CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022063Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 022063
Review# 2

Drug Name/Dosage Form	**Mydayis** (mixed salts of a single-entity amphetamine product) extended-release capsules
Strength	12.5 mg, 25 mg, 37.5 mg, 50 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Shire Development LLC

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
N-0044	*12/20/2016*	*All*
N-0028	*04/26/2017*	*Drug product*
N-0032	*5/16/2017*	*Process*
N-0033	*5/18/2017*	*Process*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Haripada Sarker	Ben Stevens
Drug Product	Dan Berger	Wendy Wilson-Lee
Process	Yahong Wang	Akm Khairuzzaman
Microbiology	Yahong Wang	Akm Khairuzzaman
Facility	Zhong Li	Peter Zhihao Qiu
Biopharmaceutics	Jing Li	Ta-Chen Wu
ORA Lead	Adam Cooke	Johnetta Walters
Regulatory Business Process Manager	Grafton Adams	
Application Technical Lead	David Claffey	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	(b) (4)	Dextroamphetamine saccharate	Adequate	12 MAY 2017	
	Type II		Amphetamine aspartate	Adequate	4 Nov 2016	
	Type II		Dextroamphetamine sulfate	Adequate	12 MAY 2017	
	Type II		Amphetamine sulfate	Adequate	9 Nov 2016	
	Type III		(b) (4)	*		
	Type III			*		
	Type IV			*		
	Type IV			*		
	Type IV			*		
	Type IV			*		

*adequate information in application.

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	66329	IND for this product
IND	58037	Adderall XR
NDA	21303	Adderall XR
NDA	11522	Adderall

2. CONSULTS

None

Executive Summary

I. Recommendations and Conclusion on Approvability

Recommend approval from a product quality perspective. The applicant resolved the drug product dissolution deficiencies and demonstrated that they are still capable of manufacturing product of adequate quality.

II. Summary of Quality Assessments

A. Product Overview

The proposed product, Mydayis extended release capsules, is similar to Adderall XR, but with a longer period of efficacy. Four strengths are proposed - 12.5 mg, 25 mg, 37.5 mg, and 50 mg. It is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). The applicant currently markets both Adderall and Adderall XR. These are immediate and extended release formulations of amphetamine mixed salts, with efficacy lasting ca. 4 and 8 hours, respectively. Patients sometimes take a dose of the immediate release product in the afternoon in order to extend the duration of efficacy of the extended release product through the evening hours. This NDA proposes the marketing of an extended release formulation of mixed amphetamine salts in a capsule dosage form with up to 16-hour duration of effect – this is intended to eliminate the need for the additional dosing of the of IR product. The pharmacokinetic profile of the formulation was targeted to be similar to a 20 mg dose of Adderall XR® followed by a 10 mg dose of ADDERALL® administered 8 hours later.

In the first review cycle an approval recommendation was made from a CMC perspective, however an approvable action was taken in 2007, because of deficiencies related to the drug product dissolution method. In this resubmission these deficiencies were adequately addressed. Several manufacturing and control changes were made since the previous submission. Additional data were provided which supported the changes. A drug product expiry period of 24 months was found acceptable.

Non-Proprietary Name Issue: Note that the non-proprietary name for this product will be (mixed salts of a single-entity amphetamine product) extended-release capsules. This is identical to Adderall XR's non-proprietary name. It is also noted that each has a 25 mg dosage strength. OPQ recognizes the potential for confusion and prescribing errors, however the non-proprietary name alone cannot be expected to describe the entire product, including its specific pharmacokinetics. Other labeling elements will be required to distinguish this product from Adderall XR, including proprietary name, ancillary carton statements, capsule colors and markings, NDC number, etc. This issue is outlined in more detail towards the end of this Executive Summary section.

Proposed Indication(s) including Intended Patient Population	***ADHD in patients (b) (4) years and older***
Duration of Treatment	***Chronic***
Maximum Daily Dose	***50 mg for adults, 25 mg pediatrics***
Alternative Methods of Administration	***Sprinkle capsule contents on apple sauce.***

B. Quality Assessment Overview

DRUG SUBSTANCE: The drug product contains equal amounts (by weight) of four amphetamine salts: dextroamphetamine sulfate and amphetamine sulfate, dextroamphetamine saccharate and amphetamine aspartate monohydrate. This results in a (b) (4) mixture of dextro- to levo- amphetamine base equivalent. All drug substance information is referenced to NDA 21303 and the related DMFs (DMF (b) (4) (dextroamphetamine saccharate), DMF (b) (4) (amphetamine aspartate), DMF (b) (4) (dextroamphetamine sulfate), DMF (b) (4) (amphetamine sulfate). Each was found adequate to support this application. This same salt mixture is used in several other amphetamine products.

DRUG PRODUCT:
The drug product will be marketed in capsule strengths of 12.5 mg, 25 mg, 37.5 mg, and 50 mg. All strengths are expressed in terms of the amount of mixed amphetamine salts. Each capsule contains immediate release beads and delayed release beads. The beads are composed of a sugar sphere core coated in a drug layer and further coated with (b) (4) layer(s) – then filled into hard gelatin capsules. The three larger strengths are dose proportional – just differing in capsule fill. The 25 mg, 37.5 mg and 50 mg strength capsule contains three types of drug-releasing beads - an immediate release and two types of delayed release beads - which release amphetamine at either pH 5.5 or pH 7.0. The former releases drug after release from the stomach while the latter will not release the drug until it reaches further down the GI tract where the pH is more neutral. The 12.5 mg strength capsules also contain immediate release beads and two types of delayed release beads. However the immediate release and first (pH 5.5) delayed release bead differs from that of the other strengths (b) (4)

Full CMC details are found in the 2007 Review #1 where an approval action was recommended from a CMC perspective – although changes to the dissolution test and acceptance criteria were requested. In this resubmission the applicant provided support

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