VMAT2 INHIBITOR

Valbenazine

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Once-daily VMAT2 inhibitor approved for tardive dyskinesia and for chorea of Huntington disease, with no titration needed for most patients.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
40-80 mg once daily PO	15-22 h (parent and metab)	Hydrolysis; CYP3A4, CYP2D6	2 wks; peak effect 6-8 wks

⚠ FDA BOXED WARNING

VMAT2 inhibitors including valbenazine can increase the risk of depression and suicidal thoughts and behavior in patients with Huntington's disease; balance that risk against the need to treat chorea and monitor closely for emerging or worsening depression, suicidal ideation, or behavior change.

INDICATIONS

- FDA-approved for the treatment of tardive dyskinesia in adults, regardless of whether the causative antipsychotic is continued.
- FDA-approved for chorea associated with Huntington disease in adults, an indication added in 2023 with the boxed warning.
- First-line pharmacologic treatment for moderate to severe tardive dyskinesia in current APA and movement disorder guidance.
- It treats tardive dyskinesia symptomatically without requiring the offending antipsychotic to be stopped or switched.
- Not indicated for acute dystonia, drug-induced parkinsonism, or akathisia, which respond to different interventions.
- Off-label use in other tardive syndromes such as tardive dystonia is described but has limited controlled evidence.

DOSING & TITRATION

- For tardive dyskinesia start **40 mg** once daily, then increase to the recommended **80 mg** once daily after 1 week.
- For Huntington chorea start **40 mg** once daily and titrate weekly in 20 mg increments to a recommended dose of **80 mg** daily.
- Some patients respond adequately to **40 mg** daily, and **60 mg** is an option when 80 mg is not tolerated.
- Reduce to **40 mg** daily with strong CYP3A4 inhibitors, with strong CYP2D6 inhibitors, and in known CYP2D6 poor metabolizers.
- Reduce to **40 mg** daily in moderate to severe hepatic impairment, and avoid concomitant strong CYP3A4 inducers entirely.
- The capsule contents may be sprinkled on soft food for patients who cannot swallow capsules; no taper is required on discontinuation.

MECHANISM OF ACTION

- Reversibly inhibits vesicular monoamine transporter 2, reducing packaging of dopamine into presynaptic vesicles and lowering synaptic release.
- Reduced striatal dopamine signaling counteracts the receptor supersensitivity thought to underlie tardive dyskinesia after chronic D2 blockade.
- Valbenazine is a prodrug hydrolyzed to the active [+]-alpha-dihydrotetrabenazine isomer, which binds VMAT2 with high selectivity.
- The single active isomer gives less off-target activity than tetrabenazine, which yields four isomers with broader receptor effects.
- It has negligible affinity for dopamine, serotonin, adrenergic, and muscarinic receptors, limiting sedation and autonomic effects.

PHARMACOKINETICS

- Oral absorption gives peak concentrations in about 30 minutes to 1 hour, and a high-fat meal reduces exposure modestly without clinical importance.
- Both valbenazine and its active metabolite have half-lives of roughly 15 to 22 hours, supporting reliable once-daily dosing.
- Hydrolysis produces the active metabolite, which is further metabolized by CYP3A4 and CYP3A5, while CYP2D6 handles the parent drug.
- Steady state is reached in about 1 week, and clinically meaningful benefit typically emerges within 2 to 6 weeks of the target dose.
- Excretion is largely as metabolites, and use is not recommended when creatinine clearance falls below 30 mL per minute.

ADVERSE EFFECTS

- Somnolence and sedation are the most common effects, reported in roughly 10 percent versus 4 percent on placebo in registration trials.
- Balance problems, gait disturbance, and falls occur more often than with placebo and matter most in older or frail patients.
- Dose-dependent QT prolongation is small at usual doses but becomes clinically relevant in poor metabolizers or with enzyme inhibitors.
- Drug-induced parkinsonism and akathisia can emerge from excessive dopamine depletion and usually respond to dose reduction.
- Depression and suicidal ideation are the defining risk in Huntington disease and drive the boxed warning for that population.
- Headache, dry mouth, urinary retention, anticholinergic-like complaints, and arthralgia are reported at low but appreciable rates.

MONITORING

- Assess mood and suicidality at baseline and at every visit in Huntington disease, and involve caregivers in reporting behavior change.
- Use the AIMS at baseline and every 3 to 6 months to document response and to guide dose decisions objectively.
- Obtain an ECG at baseline and after dose escalation in patients with congenital long QT, arrhythmia history, or interacting drugs.
- Monitor for emergent parkinsonism, sedation, and gait instability, all of which signal excessive dopamine depletion.
- Review hepatic function and CYP2D6 status when choosing the dose, since both shift exposure substantially.

INTERACTIONS & CAUTIONS

- Strong CYP3A4 inhibitors such as ketoconazole and clarithromycin raise active metabolite exposure and require a **40 mg** daily dose.
- Strong CYP3A4 inducers including rifampin, carbamazepine, phenytoin, and St. John's wort reduce exposure and should be avoided.
- Strong CYP2D6 inhibitors such as paroxetine, fluoxetine, and bupropion raise levels, so use the lower dose in those patients.
- Concomitant MAO inhibitors are not recommended because monoamine depletion combined with MAO inhibition has unpredictable effects.
- Additive QT effects with other QT-prolonging drugs warrant ECG monitoring; additive sedation occurs with alcohol and CNS depressants.

SPECIAL POPULATIONS

- Pregnancy data are limited and animal data show developmental toxicity, so use only when the benefit clearly outweighs the risk.
- Because of a long half-life and animal lactation data, breastfeeding is not recommended during and for 5 days after treatment.
- Safety and efficacy in patients under 18 years have not been established for either approved indication.
- In older adults, sedation, gait instability, and falls are the main concerns; consider the 40 mg dose and monitor mobility.
- Use 40 mg daily in moderate to severe hepatic impairment, and avoid use when creatinine clearance is below 30 mL per minute.

PRESCRIBING PEARLS

- No need to stop the antipsychotic; valbenazine treats tardive dyskinesia while the antipsychotic continues.
- Anticholinergics do not help tardive dyskinesia and often worsen it; taper benztropine as valbenazine starts.
- Poor CYP2D6 metabolizers and patients on paroxetine or fluoxetine should stay at **40 mg** daily.

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.