The Ohio State University College of Pharmacy
Drug Monograph Assignment

viloxazine (QELBREE®)

Supernus Pharmaceuticals

AHFS THERAPEUTIC CLASS: 28:92 - Central Nervous System Agents, Miscellaneous

MECHANISM OF ACTION: inhibits the reuptake of norepinephrine.
The exact mechanism underlying the beneficial effects of viloxazine for the treatment of ADHD has not been fully elucidated.
Some data (in vitro) suggest that it appears to inhibit 5-HT2B receptor and activate 5-HT2C receptor

FDA APPROVED INDICATION: treatment of ADHD in pediatric patients 6 to 17 years of age.

CLINICAL EFFICACY: Efficacy was evaluated in three short-term, multicenter, randomized, double-blind, three-arm, placebo-controlled, parallel-group monotherapy trials. The first two studies included children (6-11 years old) with ADHD at varying strengths, while the third study included adolescents (12 to 17 years old). In all trials, the primary endpoint was the change from baseline in the ADHD-RS-5 total score; the CGI-I score at the end of the study was a key secondary endpoint. All trials demonstrated a statistically significant reduction (improvement) in ADHD-RS-5 and CGI-I score in patients treated with viloxazine vs. placebo.

	Study 1 (NCT03247530)	Study 2 (NCT03247543)	Study 3 (NCT03247517)
Study Design	Trials: multicenter, randomized, double-blind, placebo-controlled, three-arm, parallel-group studies Analysis: intention-to-treat Inclusion: ADHD diagnosis by DSM-5, confirmed by MINI-KID; ADHD-RS-5 ≥28; CGI-S ≥4 Exclusion: major psychiatric/neurologic disorder (MDD allowed); hx seizures; evidence of suicidality Primary endpoint: change from baseline in the ADHD-RS-5 total score at end of study Secondary endpoint: CGI-I score		
Population	6 to 11 years old (N=460); 63% male; 44% AA; Mean Baseline ADHD-RS-5 of 44	6 to 11 years old (N=301); 65% male; 42% AA; Mean Baseline ADHD-RS-5 of 44	11 to 17 years old (N=301); 64% male; 39% AA; Mean Baseline ADHD-RS-5 of 40
Duration	6 weeks (1-wk titration, 5-wk maintenance)	8 weeks (3-wk titration, 5-wk maintenance)	6 weeks (1-wk titration, 5-wk maintenance)
Purpose	The purpose of the studies was to evaluate whether treatment with SPN-812 (viloxazine extended-release) significantly reduces symptoms of ADHD in children.		
Intervention	100mg, 200mg vs. placebo	200mg, 400mg vs. placebo	200mg, 400mg vs. placebo
Outcomes	Both primary and secondary endpoint total scores at EOS were significantly reduced with viloxazine vs. placebo.		
	CFB in ADHD-RS-5: 100mg (-16.6), 200mg (-17.7), placebo (-10.9)	CFB in ADHD-RS-5: 200mg (-17.6), 400mg (-17.5), placebo (-11.7)	CFB in ADHD-RS-5: 200mg (-16.0), 400mg (-16.5), placebo (-11.4)
Conclusion	Improvement in symptoms of inattention, hyperactivity, and impulsivity consistently observed as early as week 1. - delivers significant effect on subscales of both inattention and hyperactivity/impulsivity. - demonstrates proven safety and tolerability and low discontinuation rates due to AEs. Limitations: subjective scaling; short-term study		

PHARMACOKINETICS
Cmax and AUC increase proportionally over a range of 100-400mg. Steady-state reached after two days; no accumulation observed.
Absorption: Bioavailability: ~88%. Time to peak (Tmax): ~5 hours (range 3-9 hours). Tmax increased by ~2 hours after high-fat meal.
Effects of food: administration with a high-fat meal (800-1,000 calories) decreases Cmax and AUC 9% and 8%, respectively.
Distribution: Protein binding: 76-82% over blood concentration range of 0.5-10mcg/ml.
Metabolism: Metabolized by CYP2D6, UGT1A9, UGT2B15. Major metabolite: 5-hydroxy-viloxazine glucuronide.
Elimination: Half-life: 7.02 +/- 4.74 hours. Excretion: Primarily renal (urine: 90%; feces: <1%).

PHARMACODYNAMICS
Binds to the norepinephrine transporter (NET, Ki=0.63 μM) and inhibits the reuptake of norepinephrine (IC50=0.2 μM).
No clinically relevant QT prolonging at a dose of 4.5 times maximum dose; no effect on PR interval or QRS duration.

ADVERSE REACTIONS

- Suicidal thoughts and behaviors (<1%)
- Increased diastolic blood pressure (25%) and increased heart rate (22-34%)
- Somnolence (including lethargy and sedation; 12-19%), headache (including migraine; 10-11%), fatigue (4-9%)
- Others: upper respiratory tract infection (5-8%), decreased appetite (5-8%), abdominal pain (6-7%), vomiting (3-6%)

SAFETY CONSIDERATIONS

- Medications with similar names (Look-alike/Sound-alike): may be confused with vilazodone
- Hazardous Risk Category: not on NIOSH list; may meet criteria (may cause teratogenicity/reproductive toxicity)
- Precautions:
    - Suicidal Thoughts and Behaviors
    - Blood Pressure and Heart Rate Increases
    - Somnolence and Fatigue
    - Activation of Mania or Hypomania
- Contraindications:
    - Concomitant use with or within 14 days of MAOIs
    - Concomitant use of sensitive CYP1A2 substrates or CYP1A2 substrates with a narrow therapeutic range
- Boxed Warnings: Suicidal Thoughts and Behaviors
- Sentinel Events Advisory: No
- REMS Program: No

SPECIAL POPULATIONS

- Pregnancy: may cause fetal harm (animal studies); consider discontinuing viloxazine if pregnancy occurs.
- Lactation: no data on presence in human milk, effects on breastfed infant, effects of milk production.
- Geriatrics: the safety and effectiveness have not been established in patients 65yo and older.
- Pediatrics: safety and effectiveness have not been established in patients younger than 6yo.
    - Steady-state Cmax and AUC at dosages of 100-400mg were 40-50% higher in 6-11yo than 12-17yo.
- Hepatic Impairment (mild to severe): not recommended as effect of impairment on pharmacokinetics is unknown.
- Renal Impairment
    - Mild to moderate impairment (eGFR 30-89 ml/min/1.73m2): no dosage adjustment necessary.
    - Severe impairment (eGFR <30ml/min/1.73m2): initial 100mg once daily; may titrate by 50-100mg increments at weekly intervals; maximum 200mg/day.

DRUG INTERACTIONS:

- Viloxazine coadministration with an MAOI may lead to life-threatening hypertensive crisis. Concomitant use with an MAOI or within 2 weeks after discontinuing an MAOI is contraindicated.
- Viloxazine is a strong 1A2 inhibitor; increases total exposure, but not peak exposure, when coadministered.
    - Use with sensitive 1A2 substrates or 1A2 substrates with narrow therapeutic range is contraindicated (e.g., duloxetine, ramelteon, tizanidine, theophylline).
    - Use with moderate sensitive 1A2 substrates is not recommended (e.g., clozapine).
- Viloxazine is a weak CYP2D6 inhibitor; increases exposure when coadministered. Monitor and adjust dosages as necessary.
- Viloxazine is a weak CYP3A4 inhibitor; increases exposure when coadministered. Monitor and adjust dosages as necessary.
- Alcohol with <20% has no significant effect. With 40% alcohol, Cmax and AUC decreased by 32% and 19%, respectively.
- No significant interactions with other stimulants (amphetamines, methylphenidate).

DOSAGE FORMS AVAILABLE: extended-release (ER) capsules: 100mg, 150mg, 200mg

DOSING:

6-11 years old: initial 100mg once daily; may titrate by 100mg increments at weekly intervals; maximum 400mg/day.
12-17 years old: initial 200mg once daily; may increase to 400mg once daily after 1 week; maximum 400mg/day.

ADMINISTRATION: Capsules may be swallowed whole or opened and the entire contents sprinkled into applesauce.

COST COMPARISON:

Drug	Dosage	Average Wholesale Price (AWP)		Actual Acquisition Cost (AAC)	
		Unit Cost	30-Day Cost	Unit Cost	30-Day Cost
Qelbree ER caps	1 po qday	11.96	358.80	9.4483	283.45
atomoxetine caps	1 po qday	15.466	463.98	0.389	11.67
guanfacine ER tabs	1 po qday	10.491	314.73	0.1091	3.27
clonidine tabs	1 po qday-qid	0.259	31.08	0.0343	4.12
Adderall XR generic caps	1 po qday	6.135	184.05	0.5426	16.28
Concerta generic tabs	1 po qday	13.209	396.27	0.5209	15.63
Vyvanse caps	1 po qday	13.399	401.97	10.586	317.58

MEDICATION MONITORING PLAN:

- Prior to initiation, conduct thorough physical exam to assess for cardiac disease. All patients should be screened for personal history of suicidal ideation, bipolar disorder, and depression.
- Monitor blood pressure and pulse at baseline, following dose increases, and periodically during treatment. Monitor weight, liver enzymes, serum creatinine and GFR periodically.

CONCLUSION:

- Arguments supporting addition
  - Non-stimulant treatment for ADHD; not scheduled; lower risk for abuse
  - Once-daily dosing
  - Generally safer and has a milder side effect profile compared to stimulants
- Arguments against addition
  - Narrow treatment group and age range
  - Relatively expensive
  - Minimal clinical expertise

RECOMMENDATION: Qelbree can be considered an appropriate option for the treatment of ADHD in children and adolescents. As a non-controlled selective norepinephrine reuptake inhibitor, viloxazine may have relatively milder side effects, lower abuse potential, and may be an option in those who are unable to tolerate stimulants. As a newer drug on the market Qelbree has limited clinical experience and its place in therapy and overall clinical benefit may be better understood following practical experience and further research.

GLOSSARY: ADHD-RS-5: ADHD Rating Scale, 5th Ed.; CGI-I: Clinical Global Impression-Improvement; CFB: change from baseline; EOS: end of study

REFERENCES:

Drugs@FDA: FDA-Approved Drugs. Accessdata.fda.gov. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=211964. Published 2021. Accessed July 15, 2021.

Evaluation of SPN-812 (Viloxazine Extended-release Capsule) Low Dose in Children With ADHD. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT03247530. Published 2021. Accessed July 15, 2021.

Evaluation of SPN-812 (Viloxazine Extended-release Capsule) High Dose in Children With ADHD. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT03247543. Published 2021. Accessed July 15, 2021.

Evaluation of SPN-812 (Viloxazine Extended-release Capsule) Low Dose in Adolescents With ADHD. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT03247517. Published 2021. Accessed July 15, 2021.

Lexicomp, viloxazine. Lex-Drugs. Lexicomp. Wolters Kluwer. Hudson, OH. [Updated July 19, 2021; Accessed July 20, 2021]. https://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/7090827.

Nasser A, Liranso T, Adewole T et al. A Phase III, Randomized, Placebo-controlled Trial to Assess the Efficacy and Safety of Once-daily SPN-812 (Viloxazine Extended-release) in the Treatment of Attention-deficit/Hyperactivity Disorder in School-age Children. *Clin Ther*. 2020;42(8):1452-1466. doi:10.1016/j.clinthera.2020.05.021

Viloxazine [package insert]. Rockville, MD. Supernus Pharmaceuticals, Inc; Published April 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/211964s000lbl.pdf. Accessed July 15, 2021.