NEW DRUG APPROVAL

Brand Name	Qelbree™
Generic Name	viloxazine
Drug Manufacturer	Supernus Pharmaceuticals Inc.

New Drug Approval

FDA Approval Date: April 2, 2021
Review Designation: Standard
Type of Review: Type 1 - New Molecular Entity, New Drug Application (NDA): 211964
Dispensing Restriction: Open Distribution

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Attention-deficit/hyperactivity disorder (ADHD) is a disorder marked by an ongoing pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development.

- Inattention means a person wanders off task, lacks persistence, has difficulty sustaining focus, and is disorganized; and these problems are not due to defiance or lack of comprehension.
- Hyperactivity means a person seems to move about constantly, including in situations in which it is not appropriate, or excessively fidgets, taps, or talks. In adults, it may be extreme restlessness or wearing others out with constant activity.
- Impulsivity means a person makes hasty actions that occur in the moment without first thinking about them and that may have a high potential for harm, or a desire for immediate rewards or inability to delay gratification.

Attention deficit hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders of childhood, and it can last into adulthood. Prevalence estimates vary, but the U.S. Centers for Disease Control and Prevention (CDC) reports that more than 6 million children between 2 and 17 years of age have been diagnosed with ADHD in the United States.

Efficacy

The efficacy of Qelbree™ in the treatment of ADHD in pediatric patients 6 to 17 years of age was evaluated in three short-term, randomized, placebo-controlled monotherapy trials (Studies 1, 2, and 3).

Table 1. Qelbree™ Clinical Trials in Patients 6 to 11 Years of Age (Study 1 and Study 2)

	Study 1 (NCT03247530)	Study 2 (NCT03247543)
Study Design -*/	Two Multicenter, randomized, double-blind, 3-arm, placebo-controlled, parallel group monotherapy trials	
Study Population	• 477 patients were randomized (399 completed the study; 78 discontinued)	• 313 patients were randomized (251 completed the study; 62 discontinued)

	○ Mean age: 8.5 years (range, 6–11 years; SD = 1.69) ○ Mean height: 134.46 cm (SD = 11.30) ○ Mean weight: 31.63 kg (SD = 8.40)	
Key Inclusion Criteria	• Healthy male or female patients, 6–11 years of age, inclusive • Diagnosis of ADHD according to the DSM-5, confirmed with the MINI-KID • ADHD-RS-5 total score of 28 at screening and baseline; minimum CGI-S score of 4 at screening • Weight of at least 20 kg • Free of medication for the treatment of ADHD for at least 1 week prior to randomization and agreement to remain so throughout the study	
Key Exclusion Criteria	• Current diagnosis of any major psychiatric disorders (major depressive disorder was allowed if the subject was free of episodes at the time of screening and for 6 months prior) • Major neurological disorders or history of seizure disorder within the immediate family • Current evidence of significant systemic disease • Evidence of suicidality within 6 months • Body mass index (BMI) >95th percentile for age and gender	
Study Duration	6 weeks, including a 1-week titration period (starting at 100 mg once daily) and a 5-week maintenance phase	8 weeks, including a 3-week titration period (starting at 100 mg once daily), and a 5-week maintenance phase
Interventions	Patients were randomized 1:1:1 to receive one of the following, given once daily as a single dose: • Qelbree™ 100 mg (n = 147) • Qelbree™ 200 mg (n = 158) • Placebo (n = 155)	Patients were randomized 1:1:1 to receive one of the following, given once daily as a single dose: • Qelbree™ 200 mg (n = 107) • Qelbree™ 400 mg (n = 97) • Placebo (n = 97)
Endpoints	• **Primary endpoint:** Change from baseline in ADHD-RS-5 • **Key secondary endpoints:** ○ CGI-I score ○ Change from baseline at end of study in the WFIRS-P total average score	

Efficacy and Safety Results	• Treatment with Qelbree™ resulted in statistically significantly greater reductions in the ADHD-RS-5 total score compared with placebo. In Study 1, the mean change from the mean baseline score was −16.6 points for the 100 mg dose (baseline, 45.0), −17.7 points (baseline, 44.0) for the 200 mg dose, and −10.9 points (baseline, 43.6) for placebo. • A statistically significantly greater reduction in CGI-I score was observed with Qelbree™. • Qelbree™ demonstrated a favorable profile with a low occurrence of adverse events. • The most common treatment-emergent adverse events reported were somnolence, decreased appetite, fatigue, nausea, vomiting, insomnia, and irritability.

Table 2. Qelbree™ Clinical Trials in Patients 12 to 17 Years of Age (Study 3; NCT03247517)	
Study Design	Multicenter, randomized, double-blind, 3-arm, placebo-controlled, parallel-group monotherapy trial
Study Population	• 310 patients were randomized (266 completed the study; 44 discontinued) ○ Mean age: 13.9 years (range, 12–17 years; SD = 1.58) ○ Mean height: 163.26 cm (SD = 10.36) ○ Mean weight: 57.27 kg (SD = 13.02)
Key Inclusion Criteria	• Healthy male or female, 12–17 years of age, inclusive • Diagnosis of ADHD according to the DSM-5, confirmed with the MINI-KID • ADHD-RS-5 score of at least 28 • CGI-S score of at least 4 at screening • Weight of at least 35 kg • Free of medication for the treatment of ADHD for at least 1 week prior to randomization and agreement to remain so throughout the study
Key Exclusion Criteria	• Current diagnosis of any major psychiatric disorders (major depressive disorder was allowed if the subject was free of episodes at the time of screening and for 6 months prior) • Major neurological disorders or history of seizure disorder within the immediate family • Current evidence of significant systemic disease • Evidence of suicidality within 6 months • Body mass index (BMI) > 95th percentile for age and gender

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Study Duration	Treatment duration: 6 weeks, including a 1-week titration period (starting at 200 mg once daily) and 5-week maintenance phase
Interventions	• Patients were randomized to receive the following, given once daily as a single dose: ○ Qelbree™ 200 mg (n = 94) ○ Qelbree™ 400 mg (n = 103) ○ Placebo (n = 104)
Endpoints	• **Primary endpoint:** Change from baseline in ADHD-RS-5 • **Key secondary endpoints:** ○ CGI-I score ○ Change from baseline at the end of study in the WFIRS-P total average score
Efficacy and Safety Results	• Treatment with Qelbree™ resulted in statistically significantly greater reductions in ADHDRS-5 total score compared with placebo. In Study 3, the mean change from the mean baseline score was −16.0 points (baseline, 39.9) for the 200 mg dose, −16.5 points (baseline, 39.4) for the 400 mg dose, and −11.4 points (baseline, 40.5) for placebo. • A statistically significantly greater reduction in CGI-I score was observed with Qelbree™. • Qelbree™ demonstrated a favorable profile that was consistent across all Phase 3 studies, with a low occurrence of adverse events. • The most common treatment-emergent adverse events reported were somnolence, decreased appetite, fatigue, nausea, vomiting, insomnia, and irritability.

Safety

ADVERSE EVENTS

Most commonly observed adverse reactions (≥5% and at least twice the rate of placebo) were: somnolence, decreased appetite, fatigue, nausea, vomiting, insomnia, and irritability.

WARNINGS & PRECAUTIONS

- **Suicidal Thoughts and Behaviors**: In clinical studies, higher rates of suicidal thoughts and behavior were reported in pediatric patients treated with Qelbree™ than in patients treated with placebo. Closely monitor for clinical worsening and the emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy and at times for dose change. Advise family members or caregivers of patients to monitor for the emergence of suicidal ideation or behavior, and to report such symptoms immediately to the healthcare provider.
- **Blood Pressure and Heart Rate Increases:** Assess heart rate and blood pressure prior to initiating treatment, following increases in dosage, and periodically while on therapy.
- **Activation of Mania or Hypomania:** Screen patients for bipolar disorder.
- **Somnolence and Fatigue:** Advise patients to use caution when driving or operating hazardous machinery due to potential somnolence (including sedation and lethargy) and fatigue.

CONTRAINDICATIONS

- Concomitant administration of monoamine oxidase inhibitors (MAOI), or dosing within 14 days after discontinuing an MAOI, because of an increased risk of hypertensive crisis.
- Concomitant administration of sensitive CYP1A2 substrates or CYP1A2 substrates with a narrow therapeutic range.

Clinical Pharmacology

MECHANISMS OF ACTION

The mechanism of action of viloxazine in the treatment of ADHD is unclear; however, it is thought to be through inhibiting the reuptake of norepinephrine.

Dose & Administration

ADULTS

Safety and efficacy have not been established.

PEDIATRICS

Pediatric patients 6 to 11 years of age: Recommended starting dosage is 100 mg once daily. May titrate in increments of 100 mg weekly to the maximum recommended dosage of 400 mg once daily depending on response and tolerability; treatment may be needed for extended periods; periodically re-evaluate the long-term use and adjust dosage as needed.

Pediatric patients 12 to 17 years of age: Recommended starting dosage is 200 mg once daily. May titrate after 1 week, by an increment of 200mg, to the maximum recommended dosage of 400 mg once daily depending on response and tolerability; treatment may be needed for extended periods; periodically re-evaluate the long-term use and adjust dosage as needed.

GERIATRICS

Safety and efficacy have not been established.

RENAL IMPAIRMENT

- eGFR 30 mL/minute/1.73 m^2 or more: No dosage adjustment is necessary.
- eGFR less than 30 mL/minute/1.73 m^2: Initially, 100 mg PO once daily. May titrate dosage in weekly increments of 50 to 100 mg once daily, up to a maximum of 200 mg PO once daily.

HEPATIC IMPAIRMENT

Qelbree™ is not recommended in patients with hepatic impairment.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Oral Capsule, Extended Release: 100 mg, 150 mg, 200 mg