FDA approved VMAT2 Inhibitors for the treatment of Tardive Dyskinesia

	Valbenazine (Ingrezza®) approved April 2017	**Deutetrabenazine (Austedo®) approved August 2017**
Indications	Tardive Dyskinesia (TD) in adults	• Chorea associated with Huntington's disease (HD) • Tardive Dyskinesia in adults
Pharmacology & Pharmacodynamics • The PK/PD of tetrabenazine were changed to create valbenazine (VBZ) & deutetrabenazine (DTB) • Both designated as break through therapies by the FDA for treating 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	• A deuterated form of tetrabenazine • Deuterium, a heavy hydrogen creates a stronger bond compared to hydrogen • Longer duration of action, less frequent dosing (BID vs TID) • The combination of lower Cmax (a smaller dose suffice to provide continuous exposure), less dramatically fluctuating serum levels, & less rapid rise after a dose may provide better tolerability
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	
Dosage forms/strengths	Capsules: 40 mg	Tablets: 6 mg, 9 mg, and 12 mg
Dosage & Administration	Initial: 40 mg/d; Recommended: 80 mg/d; Max: 80 mg/d • 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 for some clts based on response & tolerability	Initial: 12 mg/d; Recommended: 12 to 48 mg/d; Max: 48 mg/d • Taken <u>twice</u> daily <u>with food</u> • <u>Titrate</u> at weekly intervals by 6 mg/d based on reduction of TD & tolerability • Swallow tablets whole; <u>do not chew, crush, or break</u>
Dose Adjustments		
• Hepatic impairment • Renal impairment • Clts at r/o QT prolongation	• Moderate to severe: 40 mg once daily • Severe: Use not recommended • Assess QT interval before increasing valbenazine dose	• Contraindicated • Not studied • Assess QT interval before & after increasing dose >24 mg/d
Drug Drug Interactions		
• Alcohol/sedating drugs • Strong 2D6 Inhibitor • Strong 3A4 Inhibitor • Strong 3A4 Inducer • MAOIs	• Consider dose reduction based on tolerability • Reduce dose to 40 mg • Concomitant use not recommended • Avoid concomitant use with MAOIs	• May have additive sedation &somnolence • 36 mg per day (18 mg BID)
Clinical studies		
• **Efficacy|** • Primary endpoint: mean change in Abnormal	<u>6 week</u> fixed dose DBRPC KINECT3 study • 234 participants (mean age 56, 57% Caucasian, 38% African-American) with moderate to severe TD plus stable	<u>12-week</u> fixed dose DBRPC AIM-TD study 1 • 222 participants (mean age 57, 79% Caucasian) with moderate to severe TD (AIMS score ≥6) plus stable schizophrenia,

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<td>Involuntary Movement Scale (AIMS) from baseline to week 6 for VBZ & week 12 for DTB
• A lower score on the AIMS (scale of 0-28) is better
• Secondary endpoint: Clinical Global Impression of Change–(CGI-TD for valbenazine & CGIC for DTB) a 7-point scale from 1 (“very much improved”) to 7 (“very much worsened”)</td>
<td>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 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>schizoaffective disorder, or a mood disorder were randomized 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</td>
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<td>Safety</td>
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<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>Adverse Reactions in 2 PC 12 week studies reported at ≥2% and > placebo
<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>
• The 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>
• The most common AEs by Exposure-adjusted incidence rates (EAIRs) were similar between DTB & placebo: anxiety, somnolence, depression, & headache (0.1); diarrhea & nasopharyngitis (0.08)
• SAEs were experienced by 29 pts, 3 SAEs were considered possibly DTB related (stress urinary incontinence, intentional</td>
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<table>
<tr><td></td><td></td><td>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>• AEs leading to discontinuation of treatment</td><td>3% of valbenazine & 2% of placebo-treated patients (n=445, fixed dose, dose escalation, & dose reduction studies) discontinued because of AEs</td><td><u>AIM-TD (study 1)</u>
4% of DTB (out of 221 pts) & 3% of placebo (out of 72 pts) discontinued because of AEs
<u>ARM-TD (study 2)</u>
1.7% of DTB (out of 58 pts) & 3.4% of placebo (out of 59 pts) discontinued because of AEs</td></tr>
<tr><td>• Warnings & precautions</td><td>• QT prolongation: Avoid use in patients with congenital long QT syndrome or with arrhythmias associated with a prolonged QT interval. CYP2D6 poor metabolizers or concomitant use with a strong CYP2D6 or CYP3A4 inhibitor, may lead to clinically significant QT prolongation
• Somnolence: Patients should not drive or perform activities that require mental alertness until they learn their response to valbenazine</td><td>• QT Prolongation: Avoid use in patients with congenital long QT syndrome or with arrhythmias associated with a prolonged QT interval. Dose reduction may be necessary in CYP2D6 poor metabolizers or concomitant use with a strong CYP2D6 inhibitor
• Neuroleptic Malignant Syndrome: Discontinue if NMS occurs
• Akathisia, agitation, restlessness, & parkinsonism: Reduce dose or discontinue
• Sedation/somnolence: May impair ability to drive or operate complex machinery</td></tr>
<tr><td>• Contraindications</td><td>None</td><td>• Hepatic impairment
• Pts taking reserpine, MAOIs, tetrabenazine, or valbenazine</td></tr>
<tr><td>• Black box warnings</td><td>• None
• FDA did not require the depression or suicidality warning possibly because valbenazine is considered pharmacodynamically different from tetrabenazine</td><td>• None
• DTB for TD was reviewed by the psychiatry arm of the FDA, but DTB for HD by the neurology arm and the path for approval was based on tetrabenazine (approved only in HD). Based on DTB’s safety profile in the ARM-TD & AIM-TD trials, the black box warning was not included for TD</td></tr>
<tr><td>Pharmacokinetics</td><td colspan="2"><table><tr><td></td><td>Valbenazine</td><td>Deutetrabenazine</td></tr><tr><td>Tmax</td><td>Valbenazine: 0.5 to 1 hour, active metabolite: 4 to 8 hours</td><td>3 to 4 hours</td></tr><tr><td>Half-life</td><td>15-22 hours</td><td>9 to 10 hours</td></tr><tr><td>Metabolism</td><td>Hydrolysis to form active metabolite & oxidative metabolism, primarily by CYP 3A4/5, to form inactive metabolites. The active metabolite is further metabolized in part by CYP2D6</td><td>Extensive hepatic metabolism</td></tr><tr><td>Excretion</td><td>Urine (~60%); feces (~30%)</td><td>Urine (75 to 86%); feces (8 to 11%)</td></tr></table></td></tr>
<tr><td>Cost</td><td colspan="2">$11,474 for 80mg/day x 30DS $10,727 for 48mg/day x 30DS</td></tr>
<tr><td>Comments</td><td colspan="2">Both valbenazine and deutetrabenazine may be an effective and well tolerated treatment option</td></tr>
</table>

	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 pt response ratings were not significantly better than the placebo group) • VMAT2 inhibitors act pre-synaptically, may potentially avoid some of the long-term AEs of receptor blockade, (eg. Parkinsonism) • Multiple drug interactions, can prolong 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 • Both available through specialty pharmacies • Expensive, symptoms reappear when the medication is stopped • Monitor underlying psychiatric conditions, depression, suicidality, parkinsonism (dopamine depletion) • Long term experience in routine clinical patients would further define deutetrabenazine & valbenazine's benefits and risks not yet well-defined • Other treatment options o Medication review, discontinuation of anticholinergics if part of the medication regimen 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 11RCTs indicated no clear difference between Vit E & placebo treated pts in severity of dyskinesia, but pts taking placebo presented more worsening of symptoms ▪ One study showed 35% mean reduction in AIMS in pts with TD >5 years
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 • Valbenazine and deutetrabenazine is being studied for Tourette syndrome
Formulary Status	**Nonformulary for all lines of business**

AEs: Adverse effects, AR: Adverse reaction, DBRPC=double-blind, randomized, placebo-controlled, DTB: Deutetrabenazine, PC: Placebo-Controlled, RCTs: Randomized-control trials, SAEs: Serious AEs, VBZ: Valbenazine

References available upon request