Public Testimony for (State) Medicaid-Austedo® (deutetrabenazine)

Topic	Austedo® (deutetrabenazine)
Introduction	• Good day, my name is Rochelle Yang I am with Teva Pharmaceuticals Field Value Evidence & Outcomes Team. I am here to provide information about Austedo® (deutetrabenazine) tablets.
Burden of Disease	• Tardive dyskinesia (TD) is a delayed-onset and often irreversible hyperkinetic movement disorder, caused by long-term exposure to dopamine receptor blocking agents (DRBAs), including first and second generation antipsychotics, used for the treatment of mental illnesses, including bipolar disorder, major depressive disorder, and schizophrenia [8,9,17] • TD tends to persist for years or decades in the majority of patients, even after elimination of the offending drug[10] and is associated with worse health-related quality of life (HRQoL) and social withdrawal[17] • Huntington's Disease (HD) is an inherited neurological disorder characterized by a triad of symptoms including, cognitive decline, psychiatric symptoms and movement disorders [11], such as hyperkinetic movements known as chorea.
Please refer to the full prescribing information for Austedo®.	
Guidelines[19]	• APA recommends (1B) that patients who have moderate to severe or disabling tardive dyskinesia associated with antipsychotic therapy be treated with a reversible inhibitor of the vesicular monoamine transporter 2 (VMAT2). • Potential modifications to stable antipsychotic regimens should be weighed against the possibility of recurrent symptoms or relapse. • Anticholinergic medications do not improve and may even worsen tardive dyskinesia in addition to producing significant side effects. • In general, deutetrabenazine or valbenazine is preferred over tetrabenazine because of the greater evidence base supporting their use • Regular assessment through clinical examination or through the use of a structured evaluative tools; however when using scales such as the AIMS or the DISCUS, it should be noted that there is no specific score threshold that suggests a need for intervention
Indication	• Austedo® is a vesicular monoamine transporter 2 (VMAT2) inhibitor and is the only FDA approved therapy indicated in adults for treatment of TD and chorea associated with Huntington's disease[1], (granted orphan drug designation for HD-chorea)[22]
Structure and MOA	• Austedo® is the first deuterated drug to receive FDA approval; deuterium substitution results in a differentiated pharmacokinetic profile allowing for lower dosing, less frequent administration and reduced fluctuations in plasma drug concentrations versus tetrabenazine[18] • The mechanism of action is believed to be reversible modulation of monoamine transport (dopamine, serotonin, norepinephrine, and histamine) into synaptic vesicles, resulting in a reduction and depletion of monoamine stores.[1]
Warnings/ Contraindications	• A boxed warning exists for the use of Austedo® in patients with Huntington's disease however this warning is not associated with patients using Austedo® for Tardive Dyskinesia [1] • In December 2020, Austedo® labeling was updated to reflect the following: at the maximum recommended dose, Austedo® does not prolong the QT interval to any clinically relevant extent. Labeling no longer requires assessment of the QTc interval before and after increasing the dose of Austedo® to greater than 24 mg, in patients who are at risk of QT prolongation, or in patients using other drugs known to prolong QTc.[1] • Please refer to the prescribing information for additional information and complete safety information[1].

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Common Adverse Reactions	• In TD patients, the most common adverse reactions occurring in greater than 3% of Austedo®-treated patients and greater than placebo were nasopharyngitis and insomnia. [1] • In Patients with Huntington's Disease, the most common adverse reactions occurring in greater than 8% of Austedo®-treated patients were somnolence, diarrhea, dry mouth, and fatigue. [1] • Compared with tetrabenazine, deutetrabenazine was associated with significantly lower risk of moderate to severe adverse events and neuropsychiatric AEs including agitation, akathisia, depression/agitated depression, drowsiness/somnolence, insomnia, and parkinsonism ($p<0.05$).[16]
Dosing and Administration	• Austedo® provides response driven dosing options with 6mg, 9mg, and 12mg oral tablets • In an analysis based on real world data, the mean daily dose of Austedo® was determined to be 25.6 mg and 28.5 mg in TD and HD patients, respectively.[6]
Clinical Trial Experience Exposure	• The efficacy for Austedo® was established in three 12-week, randomized, double-blind, placebo-controlled, multi-center trials (FIRST-HD, ARM-TD and AIM-TD)[2,4,7] conducted in 505 ambulatory patients (90 HD & 415 TD).
First-HD Pivotal Trial[4]	• In the First-HD trial, 90 patients with HD were randomized to receive deutetrabenazine (n = 45) or placebo (n = 45), titrated to optimal dose level over 8 weeks and maintained for 4 weeks, followed by a 1-week washout. The primary efficacy endpoint was the Total Maximal Chorea (TMC) Score, an item of the Unified Huntington's Disease Rating Scale (UHDRS). • From baseline to maintenance therapy, the percentage change in the TMC score improved by –37% (95%CI, –44 to –30) in the deutetrabenazine group vs –16% (95%CI, –23 to –9) improvement in the placebo group, for a between-group difference of –21% (95% CI, –30% to –11%; P<0.001) • In addition to change in TMC score, twenty-three patients (51%) in the deutetrabenazine group reported treatment success by the PGIC scale, whereas 9 patients (20%) in the placebo group reported treatment success, for a treatment difference of 31.1 (95% CI, 12.4-49.8; P = .002). Similarly 19 patients (42%) in the deutetrabenazine group reported treatment success using the CGIC scale vs 6 patients (13%) in the placebo group, for a treatment difference of 28.9 (95% CI, 11.4 to 46.4; P = .002). • Other secondary endpoints include the SF-36 physical functioning subscore, which improved by 0.7 (95%CI,–2.0 to 3.4) for deutetrabenazine, and worsened by –3.6 (95%CI, –6.4 to –0.8) for the placebo group, for a treatment difference of 4.34 (95%CI,0.4 to 8.3; P=0.03). There was no significant difference in improvement in Berg Balance Test. The mean between-group difference was 1.0 (95% CI, –0.3 to 2.3; P=0.14).
Aim to Reduce Movements in Tardive Dyskinesia (ARM-TD) [7]	• ARM-TD was a 12-week, double-blind randomized, placebo-controlled, flexible-dose trial and included 117 patients with moderate to severe TD. The primary endpoint was the change in Abnormal Involuntary Movement Scale (AIMS) score from baseline to week 12 • For the primary endpoint, Austedo® significantly reduced AIMS scores from baseline to week 12 compared with placebo (least-squares [LS] mean [standard error (SE)]: -3.0 [0.45] vs -1.6 [0.46], p=0.019; treatment difference -1.4 [0.60], 95% confidence interval [CI] -2.6 to -0.2). Improvement in AIMS score was different between the deutetrabenazine and placebo groups by week 4 with a treatment effect of -1.5 (95% CI -2.6 to -0.4, p= 0.007). • For secondary endpoints (CGIC and PGIC treatment success; CDQ-24 mean change from baseline), numerical results favored Austedo® over placebo, although differences between groups were not statistically significant.
Addressing Involuntary Movements in Tardive Dyskinesia (AIM-TD[2]	• AIM-TD was a 12-week double-blind, randomized, placebo-controlled, phase 3 fixed-dose trial. 298 patients with TD were randomized to receive placebo (n=74), or fixed doses of Austedo® 12 mg/day (n=75), 24 mg/day (n=74), or 36 mg/day (n=75) for 12 weeks. • Austedo® 24 mg/day and 36 mg/day doses were associated with significant reduction from baseline AIMS (–3·4 points (SE 0.53) in 36 mg patients; difference vs placebo –1.7 points [SE 0.70], 95% CI –3.06 to –0.31; p=0·017) and –3.2 points (0·52) in the 24 mg/day group (–1.5 points [0·69], –2.82 to –0.10; p=0·036), versus –1.7 points (0·46) in the placebo group. The 12 mg group, –2.0 points (SE 0.46), versus placebo (difference –0.2 points [SE 0.65], was not statistically significant 95% CI –1.50 to 1.07; p=0·745). • The proportion of patients who had at least a 50% improvement in AIMS score was greater in the Austedo® 24 mg/day group (35%; odds ratio [OR] 3.96, 95% CI 1.46–10.72; p=0·005) and the 36 mg/day group (33%; 3.80, 1.40–10.36; p=0·007) than in the placebo group (12%)

	• Treatment success on the CGIC, defined as "much improved" or "very much improved", was achieved at week 12 in 24 (44%) patients in the deutetrabenazine 36 mg/day group (p=0.059), 24 (49%) patients in the 24 mg/day group (p=0.014), and 17 (28%) patients in the 12 mg/day group (p=0.734), compared with 15 (26%) patients in the placebo group.
ARM-TD and AIM-TD Pooled Data	• In a pooled analysis of Austedo®-treated patients in both pivotal trials, Austedo® was associated with significant reduction in AIMS score and significantly greater attainment of treatment success compared with placebo[12-14] • The reduction in AIMS score was significantly greater among pooled Austedo®-treated patients from AIM-TD (24 mg/day and 36 mg/day doses) and ARM-TD than among pooled placebo-treated patients (deutetrabenazine -3.3 v. placebo -1.5, P<0.001) [12] • The percentage of patients attaining CGIC & PGIC treatment success were significantly greater among pooled Austedo®-treated patients than among those who received placebo (CGIC OR 2.12, *P*=0.005)[13] (PGIC OR 1.81, *P*=0.026)[14] • Rates of overall AEs, study discontinuations, dose reductions, and dose suspensions occurred at similar low rates between the deutetrabenazine and placebo groups [12-14]
Long-term Safety	• A combined number of 462 total patients (343 RIM-TD and 119 ARC-HD) enrolled in their respective extension studies. [5,15] • In the ARC-HD Study, deutetrabenazine was well tolerated across both cohorts and EAIRs of treatment Related AEs were lower than those in First-HD with a follow-up period of up to 171 weeks [5] • In the RIM-TD Study, deutetrabenazine was generally well tolerated across 723 patient-years of exposure through 3 years [15]
RIM-TD[15]	• 3-year Open-Label Extension study to evaluate the long-term safety and efficacy of Austedo® in patients with TD. • 343 patients were titrated using response-driven dosing, up to 48mg/day (36mg/day for patients receiving a strong CYP 2D6 inhibitor). • Patients treated with Austedo® experienced sustained improvements in AIMs score over time with a mean change in AIMS score of -6.6 (±SE 0.37) at week 145. • The percentage of patients who achieved ≥50% and ≥70% improvements in AIMS score from baseline increased over time, with the majority of patients (67%) experiencing ≥50% improvement by Week 145. 117 (73%) patients achieved treatment success based on CGIC. • Deutetrabenazine was generally well tolerated across 723 patient-years of exposure through Week 158.
ARC-HD[5]	• Evaluated safety, tolerability and pharmacokinetics of Austedo® in patients switching from tetrabenazine to Austedo®, as well as safety and tolerability of long-term treatment with Austedo®. • 119 patients (n=82, Rollover cohort; n=37, Switch cohort) were enrolled and 100 (84%) patients completed ≥ 1 year of treatment; mean duration of follow-up was 119 (SD 48) weeks. • The EAIRs of patients reporting any AEs, serious AEs and AEs leading to withdrawal were similar between the rollover and switch cohorts. EAIRs were similar to the rates observed in the Austedo® and placebo groups in First-HD. • Generally, deutetrabenazine was well tolerated across both cohorts and EAIRs of treatment related AEs were lower than those in First-HD • The most common AEs possibly related to study drug were somnolence, depression, anxiety, insomnia, and akathisia. • From baseline to Week 8, mean TMC and TMS scores decreased in both cohorts. Mean TMC score changed minimally from Week 8 to Week 132 (or end of treatment), and mean TMS score increased during the same period. Upon withdrawal of deutetrabenazine, mean (SD) TMC scores increased by 4.4 (3.7) units compared to end of treatment.
Real World Evidence[20]	Real-World Adherence to Deutetrabenazine or Valbenazine Among Patients With Tardive Dyskinesia • Retrospective study using insurance claims data from the Symphony Health Solutions (SHS) Integrated Dataverse (May 2017- May 2019) for patients (age 18 to 65) with a diagnosis of TD and ≥1 prescription for deutetrabenazine (DTBZ) or valbenazine (VBZ) • Approximately 30% of patients in both groups discontinued therapy within the first 30 days from the index date

	• After the 30 day titration period: a greater proportion of patients were adherent in the deutetrabenazine vs valbenazine cohorts, but the difference was not significant (53.3% vs 50.9%, P=0.6098) • The proportion of patients who discontinued their index treatment during the 6-month follow-up period starting from 30 days after the index date was also not significantly different between DTBZ and VBZ cohorts (1 month, 5.4% vs 8.0%; 3 months, 22.3% vs 27.6%; 6 months, 36.2% vs 40.6%; log-rank P=.227)
On-going clinical development	• The safety and efficacy of Austedo® is currently being investigated for treatment of dyskinesia in cerebral palsy in children and adolescents in a phase III randomized controlled trial. (NCT03813238)
Special considerations	• I will remind the committee/board that, to date, no direct head-to-head trials of VMAT2 inhibitors have been conducted. Any indirect treatment comparison or cost-effectiveness analyses between deutetrabenazine and valbenazine should be interpreted cautiously.[21] • Due to relative lack of FDA approved treatments to treat TD or chorea in Huntington's disease, I respectfully ask the members of the committee to consider these data to enable preferred access of Austedo® in the state of _____.
	<u>References:</u> 1. Austedo® [package insert] Parsippany, NJ: Teva Pharmaceuticals USA, Inc.; Dec 2020. 2. Anderson KE et al. Deutetrabenazine for treatment of involuntary movements in patients with tardive dyskinesia (AIM-TD): a double-blind, randomized, placebo-controlled, phase 3 trial. Lancet Psychiatry. 2017 Aug;4(8):595-604 3. FDA Orphan Drug Designations and Approvals https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=383212 Date Designated November 5th, 2014. Accessed December 7th, 2021 4. Huntington Study Group, Effect of Deutetrabenazine on Chorea Among Patients With Huntington Disease: A Randomized Clinical Trial. JAMA. 2016 Jul 5;316(1):40-50 5. Frank S, et al. Long-Term Efficacy and Safety of Deutetrabenazine for Chorea in Huntington's disease: Results From the ARC-HD Open-Label Study. Presented at the Neuroscience Education Institute (NEI) MAX! Virtual Congress; November 5-8, 2020 6. Ayyagari et al. Real-World Deutetrabenazine Dosing Patterns in Patients with Huntington's disease or Tardive Dyskinesia. Presented at the International Congress of Parkinson's Disease and Movement Disorders (MDS) Virtual Congress; September 12-16, 2020 7. Fernandez HH et al.Randomized controlled trial of deutetrabenazine for tardive dyskinesia: The ARM-TD study. Neurology. 2017 May 23;88(21):2003-2010 8. Kouzam HR. Identification and management of tardive dyskinesia: A case series and literature review. Postgrad Med. J. 2015;127(7):726-37. 9. Lerner PP et al. Tardive dyskinesia (syndrome): Current concept and modern approaches to its management. Psychiatry Clin Neurosci. 2015;69(6):321-34. 10. Waln O et al. An update on tardive dyskinesia: from phenomenology to treatment. Tremor Other Hyperkinet Mov (N.Y.). 2013;3. 11. Jankovic, et al. Chorea associated with Huntington's disease: to treat or not to treat? 2014;29:1414-1418 12. Fernandez et al. Int Congress Parkinson's Dis and Mov Disord [Abstract #412]. 2017. 13. Fernandez et al. Int Congress Parkinson's Dis and Mov Disord [Abstract #404]. 2017 14. Fernandez et al. Int Congress Parkinson's Dis and Mov Disord [Abstract #407]. 2017 15. Hauser, et al, Long-Term Treatment With Deutetrabenazine Is Associated With Continued Improvement in Tardive Dyskinesia: Results From the Completed, 3-Year Open-Label Extension Study. Presented at the International Congress of Parkinson's Disease and Movement Disorders (MDS) Virtual Congress; September 12-16, 2020. 16. Claassen DO, Carroll B, De Boer LM, Wu E, Ayyagari R, Gandhi S, Stamler D. Indirect tolerability comparison of deutetrabenazine and tetrabenazine for Huntington disease. J Clin Mov Disord. 2017 Mar 1;4:3. doi: 10.1186/s40734-017-0051-5. 17. McEvoy J, Gandhi S, et. al. Effect of tardive dyskinesia on quality of life in patients with bipolar disorder, major depressive disorder, and schizophrenia. Quality of Life Research. 2019; 28:3303–3312.

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