PDL DRUG REVIEW

Proprietary Name: Qelbree®
Common Name: viloxazine hydrochloride
PDL Category: Stimulant- Other Stimulants / Like Stimulants

Comparable Products	Preferred Drug List Status
Atomoxetine	Preferred with Conditions
Guanfacine ER	Preferred with Conditions

Summary

Pharmacology/Usage: Viloxazine, the active ingredient of Qelbree®, is a selective norepinephrine reuptake inhibitor. The mechanism of action for its approved use is not clear; however, it is thought to be mediated by inhibiting the reuptake of norepinephrine.

Indication: For the treatment of Attention-Deficit Hyperactivity Disorder (ADHD) in pediatric patients 6 to 17 years of age.

There is no pregnancy category for this medication; however, the risk summary indicates that based on findings from animal reproduction studies, viloxazine may cause maternal harm when used during pregnancy. Discontinue Qelbree® when pregnancy is recognized unless the benefits of therapy outweigh the potential risk to the mother. Available data from case series with viloxazine use in pregnant women are not sufficient to determine a drug-associated risk of major birth defects, miscarriage, or adverse maternal outcomes. There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Qelbree® during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Psychiatric Mediations at 1-866-961-2388 or visiting online at www.womensmentalhealth.org/preg. The safety and efficacy of use in the pediatric population younger than 6 years of age have not been established.

Dosage Form: Extended-Release Capsules: 100mg, 150mg, 200mg. Do not cut, crush, or chew the capsules.

Swallow capsules whole or open the capsule and sprinkle the entire contents over a teaspoonful of applesauce. Consume all the sprinkled applesauce in its entirety, without chewing, within 2 hours. Do not store for future use.

Recommended Dosage: Prior to starting treatment:

- Assess heart rate and blood pressure, following increases in dosage, and periodically while on therapy.
- Screen patients for a personal or family history of suicide, bipolar disorder, and depression

For pediatric patients 6 to 11 years, start at 100mg PO QD. The dosage may be titrated in increments of 100mg at weekly intervals to the maximum recommended dosage of 400mg QD, depending on response and tolerability.

For pediatric patients 12 to 17 years, start at 200mg PO QD. After 1 week, dosage may be titrated by an increment of 200mg to the maximum recommended dosage of 400mg QD, depending on response and tolerability.

Pharmacologic treatment of ADHD may be needed for extended periods. Periodically reevaluate the long-term use of Qelbree® and adjust dosage as needed.

The effect of hepatic impairment on the pharmacokinetics of viloxazine is not known. Qelbree® is not recommended in patients with hepatic impairment. The exposure of viloxazine increases in patients with renal impairment. No dosage adjustment is recommended in patients with mild to moderate renal impairment. Dosage reduction is recommended in patients with severe renal impairment. The recommended starting dosage in this population is 100mg QD. Dosage may be titrated in weekly increments of 50 to 100mg QD to a maximum of 200mg QD.

Drug Interactions: Concomitant use of Qelbree® with an MAO inhibitor or within 2 weeks after discontinuing an MAO inhibitor is contraindicated.

Viloxazine is a strong CYP1A2 inhibitor. Concomitant use of viloxazine significantly increases the total exposure, but not peak exposure, of sensitive CYP1A2 substates, which may increase the risk of adverse reactions associated with these CYP1A2 substrates. Coadministration of Qelbree® with sensitive CYP1A2 substrates or CYP1A2 substrates with a narrow therapeutic range (e.g. alosetron, duloxetine, ramelteon, tasimelteon, tizanidine, theophylline), is contraindicated.

The concomitant use of Qelbree® with moderate sensitive CYP1A2 substrates (e.g. clozapine, pirfenidone) is not recommended. Dose reduction may be warranted if co-administered.

Monitor patients for adverse reactions and adjust dosage of CYP2D6 substrates, as clinically indicated, if Qelbree® is used concomitantly with CYP2D6 substrates.

Monitor patients for adverse reactions and adjust dosage of CYP3A4 substrates, as clinically indicated, if Qelbree® is used concomitantly with CYP3A4 substrates.

Box Warning: Qelbree® has a box warning regarding suicidal thoughts and behaviors. In clinical studies, higher rates of suicidal thoughts and behavior were reported in pediatric patients with ADHD treated with Qelbree® than in patients treated with placebo. Closely monitor all Qelbree®-treated patients for clinical worsening, and for the emergence of suicidal thoughts and behaviors.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Qelbree®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included somnolence (12%), headache (4%), decreased appetite (6.6%), upper respiratory tract infection (1%), fatigue (4%), pyrexia (1.8%), abdominal pain (1%), nausea (2%), vomiting (2%), insomnia (3%), and irritability (2%).

Regarding effects on weight, in short-term studies Qelbree®-treated patients 6 to 11 years of age gained an average of 0.2kg compared to a gain of 1kg in the same-aged patients who received placebo. Qelbree®-treated patients 12 to 17 years of age lost an average of 0.2kg compared to a weight gain of 1.5kg in same-aged patients who received placebo. In a long-term, open-label extension safety study, 1097 patients received at least 1 dose of Qelbree®. Among the 338 patients assessed at 12 months, the mean change from baseline in weight-for-age z-score was -0.2. In the absence of a control group, it is not clear whether the weight change observed in the long-term, open-label extension was attributable to the effect of Qelbree®.

As mentioned in the box warning section, higher rates of suicidal thoughts and behavior were reported in pediatric patients with ADHD treated with Qelbree® than in patients treated with placebo. Patients treated with Qelbree® had higher rates of insomnia and irritability. Although a causal link between the emergence of such symptoms and the emergence of suicidal impulses has not been established, there is a concern that these and other symptoms (such as depressed mood, anxiety, agitation, akathisia, mania, hypomania, panic attacks, impulsive behavior, and aggression) may represent precursors to emerging suicidal ideation or behavior. Closely monitor all Qelbree®-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the first few months of drug therapy and at times of dosage changes.

Qelbree® can cause an increase in heart rate and diastolic blood pressure. Assess heart rate and blood pressure prior to starting treatment, following increases in dosage, and periodically while on therapy.

Noradrenergic drugs, such as Qelbree®, may induce a manic or mixed episode in patients with bipolar disorder. Prior to starting Qelbree®, screen patients to determine if they are at risk for bipolar disorder.

Qelbree® can cause somnolence and fatigue. Patients should not perform activities requiring mental alertness, such as operating a motor vehicle or operating hazardous machinery until they know how they will be affected by Qelbree®.

Contraindications: In patients:

- Receiving concomitant treatment with monoamine oxidase inhibitors (MAO-I), or within 14 days following discontinuation of an MAO-I
- Receiving concomitant administration of sensitive CYP1A2 substrates or CYP1A2 substrates with a narrow therapeutic range

Manufacturer: Supernus Pharmaceuticals

Analysis: The safety and efficacy of Qelbree® were assessed in three short-term, randomized, placebo-controlled, monotherapy studies that included pediatric patients 6 to 17 years of age with ADHD.

Study 1 was a multicenter, randomized, double-blind, 3-arm, placebo-controlled study that included pediatric patients 6 to 11 years of age with ADHD (N=477) who were treated with Qelbree® 100mg, Qelbree® 200mg, or placebo for 6 weeks, including a 1-week titration period and a 5-week maintenance period. The primary endpoint was the change from baseline to the end of the study on the total score on the ADHD Rating Scale (ADHD-RS-5), an 18-question scale that assesses hyperactivity, impulsivity, and inattentive symptoms. Higher ADHD-RS-5 scores reflect more severe symptoms. The Clinical Global Impressions-Improvement (CGI-I) score at the end of the study was a secondary endpoint. Results suggested that the change from baseline (reduction) in AHDH-RS-5 total score was statistically significantly greater in patients treated with Qelbree® 100mg or with Qelbree® 200mg than in patients treated with placebo. In addition, compared with placebo, a statistically significantly greater reduction (improvement) in CGI-I score was observed in both Qelbree® doses.

Study 2 was a multicenter, randomized, double-blind, 3-arm, placebo-controlled study that included patients 6 to 11 years of age with ADHD (N=313) who were treated with Qelbree® 200mg, Qelbree® 400mg, or placebo for 8 weeks, including a 3-week titration period and a 5-week maintenance period. The primary endpoint was the change from baseline to the end of the study on the total score on the ADHD-RS-5, while the CGI-I score was a secondary endpoint. Results suggested that the change from baseline (reduction) in ADHD-RS-5 total score was statistically significantly greater in patients treated with Qelbree® 200g or with Qelbree® 400mg than in patients treated with placebo. Compared with placebo, a statistically significantly greater reduction (improvement) in CGI-I score was observed both in patients treated with Qelbree® 200mg and Qelbree® 400mg.

Study 3 was a multicenter, randomized, double-blind, 3-arm, placebo-controlled study that included patients 12 to 17 years of age with ADHD (N=310) who were treated with Qelbree® 200mg, Qelbree® 400mg, or placebo for 6 weeks, including a 1-week titration period and a 5-week maintenance phase. The primary endpoint was the change from baseline to the end of the study on the total score on the ADHD-RS-5, while the CGI-I score was a secondary endpoint. Results suggested that the change from baseline (reduction) in ADHD-RS-5 total score was statistically significantly greater in patients treated with Qelbree® 200mg and Qelbree® 400mg than patients treated with placebo. In addition, compared with placebo, a statistically significantly greater reduction (improvement) in CGI-I score at the end of the study was observed both in patients treated with Qelbree® 200mg and with Qelbree® 400mg.

Results from the 3 studies can be seen in the table below, which was adapted from the prescribing information.

Study #	Treatment	Primary Efficacy Measure: ADHD-RS-5 Total Score			
		N	Mean baseline score	LS mean change from baseline	Placebo-subtracted difference
1 (6-11 yrs)	100mg/d	147	45.0	-16.6	-5.8
	200mg/d	158	44.0	-17.7	-6.9
	placebo	155	43.6	-10.9	-
2 (6-11 yrs)	200mg/d	107	43.8	-17.6	-6.0
	400mg/d	97	45.0	-17.5	-5.8
	placebo	97	43.5	-11.7	-
3 (12-17 yrs)	200mg/d	94	39.9	-16.0	-4.5
	400mg/d	103	39.4	-16.5	-5.1
	Placebo	104	40.5	-11.4	-

Place in Therapy: Qelbree®, an extended-release capsule, is indicated for the treatment of ADHD in pediatric patients 6 to 17 years of age. It does have a box warning regarding suicidal thoughts and behaviors, thus all Qelbree®-treated patients should be closely monitored for clinical worsening, and for the emergence of suicidal thoughts and behaviors. Use is contraindicated in patients receiving concomitant treatment with MAO-inhibitors, or within 14 days following discontinuation of an MAO-inhibitor, as well as in those receiving concomitant administration of sensitive CYP1A2 substrates or CYP1A2 substrates with a narrow therapeutic range. The efficacy of Qelbree® for the treatment of ADHD in patients aged 6 to 17 years of age was assessed in 3 double-blind, placebo-controlled studies. All 3 studies demonstrated Qelbree® to have a statistically significantly greater change from baseline (reduction) in the ADHD-RS-5 total score as compared with placebo. Qelbree® is the first non-stimulant FDA approved in several years. Comparator trials with other agents approved for ADHD have not been found at this point.

There is no evidence at this time to support that Qelbree® is safer or more effective than the other currently preferred, more cost-effective medications. It is therefore recommended that Qelbree® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement:

- ☐ **Preferred**
- ☒ **Non-Preferred**
- ☒ **Refer to DUR for PA Criteria**

References

[1] Qelbree [package insert]. Rockville, MD: Supernus Pharmaceuticals, Inc; 2021.