### FDA approved VMAT2 Inhibitors for the treatment of Tardive Dyskinesia

<table>
<thead>
<tr>
<th>Indications</th>
<th>Valbenazine (Ingrezza®) approved April 2017</th>
<th>Deutetrabenazine (Austedo®) approved August 2017</th>
<th>Deutetrabenazine (Austedo XR®) approved February 2023</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tardive Dyskinesia (TD) in adults</td>
<td>• Chorea associated with Huntington’s disease (HD) • Tardive Dyskinesia in adults</td>
<td>• A deuterated form of tetrabenazine • Deuterium, a heavy hydrogen creates a stronger bond compared to hydrogen • Longer duration of action, less frequent dosing (QDay / BID vs TID) • Combination of lower Cmax (smaller dose suffice to provide continuous exposure), &amp; less rapidly fluctuating serum levels, &amp; less rapid rise after a dose may provide better tolerability</td>
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#### Pharmacology & Pharmacodynamics

The PK/PD of tetrabenazine were changed to create valbenazine (VBZ) & deutetrabenazine (DTB)

- replacing 1 of the amino acids with valine
- a parent drug of the active metabolite of tetrabenazine, the (+)-α-isomer
- Pharmacodynamically different due to 1 active isomer
- Hypothesis: dosing a parent molecule with a selective & potent active metabolite will result in both reduced PK variability & improved safety profile

#### Mechanism of Action

Reversible Vesicular Monoamine Transporter 2 (VMAT2) inhibitors, a transporter that regulates monoamine uptake from the cytoplasm to the synaptic vesicle for storage & release

Unclear, thought to work as a reversible depletor of monoamines like dopamine, serotonin, norepinephrine, and histamine from nerve terminals. Deutetrabenazine main metabolites, α-dihydrotetrabenazine & β-HTBZ, inhibit VMAT2 reversibly, reducing the uptake of monoamines into synaptic vesicles and depleting monoamine stores

#### How supplied

<table>
<thead>
<tr>
<th>Capsules: 40 mg</th>
<th>Tablets: 6 mg, 9 mg, and 12 mg</th>
<th>XR Tablets: 6 mg, 12 mg, and 24 mg</th>
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#### Dosage & Administration

<table>
<thead>
<tr>
<th>Initial</th>
<th>Recommended</th>
<th>Max</th>
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<tbody>
<tr>
<td>40 mg/d</td>
<td>80 mg/d</td>
<td>80 mg/d</td>
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</table>

- Taken once daily with or without food
- No dose titration needed (after 1 week, increase to 80 mg daily)
- 40 mg daily may be considered based on response & tolerability

<table>
<thead>
<tr>
<th>Initial</th>
<th>6 mg twice daily (12 mg a day)</th>
<th>12 mg once daily</th>
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<tbody>
<tr>
<td>Max</td>
<td>24 mg BID (48 mg a day)</td>
<td>48 mg once daily</td>
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</table>

Administer with food. Administer total daily dose of ≥12 mg in 2 divided doses

- Titrate at weekly intervals by 6 mg/d based on reduction of chorea or TD & tolerability
- Swallow tablets whole; do not chew, crush, or break

#### Dose Adjustments

- Hepatic impairment
- QT prolongation

- Moderate to severe: 40 mg once daily
- may prolong QTc in CYP2D6 poor metabolizers or those on strong CYP2D6 or

- Contraindicated (not studied, but concerns for greater risk for serious AEs)
- Austedo XR & Austedo may prolong QT interval, but the degree of QT prolongation is not clinically significant within the recommended dosage range
**CYP2D6 poor metabolizers**
- CYP3A4 inhibitors. Reduced dose may be necessary for CYP2D6 poor metabolizers or if strong CYP2D6 inhibitors are used. If taking strong CYP3A4 inhibitor, adjust dose to 40 mg daily.
- Recommended dose 40 mg Qday
- Max recommended dose 36 mg a day

### DDIs
- Strong 2D6 or 3A4 Inhibitor: Recommended dose 40 mg QDay
- Strong 3A4 Inducer: Not recommended
- MAOIs: Avoid use
- Alcohol/sedating drugs: may have additive sedation & somnolence
- Strong 2D6 Inhibitor: max recommended dose 36 mg a day
- Neuroleptic Drugs: increased risk of parkinsonism, NMS, & akathisia with dopamine antagonists or antipsychotics use

### Clinical studies
**6-week fixed dose DBRPC KINECT3 study**
- 234 participants (mean age 56, 57% Caucasian, 38% African American) with moderate to severe TD plus stable schizophrenia, schizoaffective disorder, or a mood disorder were randomized to receive valbenazine 40 mg, 80 mg, or placebo
- Valbenazine group had significant improvement on the AIMS at both the 80 mg (mean reduction 3.2 vs 0.1 with placebo) & the 40 mg dose (mean reduction 1.9 vs 0.1)
- Placebo response was almost zero
- Proportion of pts who had at least 50% improvement in AIMS: ~24% (40 mg group), 40% (80 mg group), & ~9% (placebo group)
- A dose-dependent effect seen at 2 weeks
- No significant difference between either dosage of valbenazine & placebo was seen

**Efficacy studies below were conducted with Austedo tablets.**
- Austedo XR efficacy is based on relative bioavailability study comparing Austedo XR administered once daily and Austedo administered BID
- **12-week fixed dose DBRPC AIM-TD study 1 conducted in ambulatory pts with tardive dyskinesia caused by dopamine receptor antagonists**
  - 222 participants (mean age 57, 79% Caucasian) with moderate to severe TD (AIMS score ≥6) plus stable schizophrenia, schizoaffective disorder, or a mood disorder were randomized 1:1:1:1 to 12 mg, 24 mg, 36 mg deutetrabenazine, or placebo (4-week dose escalation, 8-week maintenance)
  - Deutetrabenazine group had significant improvement on the AIMS at both the 36 mg (mean reduction 3.3) and 24 mg (mean reduction 3.2) compared with placebo (1.4)
  - Placebo response was -1.4 points reduction
  - Proportion of pts who had at least 50% improvement in AIMS: 35% (24 mg group), 33% (36 mg group), & 12% (placebo group)
  - Response observed for all deutetrabenazine treatment groups by week 2
  - Treatment success on the CGIC was observed in 24 (44%) patients in the 36 mg (p=0.06), 24 (49%) in the 24 mg (p=0.01), & 17 (28%) in the 12 mg (p=0.7), vs. 15 (26%) in the placebo group
  - Patient response ratings were not significantly better than for placebo
  - About 89% of patients completed the trial, psychiatric symptoms remained stable
for the secondary endpoint, CGI-TD score at week 6

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- About 90% of patients completed the trial, psychiatric symptoms remained stable

Most Common Adverse Effects

≥5% and twice the rate of placebo: somnolence

>8% and > placebo in Austedo treated HD pts: somnolence, diarrhea, dry mouth, and fatigue
4% and > placebo in Austedo treated TD pts: nasopharyngitis and insomnia

Clinical trials experience

ARs in 3 PC 6 week studies reported at ≥2% and > placebo

Studies below were conducted with Austedo tabs; AEs with Austedo XR are expected to be similar.

Adverse reactions reported at ≥2% and > placebo in 2 PC 12-week studies in pts with TD & concurrent diagnoses of mood disorder or schizophrenia/schizoaffective disorder

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Austedo (N=75) (%)</th>
<th>Placebo (N=33) (%)</th>
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<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Depression/Depressive disorder</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Akathisia/Agoraphobia/Restlessness</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

- Most common AEs from 2 pooled (AIM-TD & ARM-TD) trials: Insomnia & nasopharyngitis

12-week fixed dose AIM-TD study 1:
Depression was reported in 1% of the 12 mg/d & 4% of the 24 mg/d group

54-week open label study results (n=304)
SAEs were experienced by 29 pts, 3 SAEs were considered possibly DTB related (stress urinary incontinence, intentional overdose, suicide attempt)
Authors report no evidence of increased depression, anxiety, suicidality, akathisia & restlessness, somnolence & sedation, or parkinsonism after long-term exposure

Warnings & precautions

- Sedation/somnolence
- QT Prolongation: avoid in pts with congenital long QT syndrome or arrhythmias linked to prolonged QT interval • Parkinsonism
- Depression & suicidality in pts with HD • Clinical worsening & AEs in pts with HD
- NMS • Akathisia, agitation & restlessness • Hyperprolactinemia • Binding to Melanin-Containing Tissues QT Prolongation • Sedation/somnolence • Parkinsonism

Contraindications

- Known hypersensitivity to valbenazine components
- Suicidal, or untreated/inadequately treated depression in patients with HD
- Hepatic impairment • Pts taking reserpine, MAOIs, tetrabenazine, or valbenazine
<table>
<thead>
<tr>
<th>Black box warnings</th>
<th>None</th>
<th>• Increased risk of depression &amp; suicidality in patients with Huntington’s disease</th>
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<tbody>
<tr>
<td>Pharmacokinetics</td>
<td></td>
<td><strong>Valbenazine</strong></td>
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<tr>
<td>Tmax</td>
<td></td>
<td>Valbenazine: 0.5 to 1-hour active metabolite: 4 to 8 hours</td>
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<tr>
<td>Half-life</td>
<td></td>
<td>15-22 hours</td>
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<tr>
<td>Metabolism</td>
<td></td>
<td>Extensive hepatic metabolism</td>
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<tr>
<td>Excretion</td>
<td></td>
<td>Urine (~60%); feces (~30%)</td>
</tr>
<tr>
<td>Cost per month *</td>
<td>$8022</td>
<td>$14,161</td>
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</table>

**Comments**

Both valbenazine and deutetrabenazine may be an effective and well tolerated treatment option for patients with TD
- Improved PK profile results in reduced peak plasma concentrations and variability that may improve safety/tolerability compared to tetrabenazine
- May improve adherence to antipsychotics (reduced ED visits/inpatient stays although patients’ response ratings were not significantly better compared to placebo)
- VMAT2 inhibitors act pre-synaptically, may potentially avoid some of the long-term AEs of receptor blockade
- Multiple drug interactions, can prolong QT (apparently Ingrezza > Austedo)
- Most patients did not have an improvement in AIMS total score of ≥ 50% (heterogeneity of response to the VMAT-2 inhibitors)
- Deutetrabenazine’s dose range may enable individualized therapy based on TD control and tolerability
- Expensive, symptoms reappear when medication is stopped
- Monitor underlying psychiatric conditions, depression, suicidality, parkinsonism (dopamine depletion)
- Other treatment options
  - Medication review, discontinuation of anticholinergics
  - Atypical antipsychotics - clozapine, quetiapine, & iloperidone considered to have lower risk for EPS specially TD
  - Gingko biloba, amantadine, & clonazepam - moderate amounts of data suggest some benefit at reducing TD symptoms
  - Botulinum toxin may offer benefit for some orofacial movements
  - Vitamin E – Studies indicate Vit E 1200 - 1600 IU for 12 to 16 weeks, may protect against deterioration of TD symptoms
    - Cochrane review of 11 RCTs indicated no clear difference between Vit E & placebo treated pts in severity of dyskinesia, but pts taking placebo presented more worsening symptoms
  - 2021 APA guidelines recommend treating antipsychotics induced moderate to severe TD with a reversible VMAT2 inhibitor
    - Factors like half-life, depression, hepatic/renal function, and metabolism should be considered when selecting a medication
  - Valbenazine doesn't carry a suicidality warning as it's not approved for HD patients
  - Valbenazine 80 mg/day significantly improved patients' AIMS (50% or greater improvement from baseline) and Clinical
- Austedo XR, approved in February 2023, is new once-daily dosage form of deutetrabenazine for chorea with HD or TD
- Austedo IR should be taken with food twice daily (when total daily dose ≥12 mg)
- In two trials involving 415 pts with TD, majority (~80%) were on dopamine receptor antagonist with underlying thought or mood disorder. Deutetrabenazine significantly improved AIMS scores over placebo, with effects noticeable from week 2
Global Impression of Change - Tardive Dyskinesia (CGI-TD) scores compared to placebo at week 6 in 3 six-week and 2 long-term trials. This was consistent across age groups, with older patients (55 or older) also showing significant improvement on both scales with valbenazine 40 mg/day.

**Switching between Austedo & Austedo XR:** Use the same total daily dose

- Both Austedo & Austedo XR are not recommended for suicidal patients or those with inadequately treated depression. Monitor for worsening depression or unusual behavior & advise caregivers to report worrying behaviors. Exercise caution when treating patients with a history of depression or suicide attempts

<table>
<thead>
<tr>
<th>Future research</th>
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<tbody>
<tr>
<td>- Head to head comparisons with tetrabenazine, deutetrabenazine, and clozapine would be of interest</td>
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<tr>
<td>- Investigating if VMAT-2 inhibitors can prevent progression from early to severe TD, if they have different effects depending on TD duration, body part affected, &amp; primary type of movement disorder</td>
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<tr>
<td>- Predictors of successful discontinuation of VMAT2 inhibitors after TD symptoms improvement</td>
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**Formulary Recommendations:**

VMAT inhibitors have NF status on BHRS and HealthWorx formularies

CareAdvantage formulary contains criteria due to CMS requirement:

- Indication - All FDA-approved Indications
- Required Medical Information: Documentation of ALL the following: 1) baseline AIMS score, 2) LFTs within 6 months, 3) QT status, 4) assessment of suicidality or violent behaviors, and 5) full list of concurrent medications to assess drug interactions.
- Age Restrictions: 18 years of age or older.
- Prescriber Restrictions: Prescribed by, or in consultation with a psychiatrist or neurologist.
- Coverage Duration: Initial therapy: 3 months. Continuing therapy: 12 months
- Other Criteria: For renewals, ALL the following: 1) repeat AIMS demonstrating improvement and 2) information to demonstrate clinical improvement.
- Quantity Limit: QL for Austedo IR as 120 / 30 days for Austedo 12 mg IR and 60 / 30 days for Austedo XR to allow up to 48mg per day

References available upon request