Viloxazine Extended-Release Capsules (QELBREE)
National Drug Monograph
August 2022

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action

- Viloxazine is a selective norepinephrine reuptake inhibitor

Indication(s) Under Review in This Document

- Viloxazine is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in adults and pediatric patients 6 years and older.

Dosage Form(s) Under Review

- Extended-release capsules: 100 mg, 150 mg and 200 mg

Clinical Evidence Summary

Efficacy Considerations [1] (This review focuses on the adult patient)

- The efficacy of viloxazine, supporting its FDA approved indication for the treatment of ADHD in adults 18 years of age and older, was based on data from one phase 3, multicenter, randomized, double-blind, placebo-controlled, flexible dose, parallel-group monotherapy, 6 week industry-sponsored trial (Study 4, NCT04016779).
- Subjects were started at 200 mg once daily for week 1 and titrated up to 400 mg once daily during week 2. The dose was adjusted by 200 mg per day once a week to a minimum of 200 mg once daily and maximum of 600 mg once daily thereafter. Patients were randomized to receive viloxazine (200 mg to 600 mg), or placebo, given once daily as a single dose.
- The primary endpoint for Study 4 was the change from baseline to the end of study on the total score of the ADHD Investigator Symptom Rating Scale (AISRS). The AISRS is an 18-item scale corresponding to 18 symptoms of ADHD. Items are scored as follows: 0 (none), 1 (mild), 2 (moderate), 3 (severe). The maximum total score for the scale is 54 points, with 27 points for each subscale. The total score is the sum of the inattentive and hyperactive-impulsive subscales. Higher AISRS scores reflect more severe symptoms. To be included in the study, patients were required to have an AISRS total score of ≥ 26 at the screening visit and at the baseline visit.

- The change from baseline in the Clinical Global Impression-Severity of Illness (CGI-S) score at the end of the study was the key secondary endpoint. Patients were required to have a CGI-S score of ≥ 4 (moderately ill or worse) at the screening visit and baseline visit.
- 374 patients were randomized; 267 completed and 107 discontinued. The average dose at end of study was 504 mg per day. Eight percent received 200 mg/day, 32% received 400 mg/day and 60% received 600 mg/day.
- The change from baseline (reduction) in the AISRS Total score was statistically significantly greater in patients treated with viloxazine than in those who received placebo (Table 1).
- There was also a statistically significant improvement vs placebo on the CGI-S at week 6 (p =.0023).

Table 1. Primary Efficacy; Change from Baseline AISRS Total Score in Adults with ADHD (Study 4).[1]

	Viloxazine (200mg-600mg) N=175	Placebo N=179
AISRS baseline score Mean (SD)	38.5 (6.6)	37.6 (6.6)
LS mean (SE) change from baseline	-15.5 (0.9)	- 11.7 (0.9)
Difference vs. placebo (95% CI)	-3.7 (-6.2, -1.2)	
p-value (vs. placebo)	P=0.004	

AISRS: Attention-Deficit/Hyperactivity Disorder Investigator Symptom Rating Scale; N: sample size; SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval

Safety Considerations

Table 2. Adverse Reactions, Adults [1]

Adverse reaction	Viloxazine (200mg-600mg) N=189 (%)	Placebo N=183 (%)
Insomnia	23	7
Headache	17	7
Fatigue	12	3
Nausea	12	3
Decreased appetite	10	3
Dry mouth	10	2
Somnolence	6	2
Constipation	6	1
Tachycardia	4	1
Irritability	4	3
Dizziness	4	2
Vomiting	4	1

Contraindications:

- Concomitant treatment with MAOIs or within 14 days following discontinuation of an MAOI
- Concomitant use with sensitive CYP1A2 substrates or CYP1A2 substrates with a narrow therapeutic range

Other warnings / precautions:[1]

- **Suicidal thoughts and behaviors – boxed warning**
  - Pediatric patients: 0.9% drug vs 0.4% placebo
  - **Adults – 1.6% drug vs 0% placebo**
- Blood pressure and heart rate increases
- Activation of mania or hypomania
- Somnolence and fatigue
- Pregnancy – may cause maternal harm; discontinue when pregnancy is recognized

Other Therapeutic Options

Table 3.

Drug	Formulary status	Clinical Guidance/ Indication	Other Considerations
Viloxazine	NF	ADHD, Adults and pediatric patients 6 years and older	Box warning for suicidal thoughts and behaviors
Atomoxetine	PA-F	ADHD	Box warning for suicidal ideation in children and adolescents
Bupropion	F	MDD, SAD, smoking cessation	Off-label ADHD; increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults (≤24yo)
Dexmethylphenidate	NF	ADHD	Box warning for abuse and dependence
Methylphenidate	F	ADHD, narcolepsy	Box warning for abuse and dependence
Dextroamphetamine	F	ADHD, narcolepsy	Box warning for abuse and dependence, and cardiovascular events
Dextroamphetamine and amphetamine	F	ADHD, narcolepsy	Box warning for abuse and dependence, and cardiovascular events
Lisdexamfetamine	PA-F	ADHD, binge eating disorder	Box warning for abuse and dependence

Projected Place in Therapy

- ADHD is a neurodevelopmental disorder, of childhood-onset, characterized by hyperactivity, impulsivity, or inattention that results in functional impairment. The prevalence of ADHD among adults aged 18 to 64 years increased from 3.4% in 2007 to 4.3% in 2012[4]. Stimulants are first line agents while nonstimulants provide a second line option for providers when patients are unable to tolerate, or are not good candidates for, stimulants.
- The results from Study 4 support the efficacy of viloxazine in reducing ADHD symptoms (AISRS Total score) in adult patients with ADHD.
- The effectiveness of viloxazine in adult patients compared to alternative treatments has not been established.
- Viloxazine has a boxed warning for suicidal thoughts and behavior. In the clinical trial, adult patients treated with viloxazine had higher rates of suicidal thoughts and behaviors than patients treated with placebo.
- The most common adverse reactions in adults are insomnia, headache, fatigue, nausea, decreased appetite, dry mouth, somnolence and constipation.

- The use of viloxazine should be avoided in patients with treated with an MAOI (currently or within 14 days) and concurrently with sensitive CYP1A2 substrates or CYP1A2 substrates with a narrow therapeutic range.
- The use of viloxazine has not been discussed in current guideline; viloxazine was not available when guidelines were developed.
- Viloxazine represents another non-stimulant for the management of adults with ADHD who are unable to tolerate a stimulant or for whom the risk of a stimulant outweighs the benefit. However, viloxazine does not appear to provide any advantage(s) over other nonstimulants (e.g., atomoxetine).

References

1. QELBREE (viloxazine extended-release capsules) [prescribing information]. Supernus Pharmaceuticals, Inc. Rockville, MD. April 2022.
2. FDA Integrated Review. Application number 211964Orig1s000. Center for Drug Evaluation and Research. April 2, 2021.
3. NDA 211964/S-003. NDA approval letter. Department of Health and Human Services. Food and Drug Administration, Silver Spring, MD 20993. April 29, 2022.
4. London AS and Landes SD. Cohort change in the prevalence of ADHD among U.S. adults: evidence of a gender-specific historical period effect. J Atten Disord 2021;25:771-782.

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