NDA 212994

NDA APPROVAL

Commave Therapeutics SA
C/O KemPharm, Inc.
Attention: Christal Mickle
VP, Product Development and Operations, KemPharm, Inc.
1180 Celebration Blvd., Suite 103
Celebration, FL 34747

Dear Ms. Mickle:

Please refer to your new drug application (NDA) dated and received March 2, 2020, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Azstarys (serdexmethylphenidate and dexmethylphenidate) capsules.

This new drug application provides for the use of Azstarys (serdexmethylphenidate and dexmethylphenidate) capsules for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTROLLED SUBSTANCE SCHEDULING

You were previously informed that FDA intends to recommend scheduling of serdexmethylphenidate under the Controlled Substances Act (CSA). The scheduling of this substance in accordance with the CSA (21 U.S.C. 811) is not yet complete as of the date of this letter. Therefore, in accordance with the FDCA (21 U.S.C. 355(x)), the date of approval for Azstarys (serdexmethylphenidate and dexmethylphenidate) capsules shall be the date on which the Drug Enforcement Administration (DEA) publishes a notice in the Federal Register announcing the interim final scheduling of serdexmethylphenidate.

We note that, when serdexmethylphenidate is scheduled by the DEA, you will need to make appropriate revisions to the Prescribing Information by submitting a supplement to your NDA. This would include the statements in the labeling detailing the initial U.S. approval and scheduling of serdexmethylphenidate, as required under 21 CFR 201.57(a)(3) and (c)(10)(i), respectively. Therefore, Azstarys (serdexmethylphenidate and dexmethylphenidate) capsules may be marketed only after

DEA has published the notice in the Federal Register announcing the interim final scheduling of serdexmethylphenidate and you submit a supplement to your NDA to revise all applicable drug labeling to reflect the drug substance scheduling described in the notice. For changes to the Prescribing Information, you can submit a Changes Being Effected supplement described in 21 CFR 314.70(c)(6). Permission to use a Changes Being Effected for this purpose reflects a waiver by the Agency, pursuant to 21 CFR 314.90, of the requirement to submit a Prior Approval Supplement for changes to the Highlights of Prescribing Information for Azstarys (serdexmethylphenidate and dexmethylphenidate) capsules described in 21 CFR 314.70(b)(2)(v)(C).

We note that Azstarys (serdexmethylphenidate and dexmethylphenidate) capsules will be listed in the Orange Book upon the date of approval in accordance with 21 U.S.C. 355(x). With respect to the submission of patent information, as required under 21 CFR 314.53(c)(2)(ii), we note that you must submit Form FDA 3542 within 30 days after the date on which DEA has published the notice in the Federal Register announcing the interim final scheduling of serdexmethylphenidate.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

We acknowledge your March 1, 2021, submission containing final printed carton and container labeling.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Azstarys (serdexmethylphenidate and desmethylphenidate) capsules shall be 24 months from the date of manufacture when stored at 20°C to 25°C (68°F to 77°F). Excursions permitted between 15°C to 30°C (59°F to 86°F).

ADVISORY COMMITTEE

Your application for Azstrarys was not referred to an FDA advisory committee because profile of Azstrarys is acceptable for the intended population, the clinical trial designs were acceptable, and the efficacy findings were clear.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric studies requirement for ages 0 to less than 4 years because necessary studies are impossible or highly impracticable. This is because the diagnostic criteria and assessment measures for determining efficacy for the treatment of ADHD in children less than 4 years old are not well defined and studies in this age group are a challenge regarding patient safety and study validity. Pharmaceutical treatment in this age group is uncommon and non-medication interventions are preferred treatment for behavioral disorders such as ADHD in very young children (e.g., less than 4 years of age).

We are deferring submission of your pediatric studies for ages 4 to less than 6 years for this application because this product is ready for approval for use in adults and older pediatric patients and the studies in pediatric patients age 4 to less than 6 years old have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the FDCA. These required studies are listed below.

3980-1	Conduct a randomized, double-blind, placebo-controlled, parallel-group, safety and efficacy study of Azstarys in male and female children 4 to 12 years of age diagnosed with ADHD. Randomization should be stratified by two age groups (i.e., 4 to less than 6 years and 6 to 12

years of age). Also, this study must include sparse pharmacokinetic (PK) sampling in children ages 4 to less than 6 years to characterize the shape of the PK curve in this population.

Final Protocol Submission:	08/2021
Study Completion:	08/2022
Final Report Submission:	12/2022

3980-2 Conduct a 12-month, open-label study to obtain information on safety and tolerability of Azstarys in male and female children 4 to less than 6 years of age diagnosed with ADHD.

Final Protocol Submission:	08/2021
Study Completion:	08/2023
Final Report Submission:	12/2023

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit the protocol(s) to your IND 130463, with a cross-reference letter to this NDA. Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[4]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication,

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

REPORTING REQUIREMENTS

You must comply with the reporting requirements described in 21 CFR 314.80(c)(1) (e.g., 15-day alert reports) beginning on the date of **this** letter. The due dates for the periodic (including quarterly) adverse drug experience reports described in 21 CFR 314.80(c)(2) should be calculated from the date of this letter. Annual reports described in 21 CFR 314.81(b)(2) are due within 60 days of the anniversary of the date of approval in accordance with 21 U.S.C. 355(x).

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call CAPT William Bender, Senior Regulatory Project Manager, at (301) 796-2145 or email William.Bender2@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Deputy Director
Office of Neuroscience
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- Carton and Container Labeling

[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ERIC P BASTINGS
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