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Qelbree® (viloxazine extended-release capsules)

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS In clinical trials, higher rates of suicidal thoughts and behaviors were reported in patients treated with Qelbree than in patients treated with placebo. Closely monitor for worsening and for emergence of suicidal thoughts and behaviors.

Qelbree is a selective norepinephrine reuptake inhibitor indicated for the treatment of ADHD in adults and pediatric patients 6 years and older

Qelbree is contraindicated with monoamine oxidase inhibitors and sensitive CYP1A2 substrates or CYP1A2 substrates with a narrow therapeutic range.

For more specifics, including Warnings and Precautions:
Refer to complete Prescribing Information: https://www.supernus.com/sites/default/files/Qelbree-Prescribing-Info.pdf

- While there are (31) drugs approved for the treatment of ADHD, all but 3 are formulations of just 2 stimulant molecules, methylphenidate and amphetamine.[1]
- 10-30% of patients with ADHD have inadequate response to treatments due to adverse events, contraindications, or lack of efficacy. Whether for considerations of stimulant abuse/diversion, patient intolerance to stimulants or nonstimulants, inability to swallow pills, Qelbree offers an important option for the treatment of ADHD.[2-5]
- Qelbree is a selective norepinephrine reuptake inhibitor indicated for the treatment of ADHD in adults and pediatric patients 6 years and older.[4]
- Medication adherence can also be negatively impacted due to pill swallowing difficulties. Qelbree has convenient, once-daily dosing providing full-day medicine coverage; capsules can be opened and sprinkled on a spoonful of applesauce (within 2 hours) or pudding (within 15 minutes).[4-5] About one-third of adolescents and about 50% percent of children between the ages of 6 and 11 have reported some level of difficulty with pill swallowing without an intervention[6-7]
- Research shows that 52% of pediatric and adolescent patients have engaged in one of three forms of diversion of stimulants, which may be an additional consideration for adding another nonscheduled option to the category.[8] In 2015, it was estimated that, on average, 8.4 million adults 18 years of age and older living in the United States misused prescription stimulants in the previous year[9] while stimulant abuse has led to related ED visits by 156% over a 10-year period.[10]
- Up to 90% of patients diagnosed with ADHD in childhood/adolescence continue to experience difficulties in adulthood.[11] Over the first four years of having a license, drivers with ADHD are 37% more likely to get into a crash, twice as likely to drive while intoxicated, and 150% more likely to receive an alcohol, drug, or moving violation compared to their non-ADHD peers.[12]
- This new molecular entity (NME) is the first nonstimulant approved in two decades.[4] 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. Additional data from animal models and *in vitro* research suggests that viloxazine, as a moderate norepinephrine reuptake inhibitor, increases dopamine, norepinephrine, and serotonin in the prefrontal cortex. The increase in serotonin is not through reuptake inhibition, but through other mechanisms under furthered investigation. Data from animal studies may not be predictive of a mechanism for treating ADHD in humans. This combined pharmacology makes viloxazine distinct from any FDA approved medication used to treat ADHD.[4,13]
- In Phase 3 trials,[4,14-15] children and adolescents receiving certain dosages of Qelbree (100-400mg/day) demonstrated statistically significant improvement (ADHD-RS-5 scale) in ADHD symptoms occurring as early as week 1 that continued to the end of the clinical studies. In a flexible dose phase 3 study 200-

600mg/day of Qelbree, adult ADHD patients showed significant improvement on the AISRS early in treatment at week 2. Moreover, patients showed sustained symptom improvement over the course of a 1-year open label extension study. Qelbree also exhibits broad spectrum impact on ADHD hyperactivity/impulsivity and inattention symptoms. On a global measure of functional improvement adult patients on Qelbree showed significant improvement on the CGI-S at week 2 in phase 3 study. CGI-S responder rates were above 60% after 12 months of treatment.[4-5, 16]

- Warnings and Precautions with Qelbree: possible effect on blood pressure and heart rate; activation of mania or hypomania; potential somnolence and fatigue.[4]

- The most common adverse reactions in pediatric adolescents (≥ 5% and at least twice the rate of placebo for any dose) were somnolence, decreased appetite, fatigue, nausea, vomiting, insomnia, and irritability.[4] In adults, the most common treatment-related AEs reported (≥ 5% of subjects) in adults were insomnia, headache, somnolence, fatigue, nausea, decreased appetite, dry mouth and constipation[4]

- Additional clinical data that indirectly highlight areas unique to Qelbree that differentiate it from other nonstimulants including Strattera:

  There have been no head-to-head studies comparing Qelbree with other nonstimulants.

  - No evidence of hepatic injury as evidenced by minimal AST and ALT elevations in liver enzymes across all trials. No Drug-Induced Liver Injury (DILI). [4-5]

  - Qelbree has multiple metabolic routes of elimination and is unlikely to have an interaction with other drugs metabolized by CYP2D6. No dose adjustment necessary with CYP2D6 inhibitors. [4-5]

  - ~10% of the patient population has a polymorphism at the CYP2D6 enzyme. Phenotypic CYP2D6 metabolizer status appears to have only a minimal impact on Qelbree metabolism with only a 1.5-fold increase in poor metabolizers vs. extensive metabolizers. [4-5]

  - There is no dose adjustment necessary with Qelbree in patients with hepatic impairment. [4-5]

  - Qelbree has mild impacts on the cardiovascular system, with supratherapeutic doses producing no clinically significant effects on cardiac repolarization or other ECG parameters in healthy adults, suggesting that it is not associated with a risk for cardiac arrhythmias.[4-5,17]

  - Medication adherence can also be negatively impacted due to pill swallowing difficulties. Qelbree has convenient, once-daily dosing providing full-day medicine coverage; capsules can be opened and sprinkled on a teaspoonful or tablespoonful of pudding or applesauce.[4-5]

  - No clinically significant impact on growth or weight effects were observed in Qelbree trials. Advise patients and their caregivers that Qelbree can affect weight and should be monitored while using Qelbree.[4-5]

  - Lastly, Number Needed to Treat (NNT) and Number Needed to Harm (NNH) are calculations that provide an assessment on the effect size and overall tolerability, respectively. The ratio of these two calculations provides the Likelihood to be Helped or Harmed (LHH). These

calculations provide context on the clinical meaningfulness of the Qelbree data. In pediatric/adolescent patients the NNT for Qelbree is 7, NNH is 46 and LHH is 7. By contrast, for Strattera, the NNT is 8, NNH is 29 and the LHH is 3.6. For Intuniv, the NNT is 4, NNH is 15 and LHH is 3.8. NNH values greater than 10 denote a potentially tolerable intervention so the NNH of 46 for Qelbree and 29 for Strattera and 15 for Intuniv indirectly highlight another differentiating area in which Qelbree may be a more safe and tolerable intervention in ADHD patients. NNH values are calculated based on dropout rates due to adverse events. The LHH ratios suggest that the benefit to risk ratio for Qelbree is 1.5X that of Strattera and Intuniv.[5, 18]

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From: Kevin Winthrop
Sent: Thursday, June 2, 2022 11:36:31 AM (UTC-08:00) Pacific Time (US & Canada)
To: Pharmacy Drug Information <osupharm.di@oregonstate.edu>
Subject: public comment---Drug Class Review of Mycobacterium Drugs.

Dear Committee

I know this is late, but want to support these changes. I'm a former CDC TB Division staff member, and currently the medical consultant for TB at the Oregon Health Authority. I run the mycobacterial clinic and program at OHSU.

I definitely support making it easier to access rifapentine and bedaquiline. We are becoming mainstream drugs for the treatment of mycobacterial diseases, and the earlier and easier we can get them, the better

Thank you

Cheers, Kevin

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