FDA approved VMAT2 Inhibitors for the treatment of Tardive Dyskinesia

<table>
<tr><th></th><th>Valbenazine (Ingrezza,® Ingrezza Sprinkle®)
Initial approval April 2017</th><th>Deutetrabenazine (Austedo®)
approved August 2017</th><th>Deutetrabenazine (Austedo XR®)
approved February 2023</th></tr>
<tr><td>Indications</td><td colspan="3">• 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 & depleting monoamine stores</td></tr>
<tr><td>How supplied</td><td>Capsules: 40 mg, 60 mg, and 80 mg
Sprinkles: 40mg, 60mg, and 80mg</td><td>Tablets: 6 mg, 9 mg, and 12 mg</td><td>XR Tablets: 6 mg, 12 mg, 24 mg, 30mg, 36mg, 42mg, 48mg</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 once daily with or without food
• No dose titration needed (after 1 week, increase to 80 mg daily)
• 40 or 60 mg once daily may be considered based on response & tolerability
• Valbenazine Sprinkle may be opened and sprinkled over soft food (do not use milk or drinking water). Do not crush or chew
</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>
• 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
</td></tr>
<tr><td>Dose Adjustments</td><td colspan="3"></td></tr>
<tr><td>• Hepatic impairment
• QT prolongation

• CYP2D6 poor metabolizers</td><td>• Moderate to severe: 40 mg once daily
• May increase QT interval. Avoid in congenital long QT syndrome or arrhythmias with prolonged QT
• Recommended dose 40 mg Qday</td><td colspan="2">• Contraindicated (not studied, but concerns for greater risk for serious AEs)
• Avoid in congenital long QT syndrome or arrhythmias with prolonged QT. May prolong QT interval, but the degree of QT prolongation is not clinically significant within the recommended dosage range
• Max recommended dose 36 mg a day</td></tr>
<tr><td>DIs</td><td colspan="3"></td></tr>
<tr><td></td><td>• Strong 2D6 or 3A4 Inhibitor: Recommended dose 40 mg QDay
• Strong 3A4 Inducer: Not recommended
• MAOIs: Avoid use</td><td colspan="2">• Alcohol/sedating drugs: may have additive sedation & somnolence
• Strong 2D6 Inhibitor: max recommended dose 36 mg a day
• Avoid co-administration with MAOIs or reserpine
• Neuroleptic Drugs: increased risk of parkinsonism, NMS, & akathisia with dopamine antagonists or antipsychotics use</td></tr>
<tr><td>Clinical studies</td><td colspan="3"></td></tr>
<tr><td>• Efficacy|</td><td>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</td><td colspan="2">• 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</td></tr>
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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 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
Ingrezza Sprinkle’s FDA approval was based on chemistry, manufacturing, controls information, & data demonstrating the bioequivalence & tolerability of Ingrezza Sprinkle compared to Ingrezza capsules

</td><td>

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

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<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, & 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%)

48 weeks open-label KINECT 4 study:
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

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</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>
<tr><td>Black box warnings</td><td colspan="2">Increased risk of depression and suicidal ideation & behavior in patients with Huntington’s disease</td></tr>
<tr><td>Pharmacokinetics</td><td>Valbenazine Sprinkle</td><td>Valbenazine | Deutetrabenazine | Deutetrabenazine XR</td></tr>
</table>

	Tmax	Sprinkled on applesauce valbenazine: 1.5 hours active metabolite ([+]-α-HTBZ): 6 hours Swallowed whole with water valbenazine: 1 hour [+]-α-HTBZ: 6 hours	Valbenazine: 0.5 to 1 hour active metabolite: 4 to 8 hours	3 to 4 hours	3 hours, followed by sustained plateaus for several hours
	Half-life	Valbenazine & [+]-α-HTBZ: 15-22 hours	15-22 hours	9 to 11 hours	9 to 11 hours
	Metabolism	Extensive hepatic metabolism	Extensive hepatic metabolism	Extensive hepatic metabolism	Extensive hepatic metabolism
	Excretion	Urine (~60%); feces (~30%)	Urine (~60%); feces (~30%)	Urine (75 to 86%); feces (8 to 11%)	Urine (75 to 86%); feces (8 to 11%)
Cost per month * (max dose)		$7500 to $8250	$7500 to $8250	$7322 to $14643	$7322 to $14643
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). Avoid use in congenital long QT syndrome or arrhythmias associated with prolonged QT interval. • 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 • 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				
	• Valbenazine 80 mg/day significantly improved patients' AIMS (50% or greater improvement from baseline) and Clinical 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 • Avoid co-administration with MAOIs & strong CYP3A4 inducers • Higher DDI risk than deutetrabenazine		• 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 • Switching between Austedo & Austedo XR: Use the same total daily dose • Contraindicated in hepatic impairment • Avoid co-administration with MAOIs or reserpine • Do not cure the cause of involuntary movements • Deutetrabenazine ER is now available in 30mg, 36mg, 42mg, and 48mg tablets, in addition to the previous 6mg, 12mg, and 24mg options, offering broad dosing flexibility.		

	• Selective VMAT2 inhibition with one primary metabolite (+α HTBZ). Clinical significance of in vitro data is unknown. No head to head trials comparing tetrabenazine & deutetrabenazine to valbenazine • Ingrezza Sprinkle capsules contain granules that can be sprinkled over soft food for patients with difficulty swallowing or those who prefer not to take capsules. The mixture should be consumed immediately or within 2 hours if stored at room temperature. Avoid administration via NG or enteral tubes due to possible obstruction • The safety of Ingrezza Sprinkle has been established from studies of Ingrezza. Pharmacokinetic data confirm bioequivalence between Ingrezza Sprinkle and the original Ingrezza formulation	
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
- They are formulary with PA criteria on CareAdvantage due to CMS requirement:

PA Criteria for Deutetrabenazine and Valbenazine

- 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 for Austedo to allow up to 48mg per day:
  - IR 6mg #120 /30DS; 9mg, 12 mg #60/30DS
  - XR 6mg, 12mg, 24mg #60/30DS; 30mg, 36mg, 42mg, 48mg #30/30DS
- Quantity Limit for Ingrezza to allow up to 80mg per day:
  - All strengths of capsules and sprinkles #30/30DS
- Other Criteria: For renewals, ALL the following: 1) repeat AIMS demonstrating improvement and 2) information to demonstrate clinical improvement.

References available upon request