Viloxazine (Qelbree®)
FDA approved April 2021 (Supernus Pharmaceuticals)

**Indication:** Viloxazine is indicated for the treatment of ADHD in pediatric patients 6 to 17-year-old

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

**Dosage & administration**

| Dosage | Initial: 6 to 11 yo: 100 mg QDay; 12 to 17 yo: 200 mg QDay  
Max 400 mg a day | Renal impairment (severe) | Initial: 100 mg QDay; Max 200 mg a day | Hepatic impairment | Use not recommended |
|--------|-------------------------------------------------|----------------------------------|------------------|-------------------|------------------|
| 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**
Cardiovascular (CV): increased DBP & HR  
GI: abdominal pain, reduced appetite, N/V  
Neurologic: headache, insomnia, somnolence  
Psychiatric: irritability  
Respiratory: upper respiratory infection  
Other: fatigue

**Serious**
CV: increased DBP & HR  
Psychiatric: suicidal behavior and thoughts

**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  
- irritability & insomnia have been reported  
Psychiatric  
- activation of mania or hypomania: screen clts to determine if they are at risk for bipolar disorder  
- depressed mood, anxiety, agitation, akathisia, mania, hypomania, panic attacks, impulsive behavior & aggression may lead to suicidal ideation or behavior. Monitoring required
Pharmacokinetics

<table>
<thead>
<tr>
<th>Bioavailability</th>
<th>bioavailability relative to IR formulation ~ 88%</th>
</tr>
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<tbody>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt;</td>
<td>5 hours (range 3 to 9 hours)</td>
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<tr>
<td>Half-life</td>
<td>Mean 7 hours +/- 4.7 hours</td>
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<tr>
<td>Metabolism</td>
<td>primarily metabolized by CYP2D6, UGT1A0, and UGT2B15</td>
</tr>
<tr>
<td>Steady state</td>
<td>• reached after 2 days</td>
</tr>
<tr>
<td></td>
<td>• estimated steady-state C&lt;sub&gt;max&lt;/sub&gt; &amp; AUC in 6 to 11 yo was ~40% to 50% &gt;12 to 17 yo</td>
</tr>
<tr>
<td>Excretion</td>
<td>Primarily urine (90%); feces (&lt;1%)</td>
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</table>

Clinical Efficacy

- 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, risky activities).

Clinical Safety of Viloxazine

- Side effects
  - 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

- **DDI**
  - Possible interactions seen with some antiepileptics (carbamazepine, phenytoin, phenobarbital) -> increased plasma concentrations of antiepileptics noted
  - Dosing of viloxazine commonly used was higher (antidepressant dosing)
  - Effects commonly seen within 2-3 weeks, but resolved (and plasma levels returned to baseline) upon viloxazine d/c.
  - Initial monitoring, (with possible dose decreases) suggested for patients initiating this medication combination.

**Comments/Role in Therapy**

- viloxazine is a selective norepinephrine reuptake inhibitor and a new molecular entity for the treatment of ADHD in children. It is thought to work by increasing serotonin, norepinephrine, & dopamine levels
  - atomoxetine is another SNRI indicated in patients starting at 6 years of age and has been available since 2002 (also available as a generic)
  - 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 demonstrated efficacy within one to two weeks suggesting a faster onset compared to other non-stimulants
  - 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)

- viloxazine is not a new drug, was sold as an antidepressant in Europe for several decades and was withdrawn from the market due to competition from other antidepressants
- viloxazine was generally well-tolerated and is supported by robust safety data from Europe
- prior to initiating therapy assess HR, BP, and screen for a history of suicide, bipolar disorder, or depression
- an option for clts with comorbid conditions such as anxiety or depression or if stimulant therapy is not recommended or unsuccessful
- offers another non-controlled treatment option for parents and children who want to avoid stimulants
- also an option for children with substance abuse problems, those who dislike stimulants’ AEs or need additional therapy
- The manufacturer plans to submit a New Drug Application for adults in the 2nd half of this year
Clinical Practice Guideline Recommendations

- The 2019 American Academy of Pediatrics Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents recommends parent training in behavior management (PTBM) as a first line treatment for children 4-5 years of age. Methylphenidate is recommended if behavioral interventions do not provide significant improvement. Children 6-18 years of age should be treated with an FDA-approved medication for ADHD, with or without behavioral therapy.

- Although the guidelines do not recommend a particular FDA-approved medication for ADHD, they do note that for elementary school-aged students, the evidence is particularly strong for stimulant medications and is sufficient, but less strong, for atomoxetine, extended-release guanfacine, and extended-release clonidine.

- Qelbree will likely be recommended for use in patients when stimulants are not tolerated, contraindicated or if there is a concern for diversion of stimulant medications.

Price comparison

<table>
<thead>
<tr>
<th>Drug and Manufacturer</th>
<th>Dosage Form(s) &amp; Strength(s)</th>
<th>Dosing Regimen</th>
<th>Cost per 30 days³</th>
</tr>
</thead>
</table>
| Qelbree (viloxazine)  | Extended-release oral capsules: 100 mg, 150 mg, and 200 mg | Pediatric patients 6 to 11 years of age:  
• Initial dose of 100 mg once daily  
• May titrate in increments of 100 mg weekly  
• Maximum dose is 400 mg once daily  
Pediatric patients 12 to 17 years of age:  
• Initial dose of 200 mg once daily  
• May titrate after one week, by an increment of 200 mg  
• Maximum dose is 400 mg once daily | At 400mg/day  
Brand: $598 |
<table>
<thead>
<tr>
<th>Drug and Manufacturer</th>
<th>Dosage Form(s) &amp; Strength(s)</th>
<th>Dosing Regimen</th>
<th>Cost per 30 days&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
</table>
| Strattera (atomoxetine) [Lilly USA, LLC] | • Oral capsules: 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg and 100 mg | Children and adolescents up to 70 kg:  
  • Initial daily dose of 0.5 mg/kg  
  • Target total daily dose of 1.2 mg/kg  
  • Maximum total daily dose of 1.4 mg/kg  
  Children and adolescents over 70 kg and adults:  
  • Initial daily dose of 40 mg  
  • Target total daily dose of 80 mg  
  • Maximum total daily dose of 100 mg | At 100mg/day  
  Brand: $464  
  Generic: $129 |

**Formulary Recommendation:**

PA required for BHRS, MediCal and CMC formularies  
Diagnosis: All medically accepted indications  
Age: 6-17 years of age  
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
Appendix

### Article

### Introduction
Most approved medications for ADHD (especially in children) are stimulants. These trials evaluate the safety and efficacy of a recently approved non-stimulant, non-controlled medication in the states for ADHD.

### General Study Overview

<table>
<thead>
<tr>
<th>Objective</th>
<th>Evaluating the safety and efficacy of viloxazine in the treatment of ADHD in children</th>
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<tbody>
<tr>
<td>Trial Design</td>
<td>Phase III, double-blind, placebo-controlled RCT (6 weeks long)</td>
</tr>
</tbody>
</table>

### Methods

#### Inclusion Criteria
- Male and female children
- Age 6-11 years
- Confirmed DSM-V ADHD diagnosis AND ADHD-rating scale-5 score at or >28 AND Clinical Global Impression-Severity score at or >4 AND free of ADHD medication for at least 1 week prior to randomization

#### Exclusion Criteria
- Current dx of major psychiatric/neurologic disorder other than ADHD
- Significant systemic disease
- History of allergy to viloxazine/components/relevant food allergies
- Evidence of suicidality within 6 months of screening

#### Intervention
- 100 mg viloxazine ER tabs once daily
- 200 mg viloxazine ER tabs once daily
- Placebo

#### Primary Endpoint
- Change from baseline (CFB) in ADHD-RS-5 total score

#### Secondary Endpoints
- Clinical Global Impression Improvement (CGS-I) scores
- CFB in Conners 3-Parent Short Form (Conners 3-PS) composite T-score
- Weiss Functional Impairment Rating Scale-Parent (WFIRS-P) total average scores
- (Safety) AEs, lab tests, vital signs, physical exams, ECGs, Columbia-Suicide Severity Rating Scale

#### Statistical Analysis
- ANCOVA models (secondary) and MMRM (primary)
- 104 subjects per treatment group with ITT → 90% power at alpha 0.05 two-sided t-test

### Results

#### Hgb, Blood Products, Circ. Variables
Generalizability: mostly male (63%) and Caucasian (~51%) or African American (~44%) with BMI of 17. Average baseline ADHD-RS-5 score was 44-45, and baseline CGI-S score 4.8. Prior ADHD med use reported in ~10% of patients in all groups (2/3 were stimulants)
No significant differences in baseline characteristics or testing between treatment groups

<table>
<thead>
<tr>
<th>Primary Outcome</th>
<th>ADHD-RS-5 score significantly reduced in both 100 and 200 mg groups compared to placebo – results seen as early as first week (indicating fast onset of action) → change in baselines were -16 and -18 (100 and 200 mg) compared to placebo (-9).</th>
</tr>
</thead>
</table>
| Secondary Outcomes | CGI-I score significantly lower in both viloxazine groups compared to placebo  
WFIRS-P score significantly reduced in both treatment groups, EXCEPT in the self-concept and life skills domains compared with placebo  
Conners 3-SRS and PSI-4-SF scores not significantly reduced for either treatment group  
SAFETY: (testing performed weekly) mild-moderate AEs (most common >5% were somnolence, decreased appetite, and headache). Four total people with vilox had severe SEs (2 of which were not considered related to treatment), and the other 2 were still able to continue.  
Nine total AEs led to d/c (2 were in placebo): tachycardia, fatigue, ECG T-wave inversion, dizziness, aggression, pyromania (determined not related to tx) |

**Conclusion**

Treatment with viloxazine (100 and 200 mg) significantly improve symptoms of ADHD within first week of initiation compared to placebo. Both doses were considered well-tolerated.

**Critique and Clinical Application**

**Strengths**
- Adequately powered to detect differences in primary endpoint
- No cases of suicidal ideation during the trial

**Limitations**
- Self-rated and parent-rated assessments (not significantly changed with tx): lack of power to detect differences in secondary endpoints, Conners 3-SRS not validated for ages 6-7 (limited responses from patients), lack of cognizance of symptoms and experience at younger ages.
- Trial was only 6 weeks; long enough to detect a difference, but overall impact on long-term QOL is unclear from this trial (lack of later follow-up also)
- Some of the employees were associated with the manufacturing company, which also funded this study.

**Clinical Application**
- Good candidate for young patients who may not be eligible or tolerant for stimulant medications; this medication proves to have a well-tolerated profile, with effects seen as early as 1 week post-initiation.
- Improvements seen in ADHD symptoms and associated impairments: learning problems, executive functioning, defiance/aggression, peer relations; as well as improved functioning in various settings (family, school, social activities, risky activities)

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**Viloxazine DDI with Carbamazepine (in patients with epilepsy)**

**Article**


**Introduction**

Possible DDI with carbamazepine and viloxazine. Not too much data available, but some studies indicate close monitoring and possible dose decreases of carbamazepine with concomitant viloxazine.

**General Study Overview**
<table>
<thead>
<tr>
<th><strong>Objective</strong></th>
<th>To determine the clinical significance (if any) of any DDI between carbamazepine and viloxazine</th>
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<tbody>
<tr>
<td><strong>Trial Design</strong></td>
<td>Case studies (patients with epilepsy stabilized on carbamazepine initiating viloxazine 300 mg/day).</td>
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</tbody>
</table>

### Results

- Six depressed epileptic patients stabilized on carbamazepine – initiated 300 mg/day viloxazine for at least 3 weeks with average 55% increase in SS plasma carbamazepine concentrations (and increased active metabolite concentrations by 16%)  
- Three of these patients had carbamazepine intoxication (resolved after quellbree d/c)  
- One patient saw severe effects after only two weeks: 197% and 137% increase of carbamazepine and active metabolite levels  
- DDI likely due to inhibition of carbamazepine metabolism and the active metabolite  
- In similar case reports, DDI seen with phenytoin (average 37% increase in plasma concentrations with toxicity)

### Limitations

- Viloxazine was used as an antidepressant with higher dosing compared to that for ADHD

### Clinical Application

- This may be more applicable for patients requiring higher doses of viloxazine, but depending on individual metabolism, may apply to others; monitoring suggested for concomitant therapy with these two medications.  
- Effects most commonly seen within 2-3 weeks

### References:

- Drug utilization review board. (2020, October 14). *Packet Contents for DUR Board Meeting* [Webinar]. Oklahoma Health Care Authority  
- Psychiatry Drug Alerts Volume XXXV / March 2021 / Number 3
- Strattera [package insert]. Indianapolis, IN: Lilly USA, LLC; February 2020.
- Rx Outlook. 3rd Quarter 2020. 
- Trombetta S. Preliminary Medication Review: New Molecular Entity Central Nervous System Agents: Attention Deficit Hyperactivity Disorder Agents, non-amphetamines