VMAT2 INHIBITOR

Deutetrabenazine

Austedo, Austedo XR

Deuterated tetrabenazine for tardive dyskinesia and Huntington chorea, with slower metabolism and fewer peak-related adverse effects.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
12-48 mg/day PO with food	9-10 h (active HTBZ metabs)	Carbonyl reductase, CYP2D6	2-4 wks; titrate weekly

⚠ FDA BOXED WARNING

Deutetrabenazine can increase the risk of depression and suicidal thoughts and behavior in patients with Huntington's disease, and is contraindicated in patients who are suicidal or who have untreated or inadequately treated depression. Monitor closely for new or worsening depression.

INDICATIONS

- FDA-approved for chorea associated with Huntington disease in adults, the indication that carries the boxed warning.
- FDA-approved for tardive dyskinesia in adults, with efficacy established in the ARM-TD and AIM-TD randomized trials.
- Recommended alongside valbenazine as first-line pharmacotherapy for moderate to severe tardive dyskinesia in current guidance.
- Deuteration allows lower and less frequent dosing than tetrabenazine, with lower rates of depression, akathisia, and sedation.
- Off-label use for other hyperkinetic movement disorders such as tardive dystonia and tics has limited controlled support.
- Not indicated for acute extrapyramidal symptoms, drug-induced parkinsonism, or dementia-related agitation.

DOSING & TITRATION

- For tardive dyskinesia start **12 mg/day** as 6 mg twice daily, then increase by 6 mg per day at weekly intervals as tolerated.
- For Huntington chorea start **6 mg once daily** and increase by 6 mg per day weekly, guided by chorea control and tolerability.
- The maximum for both indications is **48 mg/day**, and single immediate-release doses should not exceed 24 mg.
- Cap the total at **36 mg/day** with strong CYP2D6 inhibitors or in known poor metabolizers, with a single-dose limit of 18 mg.
- Immediate-release doses of 12 mg or more per day are divided twice daily and taken with food; the extended-release tablet is once daily.
- Doses may be stopped without taper for short interruptions, but restart titration if therapy has lapsed for more than a week.

MECHANISM OF ACTION

- Reversibly inhibits vesicular monoamine transporter 2, depleting presynaptic vesicular dopamine and reducing striatal dopamine release.
- Lower dopamine tone attenuates the postsynaptic receptor supersensitivity that underlies tardive dyskinesia and dampens Huntington chorea.
- Deuterium substitution at the methoxy groups slows CYP2D6-mediated cleavage, roughly doubling the half-life of the active metabolites.
- Slower metabolism lowers peak concentrations for a given exposure, which reduces peak-related sedation, depression, and akathisia.
- Serotonin and norepinephrine stores are also depleted, contributing to the depression risk that defines the boxed warning.

PHARMACOKINETICS

- Absorption is rapid, and administration with food increases exposure of the active metabolites substantially, so it is taken with meals.
- Carbonyl reductase converts the parent drug to active alpha- and beta-dihydrotetrabenazine, which are then cleared by CYP2D6.
- The active metabolites have half-lives of about 9 to 10 hours, allowing twice-daily immediate-release or once-daily extended-release dosing.
- CYP2D6 poor metabolizers and patients on strong CYP2D6 inhibitors reach higher exposures and require lower maximum doses.
- Hepatic impairment increases active metabolite exposure several-fold, which is why any degree of hepatic impairment is a contraindication.

ADVERSE EFFECTS

- Somnolence, fatigue, and insomnia are the most frequent effects and cluster around dose increases in the first weeks.
- Depression and suicidal ideation are the critical risks in Huntington disease and require systematic screening at each visit.
- Akathisia, restlessness, and drug-induced parkinsonism reflect excessive dopamine depletion and generally improve with dose reduction.
- Diarrhea, dry mouth, nausea, and constipation are common gastrointestinal complaints, usually mild and dose-related.
- Mean QT prolongation is small at about 4 milliseconds at therapeutic doses but rises with CYP2D6 inhibition or poor metabolizer status.
- Neuroleptic malignant syndrome and akathisia severe enough to stop therapy have been reported with VMAT2 inhibitors as a class.

MONITORING

- Screen for depression and suicidality at baseline and at every visit in Huntington disease, and enlist caregivers to report changes.
- Use the AIMS at baseline and every 3 to 6 months in tardive dyskinesia to track response and justify continued dosing.
- Consider CYP2D6 genotyping or careful medication review before exceeding 36 mg per day, since exposure varies widely.
- Obtain an ECG at baseline and after escalation in patients with congenital long QT, bradycardia, or other QT-prolonging drugs.
- Watch for emergent parkinsonism, sedation, and gait instability at each visit, all of which respond to lowering the dose.

INTERACTIONS & CAUTIONS

- Strong CYP2D6 inhibitors including paroxetine, fluoxetine, bupropion, and quinidine raise exposure and cap the dose at **36 mg/day**.
- Concomitant MAO inhibitors are contraindicated, and deutetrabenazine should not be started within 14 days of stopping an MAOI.
- Reserpine must be stopped at least 20 days before starting, and tetrabenazine or valbenazine must not be given concurrently.
- Additive sedation with alcohol, benzodiazepines, and opioids, and additive parkinsonism with antipsychotics and metoclopramide.
- Any degree of hepatic impairment is a contraindication because active metabolite exposure rises severalfold.

SPECIAL POPULATIONS

- Pregnancy data in humans are lacking and animal studies show developmental effects, so use only if clearly needed.
- It is unknown whether deutetrabenazine passes into human milk; weigh the benefit of nursing against potential infant exposure.
- Safety and efficacy in patients under 18 years have not been established for either approved indication.
- Older adults tolerate it reasonably well, but sedation, falls, and parkinsonism argue for slower titration and lower targets.
- Hepatic impairment of any severity is a contraindication; formal renal impairment data are not available.

PRESCRIBING PEARLS

- Contraindicated in untreated depression or active suicidality; screen mood before every dose increase.
- Take it with food; fasting administration meaningfully lowers active metabolite exposure.
- Adding paroxetine or fluoxetine caps the total daily dose at **36 mg** through CYP2D6 inhibition.

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.