NDA 211964

NDA APPROVAL

Supernus Pharmaceuticals, Inc.
Attention: Tami Martin, RN, Esq.
Vice President, Regulatory Affairs
1550 East Gude Drive
Rockville, MD 20850

Dear Ms. Martin:

Please refer to your new drug application (NDA) dated November 8, 2019, received November 8, 2019, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Qelbree (viloxazine extended-release capsules).

We acknowledge receipt of your amendment dated February 3, 2021, which constituted a complete response to our November 6, 2020, action letter.

This new drug application provides for the use of Qelbree (viloxazine extended-release capsules) for the treatment of attention deficit hyperactivity disorder (ADHD) in pediatric patients 6 to 17 years of age.

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.

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

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

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

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling submitted on March 26, 2021, and March 30, 2021, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 211964**." Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Qelbree (viloxazine hydrochloride extended-release capsules) shall be 24 months from the date of manufacture when stored at 25°C with excursions permitted between 15°C and 30°C.

ADVISORY COMMITTEE

Your application for Qelbree was not referred to an FDA advisory committee because the safety profile is similar to that of other drugs approved for this indication, and there were no controversial issues that would benefit from advisory committee discussion.

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. Although children

[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.

under the age of 4 years can exhibit ADHD-like behaviors, diagnosis and treatment recommendations for that age group have not been codified in recognized guidelines such as the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Most of the currently accepted measures for diagnosis and efficacy of treatment of ADHD in older age groups have not been validated for children less than 4 years of age.

We deferred submission of your pediatric studies for ages 4 to less than 6 years for this application until additional safety and effectiveness data were collected in older pediatric patients.

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.

3942-1 Conduct an adequately powered, double-blind, placebo-controlled efficacy and safety study of viloxazine extended-release capsules (viloxazine ER) in male and female patients ages 4 to < 6 years with attention deficit hyperactivity disorder.

Final Protocol Submission:	06/2019
Study Completion:	03/2022
Final Report Submission:	09/2022

3942-2 Conduct a long-term (6-month), open-label safety extension study to evaluate the safety and tolerability of viloxazine extended-release capsules (viloxazine ER) as monotherapy for attention deficit hyperactivity disorder in male and female patients ages 4 to < 6 years.

Final Protocol Submission:	06/2019
Study Completion:	09/2022
Final Report Submission:	03/2023

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 108864, 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

[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.

"**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of pregnancy complications, to evaluate the concentrations of viloxazine in human milk and the effects on the breastfeeding infant, or to characterize the pharmacokinetics of viloxazine in individuals with hepatic impairment.

Furthermore, the active postmarket risk identification and analysis system, as available under section 505(k)(3) of the FDCA, will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

3942-3 Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to viloxazine extended-release capsules (viloxazine) during pregnancy to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through the first year of life. Maternal deaths through the first year postpartum will be reported. The study will collect information for a minimum of 10 years. Results will be analyzed and reported descriptively. Data collected retrospectively will be analyzed separately and reported with the interim and final study reports.

Final Protocol Submission:	11/2021
Study Completion:	11/2031
Final Report Submission:	05/2032

3942-4 Perform a lactation study in lactating women who have received therapeutic doses of viloxazine extended-release capsules (viloxazine) using a validated assay to assess concentrations of viloxazine in breast milk and the effects on the breastfed infant.

Final Protocol Submission:	11/2021
Study Completion:	11/2022
Final Report Submission:	05/2023

3942-5 Conduct a study to evaluate the pharmacokinetics of viloxazine extended-release capsules (viloxazine) in patients with hepatic impairment.

Final Protocol Submission:	06/2021
Study Completion:	09/2021
Final Report Submission:	06/2022

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.[4]

Submit clinical protocol(s) to your IND 108864 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

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*

[4] 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.

Prescription Drugs.[5]

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, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[6] Information and Instructions for completing the form can be found at FDA.gov.[7]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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, contact CAPT Kofi Ansah, PharmD, Senior Regulatory Project Manager, at (301)796-4158, or email: Kofi.Ansah@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] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[7] 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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