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APPLICATION NUMBER:

022063Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA	022063
Link to EDR	\\CDSESUB1\evsprod\NDA022063\0022
Submission Date	12/20/2016
Submission Class	Priority (Class 2 Resubmission)
Brand Name	Mydayis®
Generic Name	Mixed salts of a single entity amphetamine
Dosage Form and Strength	Extended Release Capsule 12.5 mg, 25 mg, 37.5 mg and 50 mg
Route of Administration	Oral
Proposed Indication	Attention Deficit Hyperactivity Disorder (ADHD)
Applicant	Shire
Related IND	66,329
OCP Review Team	Kofi A. Kumi, Ph.D., Michael Bewernitz, Ph.D., Kevin Krudys, Ph.D., Hao Zhu, Ph.D.
OCP Final Signatory	Mehul Mehta, Ph.D.

Table of Contents

1. Executive Summary

This NDA is a Class 2 Resubmission for a triple-bead amphetamine extended release product (SHP465) by Shire Pharmaceuticals. It is a complete response to an approvable letter that was issued for NDA 22063 in May 2007. Even though the sponsor notified the Agency in May of 2007 of intent to file an amendment to support approval, they decided not to pursue the development of SHP465 at that time for business reasons. The sponsor has reactivated the development program for SHP465 and is currently seeking approval for SHP465 under the tradename of Mydayis® for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

SHP465 is a once-daily, triple-bead, sustained-release, single-entity mixed amphetamine salt (MAS) product for oral administration. (b) (4)

Adderall XR which is manufactured by the same Sponsor and approved for ADHD. (b) (4)

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This triple-bead, sustained-release delivery is intended to extend the release of the MAS from SHP465 for symptom coverage up to 16 hours post-administration. Adderall XR reportedly lasts about 12 hours. The need for a longer duration of symptom coverage was justified by multiple reports that, in clinical practice, Adderall XR is supplemented after 8 hours with MAS immediate release (IR) to extend the duration of action to last during waking hours.

The clinical development program consisted of 16 clinical studies, 13 of which were included in the original NDA, and 3 of which (i.e., one PK 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 analysis report was also included in this resubmission.

The key review issues are: 1) is the exposure after administration of SHP465 similar to the reference drug, Adderall XR plus the administration of MAS IR after 8 hours? 2) Is the proposed dosing regimen appropriate? 3) Should SHP465 to be administered with or without food? 4) Are there dose adjustments in renal impairment patients or patients receiving a gastric pH modulator?

1.1 Recommendations

The Office of Clinical Pharmacology (OCP) has reviewed the information contained in NDA 022063 and supports the approval of the SHP465 for the treatment of Attention Deficit Hyperactivity Disorder. OCP supports limiting the use of SHP465 to patients 13 years and older. Key review issues with specific recommendations and comments are summarized below:

Review Issues	Recommendations and Comments
Supportive evidence of effectiveness	Substantial evidence of effectiveness was demonstrated in registration trials in adults and pediatric patients. The uniqueness of this formulation is that the duration of action after administration of SHP465 is about 16 hours compared to about 12 hours for currently approved mixed amphetamine salts extended release formulations.
General Dosing Instructions	Overall, the proposed dosing is acceptable in adults and pediatric

	patients 13 years and older. The proposed doses are not recommended for pediatric patients 6 to 12 years of age. The recommended starting dose in adults 18 to 55 years is 12.5 mg once daily in the morning upon awakening. Dosage may be adjusted in increments of 12.5 mg no sooner than weekly to a maximum dose of 50 mg/day. The recommended starting dose in pediatric patients 13 to 17 years old is 12.5 mg daily in the morning upon awakening. Dosage may be adjusted in increments of 12.5 mg no sooner than weekly to a maximum dose of 25 mg/day Doses may be taken with or without food. However, in order to ensure consistent clinical response, patients should endeavor to take SHP465 either with food always or without food consistently. The whole content of a capsule may be sprinkled on an apple sauce and the whole amount of apple sauce should be administered.
Dosing in specific patients	Dose adjustments are not recommended in patients with mild and moderate renal impairment. Dose in patients with severe renal impairment should start with at least (b) (4) the recommended dose and further adjustment made based on clinical response, since exposures would be higher at the recommended doses. SHP465 is not recommended for patients with End Stage Renal Disease (ESRD). Increased gastric pH due to concomitant use of a gastric pH modulator may change the exposure and pharmacokinetic profile of amphetamine. Frequently monitoring patients for changes in clinical effect is recommended. Adjust therapy based on clinical response.
Bridge between the to be marketed and approved reference drug	D- and l- amphetamine exposures (AUC, Cmax) are similar (i.e., meeting BE criteria), even though the pharmacokinetic profiles are different, after administration of equal doses of SHP465 and Adderall XR + Adderall IR 8 hours later.

OCP recommends that the Sponsor pursue a lower than 12.5 mg strength post-marketing to allow better starting dose in pediatric patients 6-12 years. A lower dosage strength may facilitate the use of SHP465 in pediatric patients 6 – 12 years old since the current recommended doses result in higher incidence of adverse events such as insomnia and decreased appetite. Refer to medical review for details of adverse event profile after administration of SHP.

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