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APPLICATION NUMBER:

022063Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	June 19, 2017
From	CDR Javier A. Muñiz, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 022063
Applicant	Shire Development, LLC
Date of Submission	December 20, 2016
PDUFA Goal Date	June 20, 2017
Proprietary Name / Established (USAN) names	Mydayis Mixed salts of a single-entity amphetamine extended-release capsules
Dosage forms / Strength	
Proposed Indication(s)	For the treatment of Attention Deficit Hyperactivity Disorder in 1. Adults 2. Children (b) (4) years old and older
Recommended:	Approval

1. Introduction and Background

This NDA is a Class 2 Resubmission for SHP465 by Shire (the Applicant). SHP465 (proposed trade name: Mydayis; previously known as SDP465) is an single-entity mixed amphetamine salt (MAS) extended-release capsule developed for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in adults and children (b) (4) years old and above. SHP465 is an extended-release formulation of the same mix of amphetamine salts that is the active component of the approved amphetamine products Adderall (NDA 011522) and Adderall XR (NDA 021303), also owned by the Applicant.

The rationale for this formulation is to extend the benefits from the 12-hour duration for Adderall XR to 16 hours for this product. Drug use data suggests that some patients with ADHD require an additional dose of immediate release (IR) amphetamine 8-10 hours after an Adderall XR dose to extend the therapeutic benefits of these drugs into the evening. This product is intended to provide a convenient single formulation to meet this need.

SHP465 contains three different beads: an IR bead, and two timed-release beads that are intended to release active drug at different rates to cover the 16-hour time period. The Applicant's proposed dose range is 12.5-50mg/day, and the available strengths would be 12.5, 25, 37.5, and 50mg.

This resubmission is a complete response to an approvable letter issued for this NDA in May 2007. The approvable letter tentatively approved 12.5 and 25mg SHP465 for the treatment of ADHD. The Applicant notified the Agency in 2007 that they intended to file an amendment to support approval; however, they later decided not to pursue further development of SHP465

for business reasons. In recent years, the Applicant reactivated the development program for proposed product and is currently seeking approval for the treatment of ADHD. The clinical development program consisted of 16 clinical studies, 13 of which were included in the original NDA (doses starting at 12.5mg up to (b) (4), and three of which (i.e., one pharmacokinetic trial in pediatric patients aged 6-17 years, one efficacy and safety trial in pediatric patients aged 6-17 years, and one efficacy and safety trial in adults aged 18-55 years) are new and included in this resubmission. A population pharmacokinetic (PK) analysis report was also included in this resubmission.

2. CMC/Device

An approval recommendation was made from a CMC perspective during the original NDA review; however, an approvable action was taken in 2007 partly 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 and data were provided which supported these changes. A drug product expiry period of 24 months was found acceptable.

The preapproval inspection of the (b) (4) drug product manufacturing site found that the drug substance analytical methods were not transferred from the (b) (4) drug substance manufacturing sites. Method transfer and validation data did not completely meet Agency GMP expectations. This was determined to be a low risk issue and the site was found to be acceptable to support this application. (b) (4) is expected to continue working this issue and the Office of Regulatory Affairs (ORA) will ensure that this is addressed in this site's next inspection.

Of note, the non-proprietary name for this product will be (mixed salts of a single-entity amphetamine product) extended-release capsules, which is identical to Adderall XR's non-proprietary name. It is also noted that Adderall XR and this new product have an overlapping 25mg dosage strength. This increases the potential for confusion and prescribing errors. The labeling groups at the Officer of Pharmaceutical Quality (OPQ) and the Office of Generic Drugs (OGD) as well as the Division of Medication Error Prevention and Analysis (DMEPA) were made aware of this during the review process although the Agency has requested that the Applicant propose ways to distinguish these products since at least the 2007 action letter. Additional labeling elements will be required to distinguish this product from Adderall XR (e.g., including proprietary name, ancillary carton statements, capsule colors and markings, NDC number, etc.). The OGD labeling team acknowledged this issue but did not have any recommendations on non-proprietary name alternatives.

In summary, the Applicant has resolved the drug product dissolution deficiencies and demonstrated the capability of manufacturing a product of adequate quality. The OPQ team recommends approval of this resubmission.

3. Nonclinical Pharmacology/Toxicology

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. All nonclinical issues have been addressed and the nonclinical team has made recommendations for the updated product label.

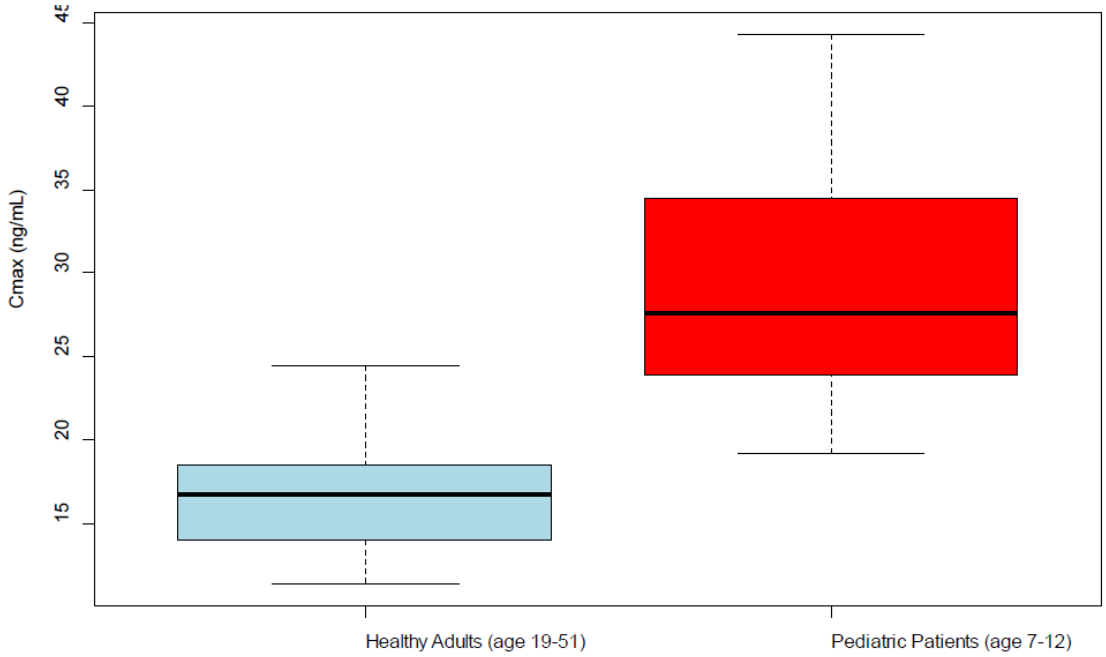
Based on the long history of clinical use of the active ingredients and the supporting nonclinical studies that demonstrate the lack of systemic absorption of a (b) (4) excipient used in this formulation (b) (4) the nonclinical reviewer, Deepa Rao, PhD, recommends approval of this resubmission.

4. Clinical Pharmacology/Biopharmaceutics

The Office of Clinical Pharmacology (OCP) team recommends approval of this resubmission only for patients aged 13 and older. The OCP team agrees with the recommended starting dose of 12.5mg once daily in the morning for adults and pediatric patients 13 -17 years old who are either starting treatment for the first time or switching from another medication regimen. Dosage may be adjusted in increments of 12.5mg no sooner than weekly up to a maximum dose of 50mg/day, based on the therapeutic needs and response in adult patients. The maximum dose in pediatric patients is 25mg/day.

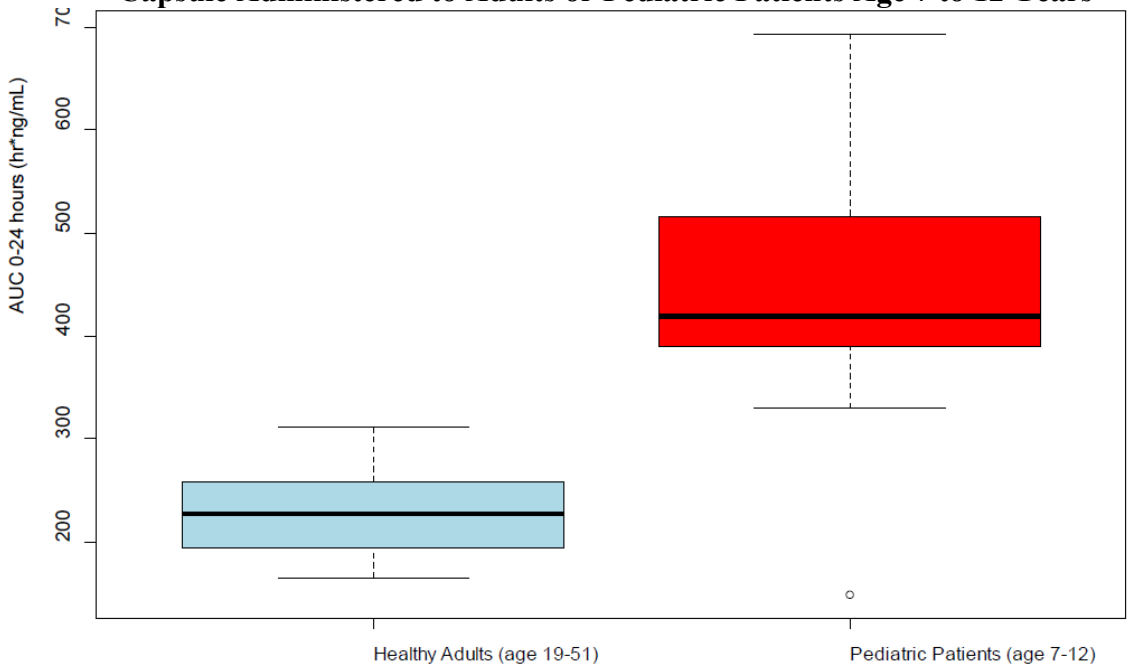
This resubmission included Study SHP-111, a Phase 1, open-label study of the PK parameters of d- and l-amphetamine after a single oral dose of SHP465 12.5mg or 25mg administered to children and adolescents aged 6 to 17 years with ADHD. A single dose of 12.5mg SHP465 produced higher d-amphetamine C_{max} and AUC_{0-24} values in children six to 12 years of age than in adults (Figure 1 and Figure 2). The same trend of higher C_{max} and AUC_{0-24} in pediatric patients six to 12 years of age compared to adults is seen for the l-amphetamine isomer.

Figure 1: Comparison of d-amphetamine C_{max} Distribution Following a Single 12.5mg Capsule Administered to Adults or Pediatric Patients Age 7 to 12 Years



[Source: OCP review, Figure 2, page 14]
Adult data from Studies 107 and 110. Pediatric data from Study 111.

Figure 2: Comparison of d-amphetamine AUC_{0-24} Distribution Following a Single 12.5mg Capsule Administered to Adults or Pediatric Patients Age 7 to 12 Years



[Source: OCP review, Figure 2, page 14]
Adult data from Studies 107 and 110. Pediatric data from Study 111.

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