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

<table>
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<tr>
<th>Indications</th>
<th>Valbenazine (Ingrezza&lt;sup&gt;®&lt;/sup&gt;) approved April 2017</th>
<th>Deutetrabenazine (Austedo&lt;sup&gt;®&lt;/sup&gt;) approved August 2017</th>
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<tbody>
<tr>
<td><strong>Tardive Dyskinesia (TD) in adults</strong></td>
<td>• Chorea associated with Huntington’s disease (HD)</td>
<td>• Tardive Dyskinesia in adults</td>
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**Pharmacology & Pharmacodynamics**
- The PK/PD of tetrabenazine were changed to create valbenazine (VBZ) & deutetrabenazine (DTB)
- Both designated as breakthrough 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
  - 12 mg/d
- **Recommended**
  - 80 mg/d
  - 12 to 48 mg/d
- **Max**
  - 80 mg/d
  - 48 mg/d

**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**
  - 6 week fixed dose DBRPC KINECT3 study
  - 234 participants (mean age 56, 57% Caucasian, 38% African-American) with moderate to severe TD plus stable
- **12-week 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,
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”)

<table>
<thead>
<tr>
<th>Schizophrenia, schizoaffective disorder, or a mood disorder were randomized to receive valbenazine 40 mg, 80 mg, or placebo</th>
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<tbody>
<tr>
<td>Valbenazine group had significant improvement on the AIMS at both the 80 mg (mean reduction 3.2 vs 0.1 with placebo) &amp; the 40 mg dose (mean reduction 1.9 vs 0.1)</td>
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<tr>
<td>Placebo response was almost zero</td>
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<td>Proportion of pts who had at least 50% improvement in AIMS: ~24% (40 mg group), 40% (80 mg group), &amp; ~9% (placebo group)</td>
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<td>A dose-dependent effect seen at 2 weeks</td>
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<td>No significant difference between either dosage of valbenazine &amp; placebo was seen for the secondary endpoint, CGI-TD score at week 6</td>
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<tr>
<td>Patient response ratings were not significantly better than for placebo</td>
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<td>About 90% of patients completed the trial, psychiatric symptoms remained stable</td>
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schizoaffective disorder, or a mood disorder were randomized to 12 mg, 24 mg, 36 mg deutetabenazine, or placebo (4-week dose escalation, 8-week maintenance)
- Deutetabenazine 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 deutetabenazine 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

Safety

- Clinical trials experience

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

<table>
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<tr>
<th>Preferred Term</th>
<th>AUSTEDO (N=274) (%)</th>
<th>Placebo (N=131) (%)</th>
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<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Insomnia</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Depression: Depressive disorder</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Akathisia: Agitation/Restlessness</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

- The most common ARs from 3 pooled Kinect trials: Somnolence (~11%), anticholinergic effects (~5%), & balance disorders/fall (4%)
- 48 weeks open-label KINJECT 4 study:
  - Fatigue & headache (10%)
  - Decreased appetite (8%)

Adverse Reactions in 2 PC 12 week studies reported at ≥2% and > placebo

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)
- The most common ARs 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
**overdose, suicide attempt)**

- Authors report no evidence of increased depression, anxiety, suicidality, akathisia & restlessness, somnolence & sedation, or parkinsonism after long-term exposure

| AEs leading to discontinuation of treatment | 3% of valbenazine & 2% of placebo-treated patients (n=445, fixed dose, dose escalation, & dose reduction studies) discontinued because of AEs | AIM-TD (study 1) 4% of DTB (out of 221 pts) & 3% of placebo (out of 72 pts) discontinued because of AEs AEs leading to discontinuation of treatment

| Warnings & precautions | 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

| Contraindications | None

| Black box warnings | None

- FDA did not require the depression or suicidality warning possibly because valbenazine is considered pharmacodynamically different from tetrabenazine

| Pharmacokinetics | Valbenazine

- **Tmax**
  - Valbenazine: 0.5 to 1 hour, active metabolite: 4 to 8 hours

- **Half-life**
  - 15-22 hours

- **Metabolism**
  - 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

- **Excretion**
  - Urine (~60%); feces (~30%)

| Deutetrabenazine |

- **Tmax**
  - 3 to 4 hours

- **Half-life**
  - 3 to 4 hours

- **Metabolism**
  - Extensive hepatic metabolism

- **Excretion**
  - Urine (75 to 86%); feces (8 to 11%)

| Cost | $11,474 for 80mg/day x 30DS $10,727 for 48mg/day x 30DS |
| 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 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
  - Medication review, discontinuation of anticholinergics if part of the medication regimen
  - 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 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