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Class Review with New Drug Evaluations: Vesicular Monoamine Transporter 2 (VMAT2) Inhibitors

Date of Review: January 2018
Generic Name: valbenazine
Generic Name: deutetrabenazine
Generic Name: tetrabenazine

End Date of Literature Search: November 2017
Brand Name (Manufacturer): Ingrezza ® (Neurocrine Biosciences Inc.)
Brand Name (Manufacturer): Austedo® (Auspex Pharmaceuticals Inc.)
Brand Name (Manufacturer): Xenazine® (Valeant Pharmaceuticals Inc.)
Dossier Received: Yes - Ingrezza®; Yes - Austedo®; Yes – Xenazine®

Purpose for Class Review:
To define place in therapy for vesicular monoamine transporter 2 (VMAT2) inhibitors recently approved by the United States (U.S.) Food and Drug Administration (FDA) for the treatment of adults with tardive dyskinesia (TD) and/or Huntington chorea (HC) as a result of Huntington's Disease (HD).

Research Questions:
1. Is there comparative evidence that VMAT2 inhibitors improve outcomes in patients with TD and HC more than comparative treatments?
2. Is there evidence that VMAT2 inhibitors are safer than other treatments used for the treatment of TD and HC?
3. Are there subgroups of patients (age, gender, ethnicity, comorbidities, disease duration or severity) with TD or HC that would particularly benefit or be harmed from VMAT2 inhibitors?

Conclusions:
Clinical Efficacy
- This review identified two guidelines (published prior to the approval of valbenazine and deutetrabenazine)[1,2], three systematic reviews[3–5] and four randomized controlled trials[6–9]. Prior to the approval of valbenazine and deutetrabenazine, the only VMAT2 inhibitor available was tetrabenazine which is approved for the use in patients with HC and used off-label for TD. Newer VMAT2 inhibitors are indicated for TD and HC symptom management. **Table 1** lists commonly used outcomes in studies of TD and HD. Recommendations included in this review come from small, short-term studies that are primarily funded by industry. The overall quality of evidence available for consideration is considered low.

Table 1. Tardive Dyskinesia and Huntington's Disease Outcomes

Outcome	Description	Minimal Clinically Significant Change	Clinical Relevance
Tardive Dyskinesia			
Abnormal Involuntary Movement Scale **(AIMS)**	Validated 12 item scale with a total score ranging from 0-28. Higher scores indicate increased severity of TD	Not defined	Interpretation of scores has not been well-established and may lack sensitivity due to

	symptoms. Amplitude and quality of movement are evaluated using a numeric severity scale ranging from zero (no abnormalities) to four (severe movements).		limited range and non-specificity for movement frequency.
Huntington's Disease			
Unified Huntington's Disease Rating Scale Total Motor Score **(UHDRS-TMS)***	Scoring ranges from 0-124 points with higher scores indicating greater disability.	Not defined	Limited evidence suggests a 1-point increase, in patients in the early stages of HD, correlates with an approximately 10% loss of the likelihood of being able to work, manage finances, drive and supervise children.
Unified Huntington's Disease Rating Scale–total chorea movement subscore **(UHDRS-TCS)***	Subscore is based on frequency and severity of chorea in 7 areas of the body on a scale of 0-28, with a higher number indicating worse disease.	Not defined	Most studies show a difference of 2-4 points which represents a 7-14% change.
Tardive Dyskinesia and Huntington's Disease			
Patients' Global Impression of Change (**PGIC)** score	PGIC measures patients' perspective on overall improvement in movement dysfunction. This is a 1-7 point Likert scale with a score of 1 representing "very much improved" and a score of 7 suggesting "very much worse".	Not defined	Patients' perception of symptom improvement is critical in justifying use of therapy.
Clinical Global Impression of Change **(CGIC)**	CGIC is a clinician perspective of the severity of the patient's symptoms using a 1-7 point Likert scale with a score of 1 representing "very much improved" and a score of 7 suggesting "very much worse".	Not defined	Limitations to this analysis is reliance on provider recall to determine symptom improvement.
Abbreviations: TD = tardive dyskinesia			

* This scoring system was designed by the Huntington Study Group which also conducted the study of deutetrabenazine for the treatment of HD.

- There is insufficient direct comparative evidence between VMAT2 inhibitors or other active treatments for TD and HD for efficacy outcomes. There is insufficient evidence for the use of VMAT2 inhibitors for treatment of dyskinesia associated with other conditions in adults (e.g., Parkinson's disease and Tourette syndrome). There is insufficient evidence to evaluate long-term efficacy or safety of VMAT2 inhibitors and long-term data in larger populations are needed to determine the significance of harms observed in short-term phase 3 trials.

Tardive Dyskinesia

Evidence

- There is low quality evidence based on one phase 3, 6-week randomized, placebo-controlled trial that valbenazine is associated with statistical improvement in the AIMS score to reduce involuntary movements in patients with TD.[6] In patients with schizophrenia, schizoaffective disorder, or mood disorder, adjusted mean improvement in AIMS score was -1.9 points with valbenazine 40 mg per day (95% CI, -3.0 to -0.7; p=0.002 vs. placebo), -3.2 points with

valbenazine 80 mg per day (95% CI, -4.2 to -2.0; p<0.001 vs. placebo), and -0.1 points with placebo.[6] Subgroup analysis found patients not using antipsychotic medications may have responded better than those on antipsychotic therapy.

- There is low quality evidence that the number of patients who reported overall improvement in their symptoms, as measured by "improved" or "very much improved" by the PGIC, were lower with valbenazine 40 mg and valbenazine 80 mg compared to placebo, 31.7%, 24.3% and 42.0%, respectively.[6] The efficacy of a medication prescribed to improve symptoms of TD that results in patients favoring placebo versus active treatment for symptom improvement raises important concerns of the benefit versus risk of prescribing valbenazine.[10]
- There is low quality evidence that deutetrabenazine decreases AIMS scores in adult patients with TD based on evidence from two 12-week, randomized controlled trials.[8,9] The first trial found deutetrabenazine 24 mg to decrease AIMS score more than placebo by a mean of -1.8 (95% CI, -3.0 to -0.63; P=0.003) and deutetrabenazine 36 mg to decrease AIMS scores more than placebo by a mean of -1.9 (95%; -3.09 to -0.79; p=0.001).[9] The number of patients with at least a 50% improvement in AIMS score was higher in patients treated with deutetrabenazine 24 mg (absolute risk reduction [ARR] 23%/NNT 5) and 36 mg (ARR 24%/ARR 5) compared to placebo.[9] The second study found deutetrabenazine (mean dose 38.8 mg) to decrease AIMS score by -3.0 compared to -1.6 in patients treated with placebo (mean difference [MD] -1.4; 95% CI, -2.6 to -0.2; P=0.019).[8]
- There is low quality evidence that PGIC scores were not improved by deutetrabenazine compared to placebo in patients with TD based on evidence from two studies.[8,9] Similar to valbenazine, it is concerning that a medication used to treat symptoms of TD isn't perceived as being more effective than placebo based on the patient's perspective.
- Patients taking tetrabenazine experienced a 54.2% reduction in AIMS scores compared to placebo (p<0.001) and a 60.4% reduction in patient AIMS self-rating score (p<0.001) based on evidence from a Class III study (non-randomized, controlled study). Institute for Clinical and Economic Review (ICER) report considers evidence insufficient to make a recommendation for tetrabenazine for the treatment of TD symptoms.[4]

Interpretation

- A mean decrease of 7% to 11% in symptoms with valbenazine is unlikely to be clinically meaningful to patients as demonstrated by patients perceiving more symptom improvement in the placebo group compared to active treatment as measured by PGIC.
- Deutetrabenazine was also found to have a 7% mean decrease in symptoms as measured by AIMS; however, this did not translate into improved symptoms over placebo based on patients' perception, as measured by the PGIC.
- The Institute for Clinical and Economic Review (ICER) found the evidence for the use of valbenazine and tetrabenazine in TD to be "promising but inconclusive" and "current prices are far out of alignment with the benefits measured in clinical trials".[4]

Huntington Chorea

- There is low quality evidence from one fair-quality study lasting 12-weeks that deutetrabenazine improved UHDRS-TCS change from baseline by -4.4 points compared to -1.9 points for placebo (MD -2.5; 95% CI, -3.7 to -1.3; p-value <0.001) in patients with mild to moderate functional impairment secondary to HD.[7]
- There is low quality evidence from one study in patients with HD that treatment success based on PGIC scores were higher with deutetrabenazine compared to placebo with an ARR of 31% and NNT of 4.[7]
- There is low quality evidence that there were no clinically or statistically significant changes in quality of life in patients treated with deutetrabenazine compared to placebo (MD 4.3; 95% CI, 0.4 to 8.3; p-value = 0.03).
- There is low quality evidence that tetrabenazine is effective in improving the UHDRS-TCS by a treatment difference of -3.5 points (95% CI, -5.2 to -1.9; p<0.0001) compared to placebo.[5]

Interpretation

- A decrease in symptoms by a mean of 9% achieved by deutetrabenazine, based on UHDRS-TCS, is unlikely to be clinically meaningful. Patients' perception of improved symptoms was higher than placebo but no difference was found in quality of life.
- Tetrabenazine was also found to minimally decrease symptoms of HC with an improvement of 13% based on UHDRS-TCS.

Safety

- Patients with an uncontrolled depression or at high risk of suicide were excluded for deutetrabenazine and tetrabenazine because of an increased risk of depression and suicidality. [11,12] Black box labeling for deutetrabenazine and tetrabenazine warns against the use of these treatments in patients with a history of depression or prior suicide attempts. Valbenazine does not carry this warning; however, patients with any unstable psychiatric condition were excluded so use the effect in this population is unknown.
- All VMAT2 inhibitors may increase the QT interval.[13,11,12] Use of VMAT2 inhibitors should be avoided in patients with congenital long QT syndromes or with arrhythmias associated with prolonged QT interval. This is a significant safety concern, as this risk may increase when VMAT2 inhibitors are used in general clinical practice and there is increased potential to be used concomitantly with other drugs that also increase the QT interval.
- Common adverse effects for VMAT2 inhibitors is somnolence and dry mouth. Valbenazine versus placebo was also found to increase the incidence of akathisia, 3.3% vs. 1.3%, respectively. Deutetrabenazine was associated with increased incidence of diarrhea and both deutetrabenazine and tetrabenazine were associated with fatigue at a higher rate than placebo.

Recommendations:

- Recommend that a new PDL class for VMAT2 inhibitors is created.
- Recommend implementing prior authorization (PA) criteria for valbenazine, deutetrabenazine and tetrabenazine to ensure use in patients with an appropriate diagnosis and who are at low risk of adverse events associated with VMAT2 inhibitors.
- Evaluate pricing in executive session.

Background:

Tardive Dyskinesia

Tardive dyskinesia is a delayed-onset involuntary movement disorder which commonly occurs in patients treated with chronic dopamine receptor blocking agents (DRBA). DRBAs may be prescribed for a wide range of psychiatric conditions or certain gastrointestinal disorders.[14] While TD typically manifests after 1-2 years of routine exposure to DRBAs, it may occur within months of starting treatment. The yearly rate of TD development in patients treated with DRBAs is approximately 2-5% with a cumulative 5-year incidence of approximately 20% to 25%.[2] It is estimated that 20-50% of patients treated with a DRBA ultimately develop TD.[14,15] Neuroleptic-induced TD is higher in women, especially those middle-aged and elderly, where incidence rates may reach as much as 30% after 1 year of cumulative exposure.[14] TD may persist for years even after discontinuation of the DRBA, and in many cases, may not be reversible.[16] The debilitating effects of TD lead to increased mortality, decreased physical functioning, medication nonadherence, and a lower quality of life.[17]

TD is one of many disorders thought to arise from dopamine receptor blockade, but it is distinct from other movement disorders such as Parkinson disease, Tourette syndrome, and Huntington's disease.[14] Genetic testing, neuroimaging, and other diagnostic work-ups may be necessary to rule out other causes of dyskinesia.[14] The Diagnostic and Statistical Manual of Mental Disorders definition for DRBA-induced TD requires exposure for a DRBA for at least 3 months (or 1 month in patients $\geq$ 60 years of age), presentation of symptoms within 4 weeks after withdrawal of an oral medication (or within 8 weeks of a depot

medication), and persistence of symptoms for 1 month after discontinuation of offending agent.[14] Irregular, repetitive, orofacial movements including lip smacking, jaw clenching, facial grimacing, and tongue protrusions are classic symptoms of TD that range in severity from mild annoyance to impairment of speech and swallowing.[16] TD patients may commonly experience random jerking movements in their upper extremities, lower extremities, and trunk which may interfere with daily living activities and create challenges for caregivers.[18]

Many explanations circulate regarding the pathophysiological link between DRBA use and TD. Chronic DRBA exposure, notably first generation antipsychotics, may cause upregulation and hypersensitization of post-synaptic dopaminergic (D2) receptors which disrupt normal dopamine recycling most notably in the nigrostriatal pathway.[19] Early removal of D2 receptor blockade may slowly reverse the dyskinesia, but the cumulative effects of long-term use of DRBAs may result in irreversible TD.[14] Increased dosages of neuroleptic agents have demonstrated temporary improvements of TD symptoms which lends credibility to the dopamine receptor upregulation hypothesis.[19] Other possible explanations under investigation include cholinergic deficit, gamma-aminobutyric acid (GABA) depletion or abnormalities of striatal GABA neurons, neurotoxicity, and oxidative stress.[14,15,19]

There is currently no curative treatment for TD, and limited evidence is available to guide its management.[1] Estimated remission rates for TD vary from as little as 1% up to 62%.[16] TD occurs in roughly one-third of patients treated with first generation antipsychotics as compared to 13% on second generation (atypical) agents.[17,19] Three broad approaches have been used to manage TD including antipsychotic dose reduction, switching antipsychotic drug therapy, or addition of adjunctive agents.[3] Pharmacologic options for adjunctive treatment of TD are limited. Off-label use of tetrabenazine, clonazepam, amantadine, levetiracetam, resveratrol, and even ginkgo biloba have been used for TD symptom management with varying levels of success.[19] Other studies have investigated off-label use of medications for TD treatment, but authors concluded that prudent use and monitoring of atypical antipsychotics is key to management of TD symptoms.[19] For cases of TD resistant to drug therapy, non-systemic options such a deep brain stimulation have been reported to provide some benefit.[19]

The assessment of TD is challenging due to the variability in research criteria and different rating scales.[20] The AIMS is a clinical tool frequently used for early detection and surveillance of TD.[3] The AIMS has 12 items which assess 7 commonly affected anatomical locations with a total score ranging from 0-28. Higher scores indicate increased severity of TD symptoms. Amplitude and quality of movement are evaluated using a numeric severity scale ranging from zero (no abnormalities) to four (severe movements) to assess.[3] The full assessment tool also contains an overall judgement of three abnormal movements also rated on a scale from 0-4, and 2 yes/no items concerning problems with teeth and dentures.[13] The AIMS can be completed in less than 10 minutes, and evaluation is suggested at least every 6 months for those on typical antipsychotics.[3] However, there is not a well-established guideline for the interpretation of AIMS scores, and there is criticism that it lacks sensitivity due to its limited range and non-specificity for movement frequency.[3] Each section of the AIMS may be totaled, but overall scores are generally not reported. There is no MCID established so interpretation of results is variable.

Huntington Disease

Huntington's disease results from a gene abnormality of an exon 1 CAG (cytosine-adenine-guanine [amino acid sequence]) trinucleotide expansion in the huntingtin (HTT) gene. Huntington Disease is a progressive, hereditary neurodegenerative disease that results in involuntary movements, cognitive dysfunction and psychiatric symptoms. Early stages of HD is often characterized by deficiencies in voluntary motor function while mid stages are associated with more of an impact on motor coordination and function.[21] Optimization of quality of life is the focus of HD treatment through symptom management since there is no cure or disease-modifying therapies. The estimated incidence if HD is 5 in 100,000 people in the US.[22]

Prior to the approval to deutetrabenazine, the only treatment FDA approved for HD chorea was tetrabenazine. The use of tetrabenazine is limited by variable CYP2D6 metabolism that often results in a dosing frequency of three times daily.[11] Tolerability is also an issue with tetrabenazine with common adverse effects such as sedation, fatigue, akathisia, anxiety and nausea. Olanzapine, risperidone, aripiprazole, clozapine, haloperidol and fluphenazine have also been used as off-label treatment options for patients with HC.[2]

The severity of HC and functional impact is measured by the Unified Huntington's Disease Rating Scale Total Motor Score (UHDRS-TMS) and is the main outcome used in many trials. The UHDRS-TMS motor scale uses 124 questions to measure chorea, parkinsonism, dystonia, eye movements, and other signs. There are 31 items that are graded 0 (not affected) to 4 (most severely affected).[21] There is limited evidence that a 1-point increase in the UHDRS-TMS, in patients in the early stages of HD, correlates with an approximately 10% loss of the likelihood of being able to work, manage finances, drive and supervise children. In studies of patients with a diagnosis of HD, the mean annual change in patients UHDRS-TMS was 3.8 points. AAN guidelines define the change in subscores as: less than a 1 point decrease in UHDRS as unimportant, 1 to less than a 2-point decrease modestly important, 2 to less than 3-point decrease moderately important and more than a 3-point decrease as very important.[2]

The UHDRS total chorea score (UHDRS-TCS) is a subscore which rates facial, bucco-oral-lingual, trunk and extremity chorea. Standardized assessment of chorea based on the UHDRS-TCS subscore is determined by frequency and severity of chorea in 7 areas of the body by a scale of 0-28, with a higher number indicating worse disease.[2]. This subscoring portion represents 23% of the overall UHDRS-TMS and is recommended for determining the impact of chorea symptoms over using the UHDRS-TMS.[21] The clinically important change for this outcome has not been determined.

Symptom Assessment Used for Both Tardive Dyskinesia and Huntington's Disease

The PGIC is used to determine the patients' perspective on overall improvement in movement dysfunction. This is a 1-7 point Likert scale with a score of 1 representing "very much improved" and a score of 7 suggesting "very much worse". The CGIC is a clinician perspective of the severity of the patient's symptoms utilizing the same scale as the PGIC.[4] Limitations to the CGIC is the reliance on provider recall of patient symptoms. Since there are no curative treatments for TD, outcomes related to improvement in symptoms are very important and should be a major consideration in treatment selection. The SF-36 quality of life assessment is also used with a higher score indicating an improved quality of life.

Recently the Food and Drug Administration (FDA) approved valbenazine, a selective, reversible vesicular monoamine transporter 2 (VMAT2) inhibitor, for the treatment of adults with TD.[12,13] Deutetrabenazine, a VMAT2 inhibitor initially approved for HC, was also recently granted FDA approval for TD treatment. A third agent, tetrabenazine was approved in 2008 for use to treat symptoms of HC and has been used off label for severe TD; however, mixed efficacy and numerous safety concerns has limited widespread use.[11] This document examines the efficacy and safety supporting the use of VMAT2 inhibitors in TD and HC. Recommendations for PDL status and PA criteria will be described.

A summary of relevant drug information is available in **Appendix 1**, which includes pharmacology and pharmacokinetic characteristics of these drugs, contraindications, warnings and precautions, including any Black Boxed Warnings and Risk Evaluation Mitigation Strategies.

Table 2. VMAT2 Inhibitors Indications and Dosing

Drug Name (Manufacturer)	Indication(s)	Strength/Route	Dose and Frequency
Valbenazine[13] (Neurocrine Biosciences, Inc.)	Tardive dyskinesia in adults	40 mg capsules	Initiate dose at 40 mg daily and increase to 80 mg daily after one week
Deutetrabenazine[12] (Teva Pharmaceuticals USA, Inc.)	Chorea associated with Huntington's disease and tardive dyskinesia in adults	6 mg, 9 mg and 12 mg tablets	Huntington's disease: initiate at 6 mg/day and increase by 6 mg per day to recommended dose of 6 -48 mg/day Tardive dyskinesia: initiate at 12 mg/day and increase by 6 mg per day to a recommended dose of 6-48 mg/day Doses of 12 mg or more should be given in two divided doses
Tetrabenazine[11] (Prestwick Pharmaceuticals)	Chorea associated with Huntington's disease in adults	12.5 mg and 25 mg tablets	Initiate dose at 12.5 mg and titrate as needed to up to 100 mg daily. Doses above 50 mg daily should be divided into 3 times daily regimen

Utilization data

While utilization for VMAT2 inhibitors is low the annual costs are estimated to be around $75,000 or more per patient per year. There are Oregon Health Plan (OHP) fee-for-service (FFS) claims for tetrabenazine.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Institute for Clinical and Economic Review (ICER) and the Canadian Agency for Drugs and Technologies2 in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

Tardive Dyskinesia

NICE – Health Technology Assessment: Systematic Review of Interventions for Treating or Preventing Anti-psychotic-induced Tardive Dyskinesia

A 2017 systematic review and meta-analysis was done on the efficacy and safety of interventions to treat TD in adults.[3] Randomized trials and observational studies of adults taking a stable dose of an antipsychotic drugs for 3 months or more were included. The search ended prior to the approval of valbenazine and deutetrabenazine and therefore these drugs were not evaluated. One hundred twelve studies were identified and most trials had a high overall risk of bias. Studies were small with a patient population of 8-170, with the exception of studies of vitamin E which enrolled up to 264 patients.[3] Interventions that were studied were dose adjustment of antipsychotics, switching antipsychotics and addition of pharmacotherapy to antipsychotics to manage symptoms.

Evidence from two small studies of very low quality found reduction of the antipsychotic dose to have no clinically important improvement compared to antipsychotic continuation (risk ratio [RR] 0.42; 95% CI, 0.17 to 1.04; p= 0.06).[3] Two studies evaluated the effect of switching antipsychotics on symptoms of TD but the results could not be combined. The first study found switching the antipsychotic to risperidone compared to antipsychotic withdrawal resulted in less patients in the risperidone group having no clinically important improvement in TD symptoms with a RR of 0.45 (95% CI, 0.23 to 0.89; P= 0.02; ARR 38%/NNT 3). A second study found switching to quetiapine versus haloperidol resulted in a RR of 0.80 (95% CI, 0.52 to 1.22; p = 0.30).[3] Evidence from observational studies found no clear evidence TD symptom improvement of antipsychotic discontinuation compared to increased or decreased dosage (very low quality evidence). Two studies evaluated the effect of benzodiazepines on TD symptoms and very low quality evidence found no effect (RR 1.12; 95% CI, 0.6 to 2.09). Vitamin E was evaluated in six studies with similar results of no benefit (RR 0.95; 95% CI, 0.89 to 1.01) based on low quality evidence. A study of the adjunctive effect of buspirone demonstrated improvement in TD symptoms with a RR of 0.53 (95% CI, 0.33 to 0.84; p=0.007; ARR 42%/NNT 3) based on a low-quality study of 42 patients. One study compared the effect of haloperidol to tetrabenazine and found no difference in the number of patients with no improvement at 18 weeks (RR 1.07; 95% CI, 0.51 to 2.23; p=0.35) based on a study of very low quality.[3] Clonazepam was found to have less patients with no clinically important improvement compared to phenobarbital (active placebo), 40% vs. 91%, based on one small study.

To summarize the only two analyses that found a decrease in TD symptoms were switching to risperidone compared to antipsychotic withdrawal and the use of buspirone over placebo. All other comparisons were not clinically or numerically significant.

ICER – Vesicular Monoamine Transport 2 Inhibitors for Tardive Dyskinesia: Effectiveness and Value
A 2017 review on the role of VMAT2 inhibitors in TD was produced by ICER.[4] The focus of the review was on valbenazine, deutetrabenazine and tetrabenazine use in adults with TD. Key intermediate outcomes were AIMS, CGIC and PGIC. Eleven studies of at least 10 patients were included. Thirteen references of conference abstracts/posters were also included.[4] Evidence identified for valbenazine and deutetrabenazine were found to be of fair to high quality studies. Evidence for tetrabenazine was determined to be of poor quality and therefore these studies were not considered in qualitative or quantitative assessments of VMAT2 inhibitors.

ICER rated both valbenazine and deutetrabenazine for the treatment of TD as "promising but inconclusive" based on improvement in AIMS scores compared to placebo but lack of consistent improvement in CGIC and PGIC scores.[4] CGIC and PGIC impression of improvements in symptoms is of critical importance since this is the indication for treatment. Lack of long-term safety data could reveal additional adverse events with both treatments. Deutetrabenazine also carries a box warning for depression and suicidality with ongoing use. The evidence for use of tetrabenazine for the treatment TD symptoms was rated by the ICER as "insufficient".[4] There were no high-quality studies on tetrabenazine use in TD but available evidence suggests a possible benefit. Tetrabenazine clinical trial safety data found tolerability issues such as somnolence, insomnia, and depression.

Huntington's Disease
Cochrane – Therapeutic Interventions for Symptomatic Treatment in Huntington's Disease
The pharmacological treatment options for the treatment of HD were reviewed by Cochrane.[5] Newer treatments, deutetrabenazine and valbenazine, were not included because they were approved after the search date of the review. Randomized, double-blind, placebo-controlled studies with at least 10 patients were included. Twenty-two studies were identified. The mean patient age was 48 years with a mean disease duration of 6.3 years. Only one trial (n=84) was identified for VMAT2 inhibitors, which was a trial comparing tetrabenazine to placebo. Patients with a confirmatory diagnosis or a compatible family history of HD were included.

The study found tetrabenazine 100 mg/day to lower the UHDRS-TCS score by 5.0 points compared to a decrease of 1.5 points for placebo (MD 3.5 points; 95% CI, -5.2 to -1.9; p<0.0001).[5] Tetrabenazine had a statistically significant change in the CGIC scale by 3.0 compared to 3.7 for placebo (p<0.007). The exploratory functional endpoints of UHDRS Functional Checklist and the 17-item Hamilton Depression scale were statistically worse with tetrabenazine compared to placebo. Five (9.2%) of patients in the tetrabenazine group compared to none in the placebo group discontinued treatment due to adverse events.[5] Randomization and allocation were found to have a low risk of bias in this study.

Other treatments have been studied for the reduction of symptoms with HD. Use of riluzole is limited by an excess of hepatic toxicity when used at the effective dose of 200 mg/day. Evidence from a study of riluzole 100 mg/day showed lack of efficacy. Two small trials studied amantadine for symptoms of chorea with HD. Pooled analysis found no difference between amantadine and placebo with a standard mean difference of -0.25 (95% CI, -0.93 to 0.43; p=0.10); however, a higher number of patients reported a subjective benefit in symptom improvement (p=0.006) and quality of life (p<0.001) with the use of amantadine.

Studies of other pharmacotherapy demonstrated no effect on HD symptoms (cannabidiol, clozapine, creatine, ethtyl-eicosapentaenoic acid, fluoxetine, ketamine, L-acetyl carnitine, minocycline, piracetam, remacemide, sulpiride, tiapride, trans-dihydrolisuride and unsaturated fatty acids).

Guidelines:

American Academy of Neurology – Treatment of Tardive Syndromes

A 2013 guideline on the management of tardive syndromes was published by the AAN.[1] Evidence was systematically reviewed and graded using a modified GRADE process for evidence synthesis. One of the guideline authors has substantial ties to industry. Treatments included in the guidelines were anticholinergics, benzodiazepines, beta-blockers, calcium channel blockers, anticholinergics, GABAergic compounds, neuroleptic medications, non-neuroleptic medications that affect the dopamine and noradrenaline systems, vitamin B6 and vitamin E. Each study was graded on quality of evidence, Class I (randomized clinical trial) to Class IV (consensus/expert opinion). Evidence was given an overall evidence rating ranging from A (established efficacy) to U (data inadequate or conflicting).

There is insufficient evidence to support or recommend against the treatment of TD by withdrawing DRBA (Level U).[1] Evidence is conflicting on the efficacy of switching from typical antipsychotics to atypical antipsychotics in reducing TD symptoms based on Level U evidence. There is insufficient evidence to support the use of or recommend against the treatment of TD with acetazolamide and thiamine (Level U). Level C evidence suggests that amantadine may be an option for the short-term treatment of TD. Neuroleptics may cause TD and mask symptoms and are not recommended to treat symptoms of TD (Level U).[1] Caution should be taken if risperidone or olanzapine is used to treat symptoms of TD. The use of tetrabenazine may be considered for the treatment of TD symptoms based on evidence from two Class III studies (Level C). Clonazepam may be effective for short-term (approximately 3 months) treatment of TD and should be considered based on Level B evidence.

There is insufficient data to recommend reserpine, alpha-methyldopa, levetiracetam or anticholinergics for TD (Level U).[1] There is insufficient evidence to support or recommend against the use of thiopropazate, molindone, sulpiride, fluperlapine, flupenthixol, bromocriptine, nifedipine, buspirone, botulinum toxin or baclofen for the treatment of TD symptoms (Level U). Evidence suggests galantamine is ineffective for the treatment of TD symptoms and is not recommended (Level C). There is insufficient evidence to determine if discontinuing biperiden is effective in treating symptoms of TD (Level U).

American Academy of Neurology – Pharmacologic Treatment of Chorea in Huntington Disease

The AAN published a treatment guideline of the management of chorea in patients with HD in 2012.[2] Each study was systematically reviewed and graded using a modified GRADE process for evidence synthesis. Evidence was given an overall evidence rating ranging from A (established efficacy) to U (data inadequate or conflicting). AAN guidelines are funded by the academy and authors of this guideline have received grants from industry. Dopamine-modifying drugs, glutamatergic-modifying drugs, energy metabolites, donepezil, coenzyme Q10, minocycline, and nabilone were included. Guidelines were developed before the approval of valbenazine and deutetrabenazine so guidance on these treatments are not available.

AAN guidelines recommend tetrabenazine up to 100 mg/day for patients needing treatment for HC based on level B evidence.[2] Two studies, graded as Class I and Class II, were used as evidence to support the recommendation. A 12-week RCT comparing tetrabenazine to placebo (n=84) found a UHDRS total maximal chorea score decrease of -5.0 points compared to -1.5 point in the placebo group (p=0.0001). CGIC scores were also significantly improved in the tetrabenazine group compared to placebo. The PGIC was not reported. A second study was a tetrabenazine withdrawal study which found that patients in the early discontinuation group had a 5.3 unit increase in UHDRS chorea score compared to patients continuing therapy (p=0.0486).[2] Reviewers felt that tetrabenazine was likely effective in decreasing HC to a very important degree but should be used cautiously as it can worsen depression and Parkinson like symptoms which are often present in HD.

Amantadine 300-400 mg/day and riluzole 200mg/day were also recommended based on Level B evidence. Nabilone can be considered a treatment option for short-term use (Level C evidence).

Randomized Controlled Trials:
A total of 41 citations were manually reviewed from the initial literature search. After further review, 37 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., outcome studied (e.g., non-clinical). The remaining 4 trials are summarized in the new drug evaluation tables below.

VALBENAZINE NEW DRUG EVALUATION:

Clinical Efficacy:
The efficacy of valbenazine for use in the treatment of TD was established primarily on the basis of a 6-week randomized, parallel, fixed-dose, placebo-controlled study (see **Table 2**).[6] Valbenazine 40 mg daily (n=76) and valbenazine 80 mg daily (n=70) were compared to placebo (n=79)in medically stable patients from various locations within the United States (59 sites), Canada (2 sites), and Puerto Rico (2 sites) with moderate to severe TD.[6] A majority of patients included in the study were diagnosed with schizophrenia or schizoaffective disorder (66.1%) or mood disorder (33.9%) and had a DSM diagnosis of DRBA-induced TD for at least 3 months. Seventeen percent of patients were taking FGA and 77% were taking SGA. Patients meeting inclusion criteria had to have moderate to severe TD as designated by a qualitative assessment by external reviewers. The mean baseline AIMS dyskinesia score was 10 and patients had an average of 7-year history of TD. Patients with severe psychiatric disease, as indicated by a Positive and Negative Syndrome Scale score of ≥70 and/or a score of ≥50 on the Brief Psychiatric Rating Scale and significant unstable comorbidities were excluded. Specifically, patients with any other movement disorder more prominent than TD, such as parkinsonism, akathisia or truncal dystonia, were not included. The primary endpoint was a mean change in the AIMS dyskinesia score for items 1-7 on AIMS (range 0-28) from baseline to week 6.[6] Global severity (questions 8-10) and problems with teeth or dentures (questions 11-12) were not assessed. The key secondary endpoint was the change in the 7-point CGIC score (range 1-7) from baseline to week 6.[6] PGIC was also a secondary endpoint with scores of 1 or 2 being classified as PGIC responders.

The primary endpoint of adjusted mean AIMS score was reduced in both 40 mg and 80 mg valbenazine groups compared to 0.1 point mean reduction with placebo (VBZ 40 mg = -1.9 points, p =0.002; VBZ 80 = -3.2 points, p <0.001).[16] The clinical significance of this magnitude of a 7% to 11% change is unlikely to be meaningful, especially in patients with less severe TD symptoms. Supportive analysis demonstrated that a reduction in AIMS dyskinesia score of greater than 50% at 6 weeks from baseline occurred in 23.8% of patients on valbenazine 40 mg (p = 0.02 vs. placebo, NNT = 7) and 40% of those treated with valbenazine 80mg (p<0.001 vs. placebo, NNT = 4).[6] However, the baseline AIMS scores of 6 or greater may indicate at least some patients with low baseline scores had marginal to no clinical value. Application of this change to the mean baseline AIMS of 10 would suggest a 5 point (18%) change in symptoms which may be clinically relevant to patients.[13] The key secondary endpoint was change in CGIC score from baseline to week 6 in which there was no significant difference. An additional secondary endpoint not reported in the published study but made available in the FDA medical review document was the PGIC. The number of responders in the valbenazine 40 mg group was 31.7%, 24.3% in the valbenazine 80 mg group and 42.0% for the placebo group. The difference between placebo and valbenazine 80 mg was significantly different in favor of placebo.

However, with no MCID established, there is a lack of evidence to support the assertion that a statistically significant reduction in AIMS dyskinesia score is associated with clinical relevance. Additionally, PGIC scores were lower with valbenazine than with placebo which suggest that patients felt their symptoms were worse with treatment prescribed to improve symptoms. With 3 types of psychiatric disorders present, it is also unknown if valbenazine had different effects within the subgroups. Details regarding the differences in number, duration, and doses of antipsychotics between groups were not reported. In addition, not all patients were on a concurrent antipsychotic, and there was evidence to suggest that those who were not using antipsychotic medications may have responded better than those on antipsychotic therapy.[6] Patients with severe depression and/or suicidal ideation were excluded from the study so the effects of valbenazine in this population is unknown. It was unclear who performed the statistical analysis for the study and whether or not blinding was maintained.

Overall, the phase 3 study used for FDA approval had moderate risk of bias. Although blinding of patients and investigators appeared adequate and attrition rates were within acceptable limits, there were baseline differences among groups in the percentage of patients on multiple and conventional APDs (see **Table 3**). Additionally, with the abundant exclusion criteria, the study results may only be applicable to healthy, stable psychiatric patients with few to no comorbidities. The effect of valbenazine in complex patients, prescribed multiple high-dose antipsychotics or patients with other types of DRBA-induced TD is unknown. It was unclear why patients were not assessed using the global judgement portion of the AIMS tool. Given the short study duration and no minimal clinically important reference standard established for the AIMS and lack of patient reported improvement, the clinical value and long-term effectiveness of valbenazine for the treatment of DRBA-induced TD remains uncertain.

Clinical Safety:

In KINECT 3, 5.3% of patients in the placebo group and 6% of patients in the valbenazine group prematurely discontinued their medication due to an adverse event.[6] Serious adverse events were reported more frequently in the valbenazine group than placebo (6.6% vs. 3.9%, respectively; p value not reported). However, the specific types of adverse events leading to early discontinuation of treatment or types of serious adverse events were not reported in the study. The most common adverse effects of valbenazine versus placebo were somnolence (5.3% vs. 3.9%, respectively), dry mouth (3.3% vs. 1.3%, respectively), and akathisia (3.3% vs. 1.3%, respectively), but no p-values for statistical comparisons were reported. [13] Pooled safety data from 3 controlled studies (n = 445) reported that somnolence was present in 11% of valbenazine subjects versus 4% for placebo which was higher than KINECT 3 findings.[6]

The FDA safety analysis noted QT prolongation with valbenazine which prompted addition of this warning to the labeling.[6] Due to potential increases in serum concentrations of valbenazine's active metabolite ([+]-α-dihydrotetrabenazine), labeling also includes recommendations to avoid concomitant use with

monoamine oxidase inhibitors (MAOI) and strong CYP3A4 inducers and to reduce valbenazine dose with co-administration of strong CYP3A4 and CYP2D6 inhibitors.[14] Valbenazine is not recommended for patients with severe renal impairment.[13]

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:
1) Functional improvement
2) Symptom improvement
3) Health-related quality of life
5) Serious adverse events
6) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) AIMS dyskinesia total (change from baseline)

Table 3. Valbenazine Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
Hauser et al. 2017[6] (KINECT 3) Ingrezza FDA Summary Review[13] DB, PC, Phase 3, RCT	1. valbenazine 40 mg daily 2. valbenazine 80 mg daily 3. Placebo Randomized patients w/ 80 mg dose started at 40 mg then titrated to 80 mg after 1 week 6-week trial	Demographics: -Mean age: 56 years -≥ 65 years: 16% -Male: 54% -White: 56% -Black: 38% -Mean AIMS dyskinesia score (items 1-7): 1. 9.8 2. 10.4 3. 9.9 -Schizophrenia/ schizoaffective disorder: 66% -Mood disorder: 34% -Concomitant medications: -Any APD: 85.5% -Atypical APD: 77% -Any antidepressant: 66.5% -Any anticholinergic: 37% Key Inclusion Criteria: -Age: 18-85 -Diagnosis of schizophrenia or schizoaffective disorder or mood disorder per DSM-IV criteria for ≥ 3 mo.	ITT: 1. 70 2. 79 3. 76 PP: 1. 52 2. 61 3. 66 Attrition: 1. 13 (17%) 2. 9 (11%) 3. 7 (9%)	Primary Endpoint: 6-week modified AIMS change from baseline: adjusted mean: 1. -1.9 2. -3.2 3. -0.1 1. VBZ 40 mg vs. PBO -1.8 (95% CI, -3.0 to -0.7) p= 0.0021 2. VBZ 80 mg vs. PBO -3.1 (95% CI, -4.2 to -2.0) p <0.0001 Supportive analysis: % participants achieved ≥ 50% decrease in AIMS total dyskinesia score: 1. 24%; p=0.02 vs. PBO 2. 40%; p<0.001 vs. PBO 3. 9% Secondary Endpoint: LS Mean CGIC at Week 6: 1. 2.9; p=0.0742 2. 2.9; p=0.0560	NA NA 1. 15%/7 2. 31%/4 NS	Any SAE 1. 5.6% 2. 7.6% 3. 3.9% DC due to AE: 1. 5.6% 2. 6.3% 3. 5.3% TEAEs: Somnolence 1. 5.6% 2. 5.1% 3. 3.9% Akathisia 1. 4.2% 2. 2.5% 3. 1.3% Dry mouth 1. 6.9% 2. 0% 3. 1.3%	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: UNCLEAR. Interactive web response system used to randomly assign participants. Details of various prognostic factors unknown: Uncertain if groups differed in percentage of patients on multiple APDs; Fewer patients on conventional APD in PBO group compared to VBZ 40mg and 80mg groups (10.5% vs. 21% and 19%, respectively); more patients in treatment group on anticholinergics (~41% VBZ vs. 29% PBO); VBZ 40 mg group had higher proportions of subjects with ultra-rapid or poor CYP2D6 activity, which could potentially affect drug concentrations. Performance Bias: LOW. Participants, investigators, study site personnel, central AIMS video raters, and the study sponsor blind to treatment assignment. Dose reduction authorized with very few modified. Subjects not authorized to modify or discontinue medications for other psychiatric and medical conditions which limited confounding. Detection Bias: UNCLEAR. Unknown who performed statistical test evaluation and whether or not blinding was maintained; AIMS examination video reviewed/scored by blinded experts via central AIMS video. Video rater pairs provided consensus scoring. Attrition Bias: UNCLEAR. 12% overall attrition, 5% differential attrition. Attrition higher in treatment groups (14% vs. 9%). Intent-to-treat population failed to include all randomized participants: VBZ 40 mg group excluded 2

		-DSM diagnosis of DRBA-induced TD for ≥ 3 mo. -Moderate to severe TD per external centralized AIMS video rating score -Maintenance meds at a stable dose for ≥30 days before screening Key Exclusion Criteria: -No prohibited medications (strong CYP3A4 inducers, dopamine agonists and precursors, MAOIs, stimulants, or VMAT2 inhibitors) within 30 days of study screening - PANSS total score ≥70 or CDSS total score ≥10 - Unstable psychiatric conditions - Suicidal or violent behavior risk - Any clinically significant unstable medical condition - History of NMS -History of long QT syndrome or cardiac tachyarrhythmia		3. 3.2		No p-values reported		participants for lack of AIMS assessment, 1 for study withdrawal, and 3 for lack of post-baseline safety data. Analyses conducted in the per-protocol population considered supportive. Reporting of Least Squares Mean may have exaggerated treatment effect size. Reporting Bias: UNCLEAR. Study funded by Neurocrine Biosciences. Of 9 study authors, 4 directly employed by Neurocrine Biosciences and 4 others have served as consultants for and/or have received honoraria from the sponsor. Support for writing and editorial assistance of the manuscript provided by Neurocrine Biosciences. Three authors have equity in Neurocrine Biosciences. Critical review of manuscript drafts provided by full-time employee of Neurocrine Biosciences. However, study protocol approved by IRB at each center and specified outcomes reported. **Applicability**: Patient: Narrow inclusion criteria limits applicability to patients with schizophrenia, schizoaffective disorder, or mood disorder w/ DRBA-induced TD (benefit in other TD patients unknown); Excluded high-risk or medically unstable, violent or suicidal patients; concomitant psychiatric medications likely representative of target population but highly variable. Intervention: Fixed dose 40 mg or 80 mg valbenazine or placebo orally once daily for 6 weeks. Unable to evaluate clinical value beyond 6 weeks. Comparator: Placebo appropriate for efficacy. Outcomes: AIMS test score change from baseline, but MCID is unclear; AIMS score results highly subjective and not linear, assesses symptom improvement not cure; secondary endpoint used CGI-TD score which has not been well validated. Setting: 63 centers in North America (59 in the United States, two in Canada, and two in Puerto Rico).

Abbreviations: AIMS = Abnormal involuntary movement scale; ARR = absolute risk reduction; APD = antipsychotic drug; CDSS = Calgary Depression Scale for Schizophrenia; CFB = change from baseline; CGI-TD = Clinical Global Impression of Change – Tardive Dyskinesia; CI = confidence interval; DRBA = dopamine receptor blocking agents; ITT = intention to treat; LS = least squares; MADRS = Montgomery-Asberg Depression Rating Scale; MAOIs = monoamine oxidase inhibitors; mITT = modified intention to treat; mo = months; N = number of subjects; NA = not applicable; NMS = neuroleptic malignant syndrome; NNH = number needed to harm; NNT = number needed to treat; NS = not significant; PP = per protocol; Positive and Negative Syndrome Scale = PANSS; SAS = Simpson-Angus Scale; TD = tardive dyskinesia; VBZ = valbenazine; VMAT2 = vesicular monoamine transporter 2; YMRS = Young Mania Rating Scale

DEUTETRABENAZINE NEW DRUG EVALUATION:

Clinical Efficacy:

Deutetrabenazine is a VMAT2 inhibitor approved for chorea associated with HD and TD in adult patients.[12] Deutetrabenazine is a chemically modified form of tetrabenazine that has a longer half-life and lower peak concentrations levels. Deutetrabenazine has been studied in one trial for HD and two trials for TD (**Table 4**). The dose of deutetrabenazine is initiated at a dose of 6 mg/day in patients with HD and 12 mg/day in patients with TD. Maximal daily dose for both indications is 48 mg/day with doses of 12 mg/day or more being divided twice daily. Deutetrabenazine received an orphan drug designation for Tourette syndrome in the pediatric population.

Huntington Chorea

Approval for the use in HC was based on a randomized, placebo-controlled, double-blind, multicenter study in 90 patients with HD.[7] Deutetrabenazine was compared to placebo over 12 weeks. Patients meeting inclusion criteria had a baseline UHDRS total maximal chorea score of 8 or higher (range 0-28 with lower scores indicating less chorea) and a UHDRS total functional capacity score of 5 or higher which correlates to mild to moderate functional impairment with a HD diagnosis for approximately 15 years. The mean patient age was 54 years and 56% were men. Mean UHDRS functional capacity score was 9.5 and mean TCS was 12.7 at baseline. Exclusion criteria included the following: uncontrolled depression as measured by a Hospital Anxiety and Depression Scale (HADS) score of 11 or more, history of significant suicidal thoughts or behavior, prolonged QT interval, hepatic or renal impairment, Unified Parkinson Disease Rating Scale (UPDRS) speech item with scores of 3 or higher, and patients with score of 11 or higher on the Swallowing Disturbance Questionnaire.[7] Patients taking antipsychotics and dopamine agonists were also not included. The primary endpoint was change in TCS from baseline (average of visits during screening period and day 0 visits) to maintenance therapy (average of values from the week-9 and week-12 visits). While a MCID has not been determined for this primary endpoint other studies have used a change of 2.7 points to indicate a treatment difference; however, this only represents a 10% change which may of little clinical benefit. Secondary endpoints of interest were the PGIC and CGIC. The PGIC and CGIC were defined as treatment success if the patient response was “much” or “very much” improved at week 12.

Improvement in the primary outcome of total maximum chorea score for patients randomized to deutetrabenazine was a mean decrease of -4.4 compared to -1.9 in the placebo group (MD -2.5; 95% CI, -3.7 to -1.3; P<0.001) at 12 weeks.[7] Treatment success, based on the PGIC scale, occurred in 23 of patients (51%) treated with deutetrabenazine compared to 9 of patients (20%) in the placebo group (MD 31.1; 95% CI, 12.4 to – 49.8; ARR 31%/NNT 4). Nineteen patients (42%) in the deutetrabenazine group experienced treatment success, based on the CGIC scale, compared to 6 patients (13%) in the placebo group (MD 28.9; 95% CI, 11.4 to 46.4; p=0.02; ARR 29%/NNT 4). Patients satisfactions scores were improved by 3 points with deutetrabenazine compared to placebo (p=0.03). After washout at week 13, total maximum chorea scores returned to baseline values.

Limitations to the evidence of deutetrabenazine use in HD included extensive exclusion criteria limiting the external validity especially in patients taking antipsychotics. The protocol was amended to allow prior use of tetrabenazine which could influence results; however, this applied to only 2 patients in the deutetrabenazine group and 3 in the placebo group. The patients in this trial had worse motor symptoms at baseline compared to a study of tetrabenazine, which make treatment comparisons difficult. Wide confidence intervals found in secondary endpoint comparisons suggest that no treatment difference could still exist between deutetrabenazine and placebo. This is particularly important because these endpoints evaluate the patient’s perception of improvement an important factor for therapies designed for only symptom management. Depression and suicide rates are high in patients with HD; therefore, it is difficult to determine the effect of deutetrabenazine on these endpoints in a small, short-term study.

Tardive Dyskinesia

Study methodology for the two multi-center, parallel design, placebo-controlled, double-blind, 12-week studies were similar.[8,9] Both studies enrolled adult patients 18-80 years with an AIMS score of at least 6 and stable psychiatric illness with use of DRBA for at least 3 months or age of 60 or older with use of DRBA for at least one month. The primary outcome was change in AIMS score from baseline for both treatments. Secondary outcomes were the number of patients experiencing treatment success based on AIMS score improvement of at least 50%, CGIC responder score of "much" or "very much" improved, and PGIC responder score of "much" or "very much" improved. Patient satisfaction was measured by the modified Craniocervial Dystonia Questionnaire (mCDQ-24) in one of the studies.

The first study was a phase 2/3 study evaluating the efficacy of deutetrabenazine compared to placebo in patients with TD.[9] The deutetrabenazine dose was titrated over 6 weeks as needed to control symptoms to a maximum dose of 48 mg/day (divided twice daily) or up to 36 mg/day in patients on strong CYP2D6 inhibitors. At the end of the titration period the mean total daily dose was 38.8 mg. Deutetrabenazine decreased AIMS scores by -3.0 points compared to -1.6 points for placebo (MD -1.4; 95% CI, -2.6 to -0.2; p= 0.019). A treatment difference of 5% is unlikely to be a clinically meaningful improvement in TD symptoms for patients. Treatment success as measured by the CGIC was 48.2% in the deutetrabenazine group compared to 40.4% in the placebo group (p-value not significant). PGIC treatment success was 42.9% in the deutetrabenazine group compared to 29.8% in the placebo group (p-value not significant). The difference in patient satisfaction, measured by the mCDQ-24, was not significantly different between deutetrabenazine and placebo, -11.1 and -8.3, respectively.

The second study was a phase 3 study which evaluated three doses of deutetrabenazine 12, 24 and 36 mg/day compared to placebo for the treatment of TD in adult patients (doses were divided twice daily).[8] The mean change in AIMS score from baseline was -3.3 in the deutetrabenazine 36 mg group, -3.2 in the deutetrabenazine 24 mg group, -2.1 in the deutetrabenazine group and -1.4 in the placebo group at week 12. The proportion of the patients who achieved at least a 50% improvement in the AIMS score was 33% for deutetrabenazine 36 mg, 35% for deutetrabenazine 24 mg, 13% for deutetrabenazine 12 mg and 12% for placebo. The differences from placebo was 21% (NNT 5; p=0.007) for deutetrabenazine 36 mg and 23% (NNT 4; p=0.005) for deutetrabenazine 24 mg. CGIC treatment success occurred in 44% of deutetrabenazine 36 mg patients (ARR 18/NNT 6; p=0.059), 49% of deutetrabenazine 24 mg patients (ARR 23%/NNT 4; p=0.014), 28% deutetrabenazine 12 mg patients (not-significant compared to placebo) and 26% of placebo patients. PGIC treatment success rates were not significantly different between deutetrabenazine and placebo for all comparisons.

The results of both studies of deutetrabenazine use in patients with TD were most applicable to patients with schizophrenia taking a DRBA with moderate TD symptoms. Risk of bias in both studies was low and they were considered fair quality. Small sample sizes and short duration of treatment for an indication which is often chronic prevents strong conclusions of efficacy.

A 5% improvement in TD symptoms is unlikely to be meaningful to patients, as demonstrated by a lack of a clinically meaningful change in the patients' perception of symptoms as measured by PGIC. Patients taking deutetrabenazine did not have a higher quality of life, as measured by mCDQ-24, compared to those taking placebo.[8] The FDA sites twice a day dosing of deutetrabenazine as the only clear advantage of it over tetrabenazine.

Other studies that did not meet our inclusion criteria were the following: an indirect tolerability study between deutetrabenazine and tetrabenazine in patients with HD[23], a long-term safety study of deutetrabenazine in patients with severe TD[24] and an ongoing, open-label, single arm study of converting tetrabenazine to deutetrabenazine[25].

Clinical Safety:
The most common adverse events seen in more than 8% of patients randomized to deutetrabenazine and more than placebo where somnolence, diarrhea, dry mouth and fatigue. Severe adverse reactions occurred in 2.2% of patients in each group. Discontinuations due to adverse events occurred in one patient in each group. The risk of depression and suicidal ideation where similar in both groups. Deutetrabenazine carries a Box Warning for its ability to increase the risk of depression and suicide in patients with HD and should be used cautiously in patients with a history of depression. In studies of deutetrabenazine there were no safety signals for worsening depression or suicidality; however, due to the small, short-term nature of approval studies the increased risk could not be ruled out.

The effect of deutetrabenazine on QT prolongation may be clinically relevant in patients who are poor CYP2D6 metabolizers or taking strong CYP2D6 inhibitors.[22] Deutetrabenazine is closely related to tetrabenazine which has been shown to prolong the corrected QT interval by approximately 8 seconds. Metabolism of deutetrabenazine is primarily due to CYP2D6. Deutetrabenazine dosage reduction may be required if administered with strong CYP2D6 inhibitors.[21]

Comparative Clinical Efficacy:

Clinically Meaningful Endpoints:
1) Functional improvement
2) Symptom improvement
3) Health-related quality of life
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Total maximal chorea score change in HD
2) AIMS score change from baseline in TD

Table 4. Deutetrabenazine Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Huntington Study Group[7] RCT, DB, DD, PC, PG, MC, Phase 3	1. Deutetrabenazine (D)* 2. Placebo (P) * Dose was titrated over 8 weeks with a maintenance dose given for 4 weeks. Initiation dose was 6 mg/day and increased weekly by 6mg/day till chorea was controlled, patient experienced adverse events or the maximum dose of 48 mg/day was achieved.	Demographics: Mean Age: 54 years Male: 56% White: 83% Mean UHDRS functional capacity: 9.5 Mean UHDRS total maximal chorea score: 12.7 Key Inclusion Criteria: - HD verified by motor examination features and an	ITT: D: 45 P: 45 PP: D: 44 P: 43 Attrition: D: 2.3% P: 4.5%	Primary Endpoint: Total maximal chorea score change from baseline: D: -4.4 P: -1.9 MD -2.5 (95% CI, -3.7 to -1.3) p<0.001 Secondary Endpoints: Treatment success determined by PGIC: D: 23 (51%) P: 9 (20%) MD 31.1 (95% CI, 12.4 to –49.8) P = 0.002 Treatment success determined by CGIC:	NA 31%/4	Somnolence: D: 5 (11.1%) P: 2 (4.4%) p-value not provided Dry mouth: D: 4 (8.9%) P: 3 (6.7%) p-value not provided Diarrhea: D: 4 (8.9%) P: 0 p-value not provided Depression or agitated depression: D: 2 (4.4%) P: 3 (6.7%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) Computerized randomization algorithm via an interactive web-based randomization system randomized patients in a 1:1 ratio. Patients were stratified by prior exposure to tetrabenazine. Performance Bias: (low) Patients, site personnel, and study personnel were blinded to treatment. Adherence was accessed via pill count. Pills were identical in each group. Detection Bias: (unclear) Blinding of accessors was not described. Attrition Bias: (low) Attrition rates were low in both groups. Results were analyzed using ITT and LOCF for missing data. Reporting Bias: (low) Outcomes were reported as specified. Trial was funded by Auspex Pharmaceuticals.

	12-week study	expanded HTT CAG repeat sequence (≥36) - UHDRS total maximum chorea score of 8 or higher - UHDRS total functional capacity score of 5 or higher <u>Key Exclusion Criteria</u>: - Untreated psychiatric illness - Patient with prolonged QT interval, left bundle-branch block - hepatic or renal impairment - Use of antipsychotics, MOIs, metoclopramide, dopamine agonists, levodopa - Drugs known to prolong the QT interval		D: 19 (42%) P: 6 (13%) MD 28.9 (95% CI, 11.4 to –46.4) P = 0.002 Patient satisfaction determined by mean SF-36: D: 0.7 P: -3.6 MD: 4.3 (95% CI, 0.4 to 8.3) p = 0.03	29%/4 NA	p-value not provided <u>Discontinuations due to adverse events</u>: D: 1 (2%) P: 1 (2%) <u>Serious Adverse Events</u>: D: 1 (2.2%) P: 1 (2.2%)		**Applicability**: <u>Patient</u>: Patient's functional scores suggest mild to moderate impairment. <u>Intervention</u>: The mean dose of deutetrabenazine was 39.7 mg at the end of the treatment period and 34.8 mg for patients with impaired CYP2D6 function (poor metabolizers or taking strong CYP2D6 inhibiting medications). The maximum deutetrabenazine dose is 48 mg/day suggesting study doses are appropriate. <u>Comparator</u>: Placebo comparison appropriate. <u>Outcomes</u>: No minimal clinically important difference is available for total maximal chorea score but this a standardized measure for patients with HD, as well as the other secondary endpoints. <u>Setting</u>: Thirty-four sites in the United States and Canada.
2. Anderson, et al[9] (AIM-TD) MC, PG, PC, DB, Phase III	1. Deutetrabenazine 12 mg (D12)* 2. Deutetrabenazine 24 mg (D24)* 3. Deutetrabenazine 36 mg (D36)* 4. Placebo	<u>Demographics</u>: Mean Age: 56 years Male: 45% TD duration: 5.6 years Baseline AIMS score (items 1-7): 8.4 <u>Key Inclusion Criteria</u>: - 18-80 years	<u>mITT</u>: D12: 60 D24: 49 D36: 55 P: 58 <u>PP</u>: D12: 60 D24: 49 D36: 55 P: 58 <u>Attrition</u>:	<u>Primary Endpoint</u>: LS Mean AIMS Change from Baseline: D12: -2.1 D24: -3.2 D36: -3.3 P: -1.4 D12 vs. P: MD -0.7 (95% CI, -1.84 to 0.42) p = 0.217	NS	<u>Somnolence:</u> D12: 0 (0%) D24: 1 (1.4%) D36: 3 (4.1%) P: 3 (4.1%) p-value not provided <u>Headache:</u> D12: 5 (6.8%) D24: 2 (2.7%) D36: 5 (6.8%) P: 4 (5.6%) p-value not provided	NA for all	**Risk of Bias (low/high/unclear)**: <u>Selection Bias</u>: (low) Patients randomized centrally 1:1:1:1 via interactive response technology. <u>Performance Bias</u>: (low) Patients, investigators and site personnel were masked to treatment assignment. <u>Detection Bias</u>: (low) Central raters that were blinded to treatment assignment assigned ratings. <u>Attrition Bias</u>: (low) Attrition was low and similar between groups.

	12-weeks * Deutetrabenazine dose was started at 12mg/day divided twice daily and titrated by 6 mg/day till the randomized dose was achieved. Maintenance period was 8 weeks.	- ≥ 3 month history of tardive dyskinesia diagnosis - AIMS score of ≥6 at screening and baseline - DRBA use for ≥3 months - stable psychiatric illness - Use of antipsychotic for ≥30 days Key Exclusion Criteria: - Untreated psychiatric illness or neurological illness besides tardive dyskinesia - Serious or unstable medical condition - Other treatment for tardive dyskinesia - Hepatic or renal impairment	D12: 11% D24: 12% D36: 13% P: 9%	D24 vs. P: TD -1.8 (95% CI, -3.0 to -0.63) p =0.003 D36 vs. P: MD -1.9 (95%; -3.09 to -0.79) p =0.001 Secondary Endpoints: **≥ 50% AIMS Improvement:** D12: 8 (13%) D24: 17 (35%) D36: 18 (33%) P: 7 (12%) D12 vs. P: Not provided D24 vs. P: OR 3.96 (95% CI, 1.46 to 10.72) p=0.005 D36 vs. P: OR 3.80 (95% CI, 1.40 to 10.36) p=0.007 **CGIC Responders:** D12: 17 (28%) D24: 24 (49%) D36: 24 (44%) P: 15 (26%) D12 vs. P: OR not provided p= 0.734 D24 vs. P: OR 2.71 (95% CI, 1.21 to 6.05) p= 0.014 D36 vs. P:	NA NA 23%/5 24%/5 NS 23%/5	Diarrhea: D12: 1 (1.4%) D24: 3 (4.1%) D36: 5 (6.8%) P: 2 (2.8%) p-value not provided Serious Adverse Events: D12: 2 (3%) D24: 6 (8%) D36: 4 (5%) P: 4 (6%) Withdrawals due to adverse events: D12: 4 (5%) D24: 2 (3%) D36: 3 (4%) P: 2 (3%)		Reporting Bias: (low) Outcomes reported as pre-specified. Study was funded by manufacturer. **Applicability**: Patient: Sixty percent or patients had a schizophrenic diagnosis, 17% a bipolar diagnosis and 19% a depression diagnosis. Improvement in primary outcome was irrespective of DRBA; however, a greater improvement was seen in patients not taking DRBAs. Intervention: Doses of deutetrabenazine were consistent with other studies. Comparator: Placebo comparison appropriate. Outcomes: No minimal clinically important difference is available for AIMS score; however, AIMS score is a common surrogate endpoint used in TD studies. Setting: Seventy-five study sites in the US and Europe.

				OR 2.11 (95% CI, 0.96 to 4.65) p = 0.059 **PGIC Responders:** D12: 14 (23%) D24: 22 (45%) D36: 22 (40%) P: 18 (31%) D12 vs. P: OR 0.69 (95% CI, 0.30 to 1.56) p=0.372 D24 vs. P: OR 1.82 (95% CI, 0.83 to 3.99) p=0.134 D36 vs. P: OR 1.51 (95% CI, 0.69 to 3.29) p=0.296	NS NS NS NS			
3. Fernandez, et al[8] (ARM-TD) MC, PG, PC, DB, Phase II/ III	1. Deutetrabenazine* (D) 2. Placebo (P) 12-weeks * Deutetrabenazine dose was started at 12mg/day divided twice daily and titrated by 6 mg/day if needed for up to 6 weeks with a maximum dose of 48mg/day (36 mg/day if taking a strong CYP2D6	Demographics: Mean Age: 55 years Male: 56% TD duration: 6.2 years Baseline AIMS score: 9.6 Key Inclusion Criteria: - 18-80 years - ≥3 month history of tardive dyskinesia diagnosis - AIMS score of ≥6 at screening and baseline	mITT: D: 58 P: 59 PP: D: 52 P: 52 Attrition: D: 10% P: 12%	Primary Endpoint: LS Mean AIMS Change from Baseline: D: -3.0 P: -1.6 MD -1.4 (95% CI, -2.6 to -0.2) p=0.019 Secondary Endpoints: CGIC Responder: D: 48.2% P: 40.4% p- value reported as NS PGIC Responders: D: 43% P: 30% p- value reported as NS	NA NS NS	Somnolence: D: 8 (13.8%) P: 6 (10.2%) p-value not reported Headache: D: 3 (5.2%) P: 6 (10.2%) p-value not reported Diarrhea: D: 3 (5.2%) P: 3 (5.1%) p-value not reported Serious Adverse Events: D: 3 (5.2%) P: 5 (8.5%) p-value not reported	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias (low) central randomization by an Interactive Technology Response System in a 1:1 ratio stratified by prior use of DRBA. Performance Bias: (low) Video assessment of TD was done by 2 investigators blinded to treatment assignment. Detection Bias: (low) Central raters that were blinded to treatment assignment assigned ratings. Attrition Bias: (low) Attrition was low for both groups and similar between deutetrabenazine and placebo. Reporting Bias: (low) Outcomes were reported as stated. The study was funded by the manufacturer. **Applicability**: Patient: Sixty-eight percent or patients had a schizophrenic diagnosis, 23% a bipolar

	inhibitor) and then a maintenance dose was given for 6-weeks.	- DRBA use for ≥3 months - stable psychiatric illness - Use of psychoactive medications if stable for ≥30 days (≥45 days for antidepressants) Key Exclusion Criteria: - Neurological condition preventing TD assessment - Serious mental illness - Patients with suicidal ideation or severe depression (≥11 on HADS) - Prolonged QT interval - Taking other tardive dyskinesia treatment		Patient satisfaction as measured by mCDQ-24: D: -11.1 P: -8.3 p- value reported as NS	NS	Withdrawals due to adverse events: D: 1 (1.7%) P: 2 (3.4%) p-value not reported		diagnosis and 26% a depression diagnosis. The mean age is somewhat older than most Medicaid patients. Eighty percent of patients were also taking DRBA. Subgroup analysis found efficacy results to be similar in patients taking deutetrabenazine irrespective of concomitant DRBA use. Intervention: The dose of deutetrabenazine used was consistent with other efficacy studies. Comparator: Placebo comparison appropriate. Outcomes: No minimal clinically important difference is available for AIMS score; however, AIMS score is a common surrogate endpoint used in TD studies. Setting: Forty-six sites in the United States and Europe.

Abbreviations [alphabetical order]: ARR = absolute risk reduction; CAG = cytosine-adenine-guanine; CI = confidence interval; CGIC = Clinical Global Impression of Change; DB = double-blind; DD = double-dummy; DRBA – dopamine receptor blocking agent; HADS = Hospital Anxiety and Depression Scale; HTT = huntingtin gene; ITT = intention to treat; LOCF = last observation carried forward; mCDQ-24 = modified Craniocervical Dystonia Questionnaire; MD = mean difference; mITT = modified intention to treat; MOI = monoamine oxidase inhibitors; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PGIC = Patient Global Impression of Change; PP = per protocol; TD = treatment difference; UHDRS = Unified Huntington's Disease Rating Scale; UPDRS = Unified Parkinson Disease Rating Scale.

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Appendix 1: Specific Drug Information

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use INGREZZA safely and effectively. See full prescribing information for INGREZZA.

INGREZZA™ (valbenazine) capsules, for oral use
Initial U.S. Approval: 2017

----------INDICATIONS AND USAGE----------
INGREZZA is a vesicular monoamine transporter 2 (VMAT2) inhibitor indicated for the treatment of adults with tardive dyskinesia. (1)

----------DOSAGE AND ADMINISTRATION----------
- The initial dose is 40 mg once daily. After one week, increase the dose to the recommended dose of 80 mg once daily. (2.1)
- Can be taken with or without food. (2.1)
- The recommended dose for patients with moderate or severe hepatic impairment is 40 mg once daily. (2.2)
- Consider dose reduction based on tolerability in known CYP2D6 poor metabolizers. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
Capsules: 40 mg. (3)

----------CONTRAINDICATIONS----------
None. (4)

----------WARNINGS AND PRECAUTIONS----------
- Somnolence: May impair patient's ability to drive or operate hazardous machinery. (5.1)
- QT Prolongation: May cause an increase in QT interval. Avoid use in patients with congenital long QT syndrome or with arrhythmias associated with a prolonged QT interval. (5.2)

----------ADVERSE REACTIONS----------
Most common adverse reaction (≥5% and twice the rate of placebo): somnolence. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Neurocrine Biosciences, Inc. at 877-641-3461 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
Dose adjustments due to drug interactions (2.3, 7):

Factors	Dose Adjustments for INGREZZA
Use of MAOIs with INGREZZA	Avoid concomitant use with MAOIs.
Use of strong CYP3A4 inducers with INGREZZA	Concomitant use is not recommended.
Use of strong CYP3A4 inhibitors with INGREZZA	Reduce dose to 40 mg.
Use of strong CYP2D6 inhibitors with INGREZZA	Consider dose reduction based on tolerability.

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: May cause fetal harm. (8.1)
- Lactation: Advise not to breastfeed. (8.2)
- Renal Impairment: No dosage adjustment is necessary for patients with mild to moderate renal impairment. Use is not recommended in patients with severe renal impairment. (8.8)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 04/2017

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use AUSTEDO safely and effectively. See full prescribing information for AUSTEDO.

AUSTEDO™ (deutetrabenazine) tablets, for oral use
Initial U.S. Approval: 2017

WARNING: DEPRESSION AND SUICIDALITY
See full prescribing information for complete boxed warning.

- Increases the risk of depression and suicidal thoughts and behavior (suicidality) in patients with Huntington's disease (5.2)
- Balance risks of depression and suicidality with the clinical need for treatment of chorea when considering the use of AUSTEDO (5.2)
- Monitor patients for the emergence or worsening of depression, suicidality, or unusual changes in behavior (5.2)
- Inform patients, caregivers and families of the risk of depression and suicidality and instruct to report behaviors of concern promptly to the treating physician (5.2)
- Exercise caution when treating patients with a history of depression or prior suicide attempts or ideation (5.2)
- AUSTEDO is contraindicated in patients who are suicidal, and in patients with untreated or inadequately treated depression (4, 5.2)

INDICATIONS AND USAGE

AUSTEDO is a vesicular monoamine transporter 2 (VMAT2) inhibitor indicated for the treatment of chorea associated with Huntington's disease (1)

DOSAGE AND ADMINISTRATION

- The starting dose is 6 mg once daily. Titrate up at weekly intervals by 6 mg per day to a tolerated dose that reduces chorea, up to a maximum recommended daily dosage of 48 mg (24 mg twice daily) (2.1)
- Administer total daily dosages of 12 mg or above in two divided doses (2.1)
- Administer with food (2.1)
- Swallow tablets whole; do not chew, crush, or break (2.1)
- If switching patients from tetrabenazine, discontinue tetrabenazine and initiate AUSTEDO the following day. See full prescribing information for recommended conversion table (2.2)
- Maximum recommended dosage of AUSTEDO in poor CYP2D6 metabolizers is 36 mg per day (i.e., 18 mg twice daily) (2.4, 8.7)

DOSAGE FORMS AND STRENGTHS

Tablets: 6 mg, 9 mg, and 12 mg (3)

CONTRAINDICATIONS

- Suicidal, or untreated/inadequately treated depression (4, 5.2)
- Hepatic impairment (4, 8.6, 12.3)
- Taking MAOIs, reserpine, or tetrabenazine (XENAZINE®) (4, 7.2, 7.3, 7.7)

WARNINGS AND PRECAUTIONS

- Neuroleptic Malignant Syndrome (NMS): Discontinue if this occurs (5.3, 7.4)
- Akathisia, agitation, restlessness, and parkinsonism: Reduce dose or discontinue if this occurs (5.4, 5.5)
- Sedation/somnolence: May impair the patient's ability to drive or operate complex machinery (5.6)

ADVERSE REACTIONS

Most common adverse reactions (>8% of AUSTEDO-treated patients and greater than placebo) were: somnolence, diarrhea, dry mouth, and fatigue (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals at 1-888-483-8279 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Concomitant use of strong CYP2D6 inhibitors: Maximum recommended dose of AUSTEDO is 36 mg per day (18 mg twice daily) (2.3, 7.1)
- Alcohol or other sedating drugs: May have additive sedation and somnolence (7.5)

USE IN SPECIFIC POPULATIONS

Pregnancy: Based on animal data, may cause fetal harm (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 4/2017

Appendix 2: Medline Search Strategy

Database(s): **Ovid MEDLINE(R)** 1946 to November Week 1 2017

Search Strategy:

#	Searches	Results
1	deutetrabenazine.mp.	12
2	valbenazine.mp.	18
3	tetrabenazine.mp. or Tetrabenazine/	1495
4	limit 3 to (english language and humans)	619
5	limit 4 to (clinical trial, phase iii or clinical trial, phase iv or guideline or meta analysis or practice guideline or randomized controlled trial or systematic reviews)	41

Vesicular Monoamine Transporter 2 (VMAT2) Inhibitors

Goal(s):
- Promote safe use of VMAT2 inhibitors in adult patients.
- Promote use that is consistent with medical evidence and product labeling.

Length of Authorization:
- Initial: Up to 2 months
- Renewal: Up to 12 months

Requires PA:
All VMAT2 inhibitors

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code. Go to #2	
2. Is the treatment diagnosis for an OHP-funded condition and is the requested treatment funded by the OHP for that condition? Note: Treatments referenced on an unfunded line of the prioritized list are not funded by the OHP.	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by OHP
3. Is the request for continuation of vesicular monoamine transporter 2 (VMAT2) inhibitor therapy previously approved (patient has completed 2-month trial)?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4

Approval Criteria		
4. Is the request for tetrabenazine or deutetrabenazine in a patient 18 and older with a diagnosis of chorea as a result of Huntington's disease?	**Yes:** Go to #5	**No:** Go to #6
5. Does the patient have a baseline total maximal chorea score of 8 or higher?	**Yes:** Go to #9 Document baseline score: _____	**No:** Pass to RPh. Deny; medical appropriateness
6. Is the request for valbenazine or deutetrabenazine in a patient 18 and older with a diagnosis of tardive dyskinesia?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Is there documentation that the patient has been diagnosed with Schizophrenia, Schizoaffective Disorder, or a Mood Disorder?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Has the prescriber documented the patient's current Abnormal Involuntary Movement Scale (AIMS) dyskinesia score is $\geq$ 10 on items 1-7?	**Yes:** Go to #9 Document baseline score: _____	**No:** Pass to RPh. Deny; medical appropriateness
9. Is the medication being prescribed by, or in consultation with, a neurologist or psychiatrist?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness
10. Has it been determined that the patient does not have uncontrolled depression or at risk of violent or suicidal behavior?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness
11. Has the patient recently been evaluated and determined to not be at risk for a prolonged QT interval?	**Yes:** Approve for 2 months. Documented evidence of benefit required for renewal consideration (see renewal criteria).	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 11/2017
Implementation: TBD

Renewal Criteria		
1. Is the request for a renewal of valbenazine or deutetrabenazine in a patient with tardive dyskinesia?	**Yes:** Go to #2	**No:** Go to #3
2. Has the patient been taking the requested VMAT2 inhibitor for >2 months and has there been documented evidence of improvement by a reduction in AIMS dyskinesia score (items 1-7) by at least 50%?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the request for tetrabenazine or deutetrabenazine in a patient with chorea as a result of Huntington's disease?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Has the patient been taking the requested VMAT2 inhibitor for >2 months and has there been documented evidence of improvement in total maximal chorea score of at least 2 points from baseline?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Has it been determined that the mental status of the patient is stable and there is no indication of uncontrolled depression or risk of violent or suicidal behavior?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 11/2017 (KS)
Implementation: TBD