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APPLICATION NUMBER:

21-303/S-001

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

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OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Date of Document: 10/26/01, 11/16/01, 1/29/02

sNDA:	21-303/S001
Name of Drug:	Adderall XR (Mixed Amphetamine and Dextroamphetamine Salts) 10 mg, 20 mg and 30 mg Capsules
Indication of Drug:	Treatment of Attention-Deficit/Hyperactivity Disorder (ADHD)
Type of Document:	New Supplement for the Addition of New Strengths, 5, 15 and 25 mg Capsules
Sponsor:	Shire Laboratories Inc., Rockville, MD
Reviewer:	Hong Zhao, Ph.D.

Overall Summary

Adderall XR is a modified-release capsule formulation based on the existing immediate-release (IR) tablet of Adderall® (mixed salts of a single-entity amphetamine product). Both Adderall XR and Adderall IR contain *d*-amphetamine and *l*-amphetamine salts in the ratio of 3:1. The Adderall XR formulation consists of two types of pellets in the ratio of — in a gelatin capsule: an IR pellet and a delayed-release (DR) pellet with the pulsatile delivery scheme mimicking the effects of taking two doses of IR medication 4 hours apart. The mechanism of drug release from the DR (enteric-coated) pellets is based on the higher pH values found in the small intestine compared with the stomach.

Adderall XR capsules in strengths of 10, 20 and 30 mg have recently been approved for the treatment of attention-deficit/hyperactivity disorder (ADHD). Adderall XR capsules in strengths of 5, 15 and 25 mg have been developed to extend the available dosing options. The 15 mg and 25 mg capsules contain the same IR and DR pellets in the same proportions as the approved strengths and have similar dissolution profiles. Therefore, the *in vivo* bioequivalence study of these two strengths are not conducted. The 5 mg capsule, however, uses the same DR pellet and a [redacted] An *in vivo* study has been conducted to assess its bioequivalence to the 20 mg Adderall XR capsule following a single dose of 20 mg (4x5 mg vs. 1x20 mg). The bioequivalence between the two strengths at the same dose has been established for both *d*- and *l*-amphetamine determined in this study.

Major Findings:

1. Bioequivalence (single dose, 4x5 mg vs. 1x20 mg): Bioequivalence was demonstrated between Adderall XR 4x5 mg capsules and Adderall XR 1x20 mg capsule in terms of rate and extent of absorption.

2. Dissolution: Taking the 20 mg biobatch as the reference and using the approved dissolution method, the value of the similarity factor for each of the new strengths was greater than 50, indicating that the dissolution profiles are similar.

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Comment to the Sponsor

The sponsor is requested to adopt the following dissolution method and specifications for all six strengths (5, 10, 15, 20, 25 and 30 mg) of Adderall XR capsules:

Apparatus: USP Apparatus II (paddle) at [redacted]
Media: [redacted]

Specifications: [redacted]

Recommendation

This submission (NDA 21-303/S001) has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) and has been found to be acceptable for allowing the approval of the three new strengths (5 mg, 15 mg and 25 mg). The sponsor is requested to adopt the dissolution methodology and specifications for all six strengths of Adderall XR capsules, as outlined in Comment to the Sponsor.

Hong Zhao, Ph.D._____

RD/FT Initialed by Raman Baweja, Ph.D._____

cc: NDA 21-303/S001 (Adderall XR) HFD-120, HFD-860 (Zhao, Baweja, Mehta), Central Documents Room (Biopharm-CDR)

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Study Review

In support of the addition of the new strength of Adderall XR capsule (5 mg) which uses the same delayed-release (DR) pellet and a [redacted] the sponsor has conducted a bioequivalence study comparing this new 5 mg strength to the approved 20 mg strength (4x5 mg to 1x20 mg capsule). Comparable dissolution profiles are provided to support the approval of the other two new strengths (15 mg and 25 mg) which contain the same IR and DR pellets in the same proportions as the approved strengths.

The following questions have been raised and answered through the review of this supplement NDA:

Question 1: ***Are the new strengths compositionally proportional to the approved strengths?***

Yes. The two new strengths (15 mg and 25 mg) contain the same IR and DR pellets in the same proportions as the approved strengths. Comparable dissolution performance using the approved dissolution method should be sufficient to support the approval for these two strengths.

No. The 5 mg capsule, however, uses the same DR pellets [redacted] An *in vivo* bioequivalence study has been conducted to support the approval of the 5 mg strength.

The compositions of these new strengths are shown in the following tables:

Table 1. Hard Gelatin Capsule Size and Intermediate Pellet Active Dose Amounts Used in the New Strengths of Adderall XR Capsules

Adderall XR Capsules	Hard Gelatin Capsule Size	Active Dose Amounts from [redacted]/IR Pellet	from DR Pellet
5-mg Capsules	Capsugel Size #	[redacted]	[redacted]
15-mg Capsules	Capsugel Size #		
25-mg Capsules	Capsugel Size #		

Table 2. Weight Percentage of Components in the Adderall XR QIR Pellets and IR Pellets

Component	[redacted]* Pellets	IR Pellets
	Weight Percent (%)	
Amphetamine Aspartate	[redacted]	
Amphetamine Sulfate, USP		
Dextroamphetamine Saccharate		
Dextroamphetamine Sulfate, USP		
Hydroxypropylmethyl Cellulose, USP		
Sugar Spheres		[redacted]
Opadry Beige (		
Total	100.00	100.00

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Question 2: ***What was the bioequivalence study design?***

This (Study 381.106) was a randomized, open-label, two-way crossover study. Twenty pediatric ADHD patients (17 males and 3 females) with 6 to 12 years of age received a single 20 mg dose of each capsule strength (4x5 mg, lot # 0H2754A and 1x20 mg, lot # 0J2712A) under fasted conditions (an overnight fast before each of the two dosing days and standard meals starting 4-h post dose on test days). The two study periods were separated by a minimum 7-day washout interval. Blood samples were collected for 48 hours (pre-dose, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 24, and 48 hours post-doing). These plasma samples were analyzed for *d*- and *l*-amphetamine concentrations using a validated LC/MS method.

The race distribution in this study was 14 Caucasians, 2 Blacks and 2 others.

Question 3: ***Was the analytical method used for determination of amphetamine plasma concentrations validated?***

quantitation (LOQ) of ⟵⟶ . This analytical method has been validated with acceptable results for linearity, precision and accuracy, recovery, sensitivity and stability. Therefore, the plasma concentrations of *d*-amphetamine and *l*-amphetamine measured by this assay for the bioequivalent study submitted in this supplement NDA are acceptable.

Question 4: ***What are results of the bioequivalence study?***

Mean plasma *d*- and *l*-amphetamine concentration profiles for the two capsule strengths were essentially superimposable (see Figure 2-1). The mean pharmacokinetic parameters and the 90% confidence intervals for the ratios of the new 5 mg capsules (4x5 mg) to the approved 20 mg capsule are summarized in the following table:

Table 3. Pharmacokinetic Parameters* from Study 381.106 (Pediatric ADHD Patients)

Single Dose (N=20)	$AUC_{0\text{-}inf}$ (ng.hr/ml)	$AUC_{0\text{-}t}$ (ng.hr/ml)	C_{max} (ng/ml)	T_{max} (h)	$t_{1/2}$ (h)
		d-Amphetamine			
Adderall XR 20 mg	815±174	795±179	51.9±15.0	4.5±1.7	8.0±1.3
Adderall XR 4x5 mg	873±184	844±188	51.9±12.7	4.7±2.3	7.9±1.0
Point of Estimate (90%CI)	**1.06 (1.01-1.10)**	**1.06 (1.01-1.12)**	**1.01 (0.92-1.10)**		
		l-Amphetamine			
Adderall XR 20 mg	269±59	247±67	15.8±4.5	4.9±1.9	9.1±1.6
Adderall XR 4x5 mg	307±69	287±76	16.7±4.0	5.0±2.5	9.0±1.1
Point of Estimate (90%CI)	**1.12 (1.07-1.18)**	**1.16 (1.09-1.24)**	**1.07 (0.99-1.15)**		

*Mean±SD

The 90% confidence intervals for C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ for *d*- and *l*-amphetamine were within the 0.80-1.25 window, demonstrating bioequivalence with respect to both compounds between the 5 mg and 20 mg capsules when administered at the same dose.

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