Viloxazine (Qelbree®)

FDA approved April 2021 for the treatment of ADHD in pediatrics 6 to 17 yo & April 2022 for the treatment of ADHD in adults

(Supernus Pharmaceuticals)

Indication: Viloxazine is indicated for the treatment of ADHD for patients ages 6 and older

Mechanism of action: Unclear, believed to be through norepinephrine reuptake inhibition

Dosage & administration

Dosage	Initial- 6 to 11 yo: 100 mg QDay; ≥12 yo: 200 mg QDay Max- 6 to 17 yo: 400 mg/d; adults: 600 mg/d
Renal impairment (severe)	Initial: 100 mg QDay; Max 200 mg a day
Hepatic impairment	No specific recommendations available
Administration	- administer with or without food - do not cut, crush, or chew capsule - swallow whole or may open the capsule & sprinkle over a teaspoonful of applesauce; consume within 2 hours without chewing
How Supplied	100 mg, 150 mg, & 200 mg caps

Adverse Reactions

Common (≥5% & at least twice the rate of placebo)	6 to 17 yo: somnolence, reduced appetite, fatigue, N/V, insomnia, & irritability Adults: insomnia, headache, somnolence, fatigue, nausea, reduced appetite, dry mouth & constipation
Serious	CV: increased BP & HR Psychiatric: suicidal behavior & thoughts, activation of mania or hypomania Neurologic: somnolence Other: fatigue

Warnings and Precautions

Boxed Warning	Suicidal thoughts and behaviors
Contraindications	• concomitant treatment with or within 14 days of MAOIs • concomitant use of sensitive CYP1A2 substrates or substrates with a narrow therapeutic range
Precautions	• somnolence & fatigue: use caution while driving/operating hazardous machinery • BP & HR increases: monitor before starting treatment, periodically during therapy (including after dosage increases) • activation of mania or hypomania: screen clts for bipolar disorder

Pharmacokinetics

Bioavailability	bioavailability relative to IR formulation ~ 88%
T_{max}	5 hours (geriatric 2 hours)
Half-life	Mean 7 hours +/- 4.7 hours
Metabolism	Liver (extensive)
Steady state	reached after 2 days
Excretion	Primarily urine (90%); feces (<1%)

Efficacy

Adults

- A phase III randomized, double blind placebo controlled trial tested safety and effectiveness of viloxazine in 354 adults with ADHD over 6 weeks
- Viloxazine was given at a starting dose of 200 mg on week 1, 400 mg on week 2, followed by flexible dosing between 200 mg and 600 mg a day
- Primary endpoint was change in ADHD Investigator Symptom Rating Scale (AISRS) total score from baseline to end of study (EOS)
- Viloxazine significantly reduced AISRS total score at EOS compared to placebo. The change from baseline in AISRS total score was -15.5 for viloxazine and -11.7 for placebo
- Viloxazine was well-tolerated with no evidence of abuse potential
- Exclusion criteria included suicidality within the past 6 months, major psychiatric or neurological disorders, a history of seizures, significant systemic disease, a positive drug screen, and female of childbearing potential

Pediatrics

- Clinical safety and efficacy was studied in a phase III, 6-week RCT in pediatrics (6-11 years old) who met DSM-V ADHD criteria with no comorbid psychiatric/neurologic disorders
    - Study was double-blinded and placebo-controlled with total 477 patients
    - Primary endpoint (efficacy): change from baseline in ADHD-RS-5 score
    - Secondary endpoints (safety): CGS-I score changes, AEs, labs, ECG changes
- Generalizability
    - Primarily males (63%) and either Caucasian (51%) or African American (44%)
    - Age group was small: only 6-11 years old, with some subjective testing only approved for ages 8-11
    - Patients were not on any other ADHD medications and had no comorbidities (specifically neurological or psychiatric conditions)
- Results
    - Treatment with viloxazine (100 or 200 mg/day) significantly reduced ADHD symptoms (ADHD-RS-5 scores, CGI-I, and WFIRS-P scores all reduced), with results seen as early as one-week post-initiation of viloxazine
    - These scores also showed a decrease in ADHD-associated impairments: learning problems, executive functioning, defiance/aggression, peer relations; as well as

improved functioning in various settings (family, school, social activities, and risky activities).

Safety

Adults

- In a clinical trial involving 189 adults with ADHD, 9% of patients who received viloxazine discontinued treatment due to an adverse reaction. The most common adverse reactions leading to discontinuation were fatigue, insomnia, constipation, & headache.
- Adverse reactions that occurred in at least 2% of Qelbree-treated patients are listed below:

Table 2. Adverse Reactions Reported in ≥2% of Adults Treated with Qelbree and at a Rate Greater than Placebo-Treated Patients in a Flexible-Dose Placebo-Controlled ADHD Study

Body System Adverse Reaction	Placebo N=183 (%)	Qelbree (200 mg to 600 mg) N=189 (%)
Psychiatric disorders		
Insomnia *	7	23
Irritability	3	4
Nervous system disorders		
Headache *	7	17
Somnolence *	2	6
Dizziness	2	4
Gastrointestinal system disorders		
Nausea	3	12
Dry mouth	2	10
Constipation	1	6
Vomiting	1	4
Gastrooesophageal reflux disease	1	2
Body as a Whole - General disorders		
Fatigue	3	12
Metabolic and nutritional disorders		
Decreased appetite	3	10
Cardiac Disorders		
Tachycardia	1	4

Pediatrics

- No cases of suicidal ideation were observed at any point in the trial
- Most common SEs: somnolence (8.9%), decreased appetite (6.0%), and headache (5.4%)
- Otherwise well-tolerated with no severe effects directly related to viloxazine therapy
    - Severe somnolence/insomnia seen in few patients resolved without treatment interruption (5 total patients)
    - One case of severe pyromania was deemed unrelated to treatment (patient withdrew from the trial).
    - One case of ECG T-wave inversion was seen with 100 mg/day; this patient withdrew from the trial and was lost to any follow-up

Comments/Role in Therapy

- Viloxazine is a selective norepinephrine reuptake inhibitor that has been approved by the FDA for the treatment of ADHD in adults and children aged 6-17
- It has been shown to be effective in improving the symptoms of ADHD in adults in clinical trials
- Viloxazine has a low risk of substance abuse and dependence compared to stimulants and may have a lower effect on dopamine levels
- It should be used with caution in patients with a history of cardiovascular events and should be monitored for suicidal thoughts or behaviors. Before starting treatment with viloxazine, healthcare providers should assess HR, BP, & history of suicide, bipolar disorder, or depression.
- In two clinical trials, viloxazine was administered in combination with methylphenidate and lisdexamfetamine to examine the pharmacokinetics of viloxazine alone and in combination with the other stimulants. Results indicate no drug-drug interactions between viloxazine and either methylphenidate or lisdexamfetamine, as demonstrated by the geometric low square mean ratios for the maximum concentrations of viloxazine and the other medications. Viloxazine was generally well tolerated with common side effects including dizziness, nausea, and somnolence. There was one case of vomiting and some reports of abnormal ECGs which was deemed insignificant.
- Atomoxetine is another norepinephrine reuptake inhibitor that is approved for the treatment of ADHD in patients starting at 6 years of age (since 2002, generic available)
    - while improvements in some symptoms may occur sooner, it may take 4 to 8 weeks to see full benefits of atomoxetine once proper dose is determined
    - Viloxazine may offer a faster onset of action compared to other non-stimulants with improvements in some symptoms observed within 1-2 weeks
    - atomoxetine has additional warnings/precautions for severe liver injury, serious CV events, emergent CV symptoms, priapism, growth delays and effects on urine outflow
    - viloxazine may offer an advantage for clts requiring a non-stimulant medication with straight-forward dosing and for clts unable to swallow capsules (atomoxetine capsules should not be opened, ocular irritant)
- Viloxazine is not a new drug, it was sold as an antidepressant in Europe for several decades and was withdrawn from the market due to competition from other antidepressants
- It may be a useful alternative for patients who want to avoid stimulants or have contraindications to their use, those with comorbid conditions such as anxiety or depression or if there is a concern for diversion of stimulant medications
- also an option for children with substance abuse complications, those who dislike stimulants' AEs or need additional therapy
- available in extended-release capsules and may be suitable for children who have difficulty swallowing capsules (may open the capsule & sprinkle over applesauce)
- Body weight may influence the pharmacokinetics of viloxazine, but further research is needed to confirm this

- Further research is also needed to compare the long-term efficacy of viloxazine with current standard-of-care treatments for ADHD especially in different subgroups of the patient population

Price comparison

Drug and Manufacturer	Dosage Form(s) & Strength(s)	Dose Range	Cost per 30 days[a]
Qelbree (viloxazine) *[Supernus Pharmaceuticals, Inc.]*	• Extended-release oral capsules: 100 mg, 150 mg, and 200 mg	100mg to 600mg Daily	Brand: $336 - $1008
Strattera (atomoxetine) *[Lilly USA, LLC]*	• Oral capsules: 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg and 100 mg	40mg to 100mg Daily	Generic: $52- $47 Brand: $429- $464

[a]WAC pricing from RxNova 1/5/2023

Formulary Recommendation:

PA required for BHRS, MediCal and CMC formularies
Diagnosis: All medically accepted indications
Age: 6 yrs of age and older
Previous trial of generic atomoxetine or if client is unable to swallow atomoxetine capsules
Quantity: limit to #30/30DS for 100mg, #60/30DS for 150mg and 200mg

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