FDA approved VMAT2 Inhibitors for the treatment of Tardive Dyskinesia

<table>
<tr><th></th><th>Valbenazine (Ingrezza®)
approved April 2017</th><th>Deutetrabenazine (Austedo®)
approved August 2017</th><th>Deutetrabenazine (Austedo XR®)
approved February 2023</th></tr>
<tr><td>Indications</td><td>Tardive Dyskinesia (TD) in adults</td><td colspan="2">• Chorea associated with Huntington’s disease (HD)
• Tardive Dyskinesia in adults</td></tr>
<tr><td>Pharmacology & Pharmacodynamics

The PK/PD of tetrabenazine were changed to create valbenazine (VBZ) & deutetrabenazine (DTB)</td><td>• 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</td><td colspan="2">• 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), less dramatically fluctuating serum levels, & less rapid rise after a dose may provide better tolerability</td></tr>
<tr><td>Mechanism of Action</td><td>Reversible Vesicular Monoamine Transporter 2 (VMAT2) inhibitors, a transporter that regulates monoamine uptake from the cytoplasm to the synaptic vesicle for storage & release</td><td colspan="2">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</td></tr>
<tr><td>How supplied</td><td>Capsules: 40 mg</td><td>Tablets: 6 mg, 9 mg, and 12 mg</td><td>XR Tablets: 6 mg, 12 mg, and 24 mg</td></tr>
<tr><td>Dosage & Administration</td><td>
<table>
<tr><th>Initial</th><th>Recommended</th><th>Max</th></tr>
<tr><td>40 mg/d</td><td>80 mg/d</td><td>80 mg/d</td></tr>
</table>
• Taken <u>once</u> daily with or without food
• <u>No dose titration needed</u> (after 1 week, increase to 80 mg daily)
• 40 mg daily may be considered based on response & tolerability
</td><td colspan="2">
<table>
<tr><th></th><th>Austedo</th><th>Austedo XR</th></tr>
<tr><td>Initial</td><td>6 mg twice daily (12 mg a day)</td><td>12 mg once daily</td></tr>
<tr><td>Max</td><td>24 mg BID (48 mg a day)</td><td>48 mg once daily</td></tr>
<tr><td>Administration</td><td>Administer with food. Administer total daily dose of ≥12 mg in 2 divided doses</td><td>ONCE daily with or without food</td></tr>
</table>
• <u>Titrate</u> at weekly intervals by 6 mg/d based on reduction of chorea or TD & tolerability
• Swallow tablets whole; <u>do not chew, crush, or break</u>
</td></tr>
<tr><td>Dose Adjustments</td><td colspan="3"></td></tr>
<tr><td>• Hepatic impairment
• QT prolongation</td><td>• Moderate to severe: 40 mg once daily
• may prolong QTc in CYP2D6 poor metabolizers or those on strong CYP2D6 or</td><td colspan="2">• 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</td></tr>
</table>

• 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		
• **Efficacy**|	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 o 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) o 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) o Placebo response was -1.4 points reduction o Proportion of pts who had at least 50% improvement in AIMS: 35% (24 mg group), 33% (36 mg group), & 12% (placebo group) o Response observed for all deutetrabenazine treatment groups by week 2 o 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 o Patient response ratings were not significantly better than for placebo o About 89% of patients completed the trial, psychiatric symptoms remained stable

<table>
<tr><td></td><td>for the secondary endpoint, CGI-TD score at week 6
• Patient response ratings were not significantly better than for placebo
• About 90% of patients completed the trial, psychiatric symptoms remained stable</td><td></td></tr>
<tr><td>Most Common Adverse Effects</td><td>≥5% and twice the rate of placebo: somnolence</td><td>>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</td></tr>
<tr><td>Clinical trials experience</td><td>ARs in 3 PC 6 week studies reported at ≥2% and > placebo
<table>
<tr><th>Adverse Reaction[1]</th><th>INGREZZA (n=262) (%)</th><th>Placebo (n=183) (%)</th></tr>
<tr><td>General Disorders</td><td></td><td></td></tr>
<tr><td>Somnolence (somnolence, fatigue, sedation)</td><td>10.9%</td><td>4.2%</td></tr>
<tr><td>Nervous System Disorders</td><td></td><td></td></tr>
<tr><td>Anticholinergic effects (dry mouth, constipation, disturbance in attention, vision blurred, urinary retention)</td><td>5.4%</td><td>4.9%</td></tr>
<tr><td>Balance disorders/fall (fall, gait disturbance, dizziness, balance disorder)</td><td>4.1%</td><td>2.2%</td></tr>
<tr><td>Headache</td><td>3.4%</td><td>2.7%</td></tr>
<tr><td>Akathisia (akathisia, restlessness)</td><td>2.7%</td><td>0.5%</td></tr>
<tr><td>Gastrointestinal Disorders</td><td></td><td></td></tr>
<tr><td>Vomiting</td><td>2.6%</td><td>0.6%</td></tr>
<tr><td>Nausea</td><td>2.3%</td><td>2.1%</td></tr>
<tr><td>Musculoskeletal Disorders</td><td></td><td></td></tr>
<tr><td>Arthralgia</td><td>2.3%</td><td>0.5%</td></tr>
</table>
[1] Within each adverse reaction category, the observed adverse reactions are listed in order of decreasing frequency.

• The most common AEs from 3 pooled Kinect trials: Somnolence (~11%), anticholinergic effects (~5%), & balance disorders/fall (4%)

<u>48 weeks open-label KINECT 4 study</u>:
• Fatigue & headache (10%)
• Decreased appetite (8%)</td><td>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>
<tr><th>Preferred Term</th><th>AUSTEDO (N=279) (%)</th><th>Placebo (N=131) (%)</th></tr>
<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/ Dysthymic disorder</td><td>2</td><td>1</td></tr>
<tr><td>Akathisia/Agitation/Restlessness</td><td>2</td><td>1</td></tr>
</table>
• Most common AEs from 2 pooled (AIM-TD & ARM-TD) trials: Insomnia & nasopharyngitis

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

<u>54-week open label study results (n=304)</u>
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</td></tr>
<tr><td>Warnings & precautions</td><td>• Sedation/somnolence
• QT Prolongation: avoid in pts with congenital long QT syndrome or arrhythmias linked to prolonged QT interval • Parkinsonism</td><td>• 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</td></tr>
<tr><td>Contraindications</td><td>Known hypersensitivity to valbenazine components</td><td>• Suicidal, or untreated/inadequately treated depression in patients with HD
• Hepatic impairment • Pts taking reserpine, MAOIs, tetrabenazine, or valbenazine</td></tr>
</table>

<table>
<tr><td>Black box warnings</td><td colspan="2">• None</td><td colspan="2">• Increased risk of depression & suicidality in patients with Huntington’s disease</td></tr>
<tr><td>Pharmacokinetics</td><td></td><td><u>Valbenazine</u></td><td><u>Deutetrabenazine</u></td><td><u>Deutetrabenazine XR</u></td></tr>
<tr><td></td><td>Tmax</td><td>Valbenazine: 0.5 to 1-hour
active metabolite: 4 to 8 hours</td><td>3 to 4 hours</td><td>3 hours, followed by sustained plateaus for several hours</td></tr>
<tr><td></td><td>Half-life</td><td>15-22 hours</td><td>9 to 11 hours</td><td>9 to 11 hours</td></tr>
<tr><td></td><td>Metabolism</td><td>Extensive hepatic metabolism</td><td>Extensive hepatic metabolism</td><td>Extensive hepatic metabolism</td></tr>
<tr><td></td><td>Excretion</td><td>Urine (~60%); feces (~30%)</td><td>Urine (75 to 86%); feces (8 to 11%)</td><td>Urine (75 to 86%); feces (8 to 11%)</td></tr>
<tr><td>Cost per month * (max dose)</td><td colspan="2">$8022</td><td>$14,161</td><td>$14,161</td></tr>
<tr><td>Comments</td><td colspan="4">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
o Medication review, discontinuation of anticholinergics
o Atypical antipsychotics - clozapine, quetiapine, & iloperidone considered to have lower risk for EPS specially TD
o Gingko biloba, amantadine, & clonazepam - moderate amounts of data suggest some benefit at reducing TD symptoms
o Botulinum toxin may offer benefit for some orofacial movements
o 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
o Factors like half-life, depression, hepatic/renal function, and metabolism should be considered when selecting a medication</td></tr>
<tr><td></td><td colspan="2">• 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</td><td colspan="2">• 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</td></tr>
</table>

	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
Future research	• Head to head comparisons with tetrabenazine, deutetrabenazine, and clozapine would be of interest • 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, & primary type of movement disorder • Predictors of successful discontinuation of VMAT2 inhibitors after TD symptoms improvement	

AEs: Adverse effects, AR: Adverse reaction, DBRPC=double-blind, randomized, placebo-controlled, DTB: Deutetrabenazine, NMS: Neuroleptic Malignant Syndrome, PC: Placebo-Controlled, RCTs: Randomized-control trials, SAEs: Serious AEs, VBZ: Valbenazine
*RxNova accessed 6/8/2023 for FDB WAC pricing

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