CLINICAL REVIEW

Application Type	Class I Resubmission
Application Number(s)	211964
Submit Date(s)	February 3, 2021
Received Date(s)	February 3, 2021
PDUFA Goal Date	April 3, 2021
Division/Office	Division of Psychiatry/Office of Neuroscience
Reviewer Name(s)	Martine Solages, MD
Team Lead Name	Bernard Fischer, MD
Review Completion Date	March 10, 2021
Established/Proper Name	Viloxazine Extended Release (ER)
(Proposed) Trade Name	Quelbree
Applicant	Supernus Pharmaceuticals, Inc.
Dosage Form(s)	Extended-release capsule
Dosing Regimen(s)	Patients ages 6 to 11 years: 100 mg to 400 mg once daily Patients ages 12 to 17 years: 200 mg to 400 mg once daily
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Treatment of attention deficit hyperactivity disorder (ADHD) in pediatric patients 6 to 17 years of age

On November 8, 2019, the Applicant submitted a 505(b)(1) new drug application (NDA) for viloxazine ER for the treatment of ADHD in children and adolescents ages 6 to 17 years. A Complete Response (CR) letter was issued on November 6, 2020, because of manufacturing facility deficiencies. The Applicant completed a CR resubmission on February 3, 2021, and has resolved the deficiencies that precluded approval of the application during the initial cycle.

The Agency and the Applicant did not reach full agreement on labeling prior to the CR action. Labeling negotiations therefore resumed after resubmission of the application. The most notable unresolved labeling issues pertained to the description of viloxazine's mechanism of action and effects on weight and suicidal ideation.

During the initial review cycle, the Applicant disagreed with the Agency on the description of viloxazine's mechanism of action and advocated for (b) (4) . In a Type A meeting following the issuance of the CR letter, the Applicant proposed including language (b) (4) . The Agency noted (b) (4) the Applicant's proposed language would not be included in labeling. The Applicant submitted draft labeling with the CR resubmission that indicated acceptance of the Agency's position.

The Agency had initially proposed including information about effects on weight in Section 5 of labeling (Warning and Precautions). The Agency noted that in the short-term controlled studies (6 to 8 weeks), viloxazine ER-treated patients 6 to 11 years of age gained an average of 0.2 kg, compared to a gain of 1 kg in same-aged patients who received placebo. Viloxazine ER-treated patients 12 to 17 years of age lost an average of 0.2 kg, compared to a weight gain of 1.5 kg in same-aged patients who received placebo. However, upon further consideration of the data from the long-term safety extension study (Study 812P310), the Agency concluded that the clinical meaningfulness of the findings over time is unclear and that the observed changes in weight in the long-term study could represent regression to the mean or the influence of confounding factors. Given the limitations of the uncontrolled data, the Agency determined that inclusion of effects on weight in Section 5 was not warranted. Nonetheless, healthcare professionals should be aware of the short-term weight effects of viloxazine. Information about weight effects was therefore included in Section 6 of labeling (Adverse Reactions). At the time of this review, whether to include the open-label weight results in labeling was under discussion. If included, long-term data in Section 6 would be the mean change from baseline in weight-for-age z-score for patients exposed to viloxazine ER for at least 12 months.

The Division also drafted new language regarding the boxed warning for suicidal ideation and behavior. The language proposed during previous labeling negotiations (b) (4) The updated boxed warning now describes data on suicidal ideation and behavior from the viloxazine ER studies and more closely aligns with the boxed warning language of atomoxetine, which shares the same mechanism.

Please see the integrated review of the NDA for full details. No additional clinical information was submitted with the CR resubmission. The assessment of the overall benefit and risk of viloxazine ER has not changed since the initial review. Viloxazine ER continues to have a favorable benefit:risk profile in pediatric patients ages 6 to 17 years with ADHD and we recommend approval.

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/

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03/23/2021 08:20:37 AM

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