencies identified in the Approvable Letter.

From a nonclinical perspective, the original application filed in 2006 was considered approvable pending the incorporation of the findings from additional nonclinical studies [pre- and postnatal reproductive toxicology study and the juvenile animal study] into the drug's label.

The new formulation (under the tradename Mydayis™ ) is a single-entity MAS product for oral administration in patients (b) (4) years old diagnosed with ADHD. MAS have been approved since 19 January, 1960 (under NDA 11522 as Adderall® IR).

It should be noted that nonclinical studies in Dr. Elayan's review refer to the drug product as SPD465, whereas this Class 2/Resubmission refers to the drug product as SHP465. Meeting Package dated 11 May, 2015 states that "The product was previously referred to as SPD465; however, it is now being studied under the code of SHP465".

The active ingredients in Mydayis™ is MAS (similar to Adderall® XR) include equal amounts of the neutral sulfate salts of dextroamphetamine and amphetamine, the dextro isomer of amphetamine saccharate and d,l-amphetamine aspartate monohydrate, with the enantiomer ratio of d-amphetamine and l-amphetamine being in 3:1. The new formulation includes an excipient (b) (4), namely, (b) (4) Moreover, the daily levels of the acrylate (b) (4) are considered to be acceptable as specified by the manufacturer of the excipient, and as expected from treatment with the high recommended dose. This is based on the fact that the levels of these (b) (4) in this drug product are much lower than levels found in other approved products containing similar (b) (4).

No additional nonclinical studies were submitted or reviewed under this Class 2/ Resubmission.

Nonclinical toxicology studies for qualification of (b) (4) were reviewed under DMF (b) (4) (see Dr. Elayan's review dated May 10, 2007 under NDA 22063), and were considered adequate based on the results indicating that the excipient is not absorbed systemically in the rat and clinical data submitted by the sponsor (see Section 2.4).

Review of the pre- and postnatal reproductive toxicology study and the juvenile animal study were completed under the original application for this NDA 22063 by Dr. Ikram Elayan (dated May 10, 2007). Changes in activity, body weight, and reproductive performance were observed in the reproductive toxicology studies as a result of treatment with amphetamine during pregnancy and lactation on the dams and the pups (F1 generation). Results from juvenile rat study indicated changes in activity, learning, and memory in pup rats treated with the Adderall mixture at a critical stage of their development (starting from post natal day 7 to maturation). Relevant changes from both studies are to be described in the labeling (see Section 1.3.3). Changes in the label (Sections 8 and 13) have been incorporated to include findings from these studies and changes to reflect consistency with the dose multiples based on the most sensitive and appropriate population age group of patients.

Information on nonclinical findings for carcinogenicity studies, genotoxicity studies, and fertility studies (reproductive toxicology studies segment 1) are minimally modified from

the label for Adderall® XR to reflect dose multiples based on the most sensitive and appropriate population age group of patients.

Other nonclinical studies were reviewed under NDA 22063 (pharmacodynamics – effect on cytochrome P450 activities), or under NDA 21303 (genotoxicity). NDA 21303 is also owned by Shire Development LLC. A list of supporting nonclinical studies with corresponding reviews is documented under Section 3.3. The original NDA for Adderall (NDA 11522) was approved by FDA on 19 January 1960.

Based on the long history of clinical use of the active ingredients, supporting nonclinical toxicology studies that demonstrate the lack of systemic absorption of the copolymer excipient (b) (4) and acceptable level of acrylate (b) (4) based on the high recommended dose when compared to other approved products, Mydayis™ appears to be reasonably safe for approval.

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/s/

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DEEPA B RAO
05/25/2017

IKRAM M ELAYAN
05/25/2017