NON-STIMULANT ADHD AGENT

Viloxazine

Qelbree

Once-daily non-stimulant norepinephrine reuptake inhibitor with serotonergic modulation, approved for ADHD in children and adults.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
200-600 mg/day PO once daily	~7 h; Tmax 5 h	CYP2D6, UGT; strong 1A2 inhib	1-2 wks; 6 wks full effect

⚠ FDA BOXED WARNING

Suicidal thoughts and behaviors: higher rates of suicidal thoughts and behavior were reported with viloxazine than with placebo in ADHD clinical studies. Monitor all treated patients closely for clinical worsening and for the emergence of suicidal thoughts and behaviors.

INDICATIONS

- FDA-approved for attention-deficit/hyperactivity disorder in pediatric patients age 6 to 17 years as a once-daily extended-release capsule.
- FDA-approved for ADHD in adults since 2022, making it the first new non-stimulant with an adult indication in nearly two decades.
- Useful when abuse, diversion, or a contraindication to controlled substances makes stimulants unsuitable for the patient or family.
- Reasonable alternative when atomoxetine failed for tolerability, since the receptor profile and time course differ despite both being noradrenergic.
- Used off-label as an adjunct to stimulant therapy for residual inattention, although controlled combination data are limited.
- Not indicated for depression, anxiety, or narcolepsy, even though viloxazine was marketed as an antidepressant in Europe decades ago.

DOSING & TITRATION

- Children 6-11 years: start **100 mg** PO once daily and titrate by **100 mg** weekly to a maximum of **400 mg/day**.
- Adolescents 12-17 years: start **200 mg** PO once daily and, after 1 week, may increase by 200 mg to a maximum of **400 mg/day**.
- Adults: start **200 mg** PO once daily and titrate in **200 mg** weekly increments to a maximum of **600 mg/day**.
- Severe renal impairment with eGFR 15-29 mL/min/1.73 m2: start 100 mg daily, titrate weekly by 50-100 mg, and do not exceed 200 mg/day.
- Capsules may be swallowed whole or opened and sprinkled onto applesauce or pudding, but the beads must not be chewed or crushed.
- No taper is required, and stopping does not produce a discontinuation syndrome, though ADHD symptoms return within days.

MECHANISM OF ACTION

- Inhibits the norepinephrine transporter, increasing synaptic norepinephrine and, in prefrontal cortex, extracellular dopamine.
- Acts as a 5-HT2B receptor antagonist and a 5-HT2C receptor agonist, a serotonergic profile that distinguishes it from atomoxetine.
- Serotonergic modulation is thought to contribute to effects on emotional dysregulation and irritability alongside core ADHD symptoms.
- No meaningful dopamine release in nucleus accumbens occurs, so there is no euphoria and the drug is not a controlled substance.
- Benefit accumulates over weeks through downstream receptor adaptation, though separation from placebo can appear as early as week 1.

PHARMACOKINETICS

- Extended-release capsules give a Tmax of about 5 hours, and food lowers peak concentration modestly without changing overall exposure.
- Elimination half-life is approximately 7 hours, and once-daily dosing is supported by the extended-release delivery system.
- Metabolized by CYP2D6 hydroxylation and by UGT1A9 and UGT2B15 conjugation, with excretion mainly renal as the glucuronide.
- Viloxazine is a strong CYP1A2 inhibitor, a weak CYP2D6 and CYP3A4 inhibitor, and this is the dominant interaction concern.
- Severe renal impairment raises exposure and requires a lower starting dose and a hard maximum of 200 mg daily.

ADVERSE EFFECTS

- In children and adolescents the common effects are somnolence, decreased appetite, fatigue, nausea, vomiting, insomnia, and irritability.
- In adults the common effects are insomnia, headache, somnolence, fatigue, nausea, decreased appetite, dry mouth, and constipation.
- Somnolence and fatigue are the usual reasons for discontinuation and can be reduced by evening rather than morning dosing.
- Blood pressure and heart rate increase modestly, so vitals should be measured before treatment, after each increase, and periodically.
- Activation of mania or hypomania can occur, so screen for bipolar disorder and family history of mania before starting.
- Suicidal thoughts and behaviors were more frequent than with placebo, the basis for the boxed warning that applies at all ages.

MONITORING

- Measure heart rate and blood pressure before starting, after each dose increase, and periodically during maintenance treatment.
- Screen for personal and family history of suicide, bipolar disorder, and depression before the first dose, as the label directs.
- Ask about new or worsening suicidal thinking, agitation, and unusual behavior change at every visit, especially in the first weeks.
- Track response with a validated ADHD rating scale at baseline and at weeks 2 and 6, since full benefit takes about 6 weeks.
- Check renal function when eGFR is uncertain in older or medically complex patients, because severe impairment caps the dose at 200 mg.

INTERACTIONS & CAUTIONS

- Coadministration with sensitive CYP1A2 substrates or CYP1A2 substrates with a narrow therapeutic index is contraindicated.
- Practically this means avoiding tizanidine and theophylline, and using caution with clozapine, olanzapine, duloxetine, and caffeine.
- Contraindicated with monoamine oxidase inhibitors and within 2 weeks of stopping one because of potential hypertensive crisis.
- As a weak CYP2D6 and CYP3A4 inhibitor it can raise levels of substrates such as atomoxetine, risperidone, and some benzodiazepines.
- Additive blood pressure and heart rate effects occur with stimulants, decongestants, and other noradrenergic drugs.

SPECIAL POPULATIONS

- Pregnancy: animal data show maternal and fetal toxicity, and the label directs discontinuation when pregnancy is recognized unless benefit outweighs risk.
- Lactation: there are no human milk data, so an alternative agent or infant monitoring for sedation and poor feeding is advisable.
- Pediatric: approved from age 6 years; safety and effectiveness in children under 6 have not been established.
- Geriatric: clinical trials did not include enough patients over 65 to determine differences in response or tolerability.
- Severe renal impairment requires the reduced dosing schedule; use in end-stage renal disease has not been studied.

☆ PRESCRIBING PEARLS

- A strong CYP1A2 inhibitor: screen for tizanidine, theophylline, clozapine, and olanzapine first.
- Move the dose to evening when somnolence appears rather than abandoning the drug.
- The boxed suicidality warning applies to adults too, unlike the atomoxetine warning.

References

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NOTE

References follow APA 7th edition style. Dosing, boxed warnings, and interaction data change; confirm every clinical decision against the current FDA prescribing information (DailyMed) and your institution's formulary. This sheet is an educational quick reference and does not replace the full label or clinical judgment.