Public Testimony for West Virginia Medicaid-Austedo™ (deutetrabenazine)

Topic	Austedo (deutetrabenazine)
Introduction	• Good day, my name is Fawad Malik I am the Sr. Mgr Medical Outcomes Liaison with Teva Pharmaceuticals.
Burden of Disease	• Tardive dyskinesia (TD) is a delayed-onset and potentially irreversible hyperkinetic movement disorder, which is caused by long-term exposure to neuroleptic agents (ie, dopamine receptor blocking agents (DRBAs)), most notably antipsychotics (FGAs and SGAs)[9,10,11] • Huntington's Disease (HD) is an inherited neurological disorder characterized by a triad of symptoms including, cognitive decline, psychiatric symptoms and movement disorders [12], such as hyperkinetic movements known as chorea.
Please refer to the full prescribing information for Austedo.	
Indication	• Austedo is the only FDA approved therapy for both the treatment of tardive dyskinesia (TD) and chorea associated with Huntington's disease[1] , (granted orphan drug designation for HD-chorea)[4]
Structure and MOA	• Austedo is the first FDA approved therapy using deuterated technology • Austedo, which leverages Teva's deuterium technology, enables a differentiated pharmacokinetic profile compared with tetrabenazine. • By reducing mean peak plasma concentrations (Cmax) while maintaining comparable drug exposure, there is the potential for decreased dosing and dosing frequency. [13] • The mechanism of action is believed to be related to its effect as a reversible modulator of monoamines (such as dopamine, serotonin, norepinephrine, and histamine) from nerve terminals, resulting in decreased uptake of monoamines into synaptic vesicles and depletion of monoamine stores.[1]
Warnings/ Contraindications	• A boxed warning exists for the use of Austedo specifically in patients with Huntington's disease.[1] • This warning is not associated with Tardive Dyskinesia patients using Austedo. • Please refer to the prescribing information for additional information regarding the boxed warning and complete safety information.
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 fatique. [1]
Dosing and Administration	• Austedo provides flexible dosing options with 6mg, 9mg, and 12mg oral tablets • In an analysis based on real world data, the median (mean) daily dose of Austedo was determined to be 24 mg and 36 mg (27.6mg & 33.7 mg) in TD and HD patients, respectively.[7] • According to CMS Utilization Data 2Q2018-1Q2019, the average dose of Austedo used was 22 mg/day (30 day month) [18]
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)[2,5,8] conducted in 505 ambulatory patients (90 HD & 415 TD)
First-HD Pivotal Trial[5]	• In addition to change in Total Maximal Chorea Score (TMC), 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). • Additional prespecified efficacy endpoints include the Unified Huntington's Disease Rating Scale (UHDRS) total motor score, which improved by –7.4 (95%CI, –9.1 to –5.6) in the deutetrabenazine group vs –3.4 (95%CI, –5.1 to –1.6) in the placebo group ,for a mean between-group difference of –4.0 points (95% CI, –6.5 to –1.5; P = 0.002). • From baseline to maintenance therapy, the percentage change in the total maximal chorea 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).

ARM-TD[8]	• 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 (PGIC treatment success; CDQ-24 mean change from baseline), numerical results favored Austedo over placebo, although differences between groups were not statistically significant. • The efficacy of Austedo was maintained in the patient subgroup with baseline AIMS scores ≥6: Austedo AIMs score [SE] vs. Placebo (3.4 [0.48] vs 1.9 [0.51], p = 0.027; treatment difference -1.5 [0.67], 95% CI -2.8 to -0.2). CGIC treatment difference in this subpopulation was 17.4% compared with 7.9% in the modified ITT cohort (95% CI −2.2 to 35.3)
AIM-TD[2]	• 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. • 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%) • Austedo 24 mg/day and 36 mg/day doses were associated with significant reduction from baseline AIMS score in patients on concomitant DRBAs at baseline (–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; In 12 mg group, –2.0 points (SE 0.46), with no significant difference versus placebo (difference –0.2 points [SE 0.65], 95% CI –1.50 to 1.07; p=0·745).
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[14-16] • 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) [14] • The percentage of patients attaining CGIC treatment success was significantly greater among pooled Austedo-treated patients than among those who received placebo (OR 2.12, *P*=0.005)[15] • The percentage of patients attaining PGIC treatment success was significantly greater among pooled Austedo-treated patients than among those who received placebo (OR 1.81, *P*=0.026)[16] • Rates of overall AEs, study discontinuations, dose reductions, and dose suspensions occurred at similar low rates between the deutetrabenazine and placebo groups [14-16]
Long-term Safety	• A combined number of 423 total patients (304 RIM-TD and 119 ARC-HD) enrolled in their respective extension studies. [3,6] • Overall, the safety profile of long-term Austedo treatment is consistent with that reported in the parent studies, indicating no new safety signals with 54 weeks of treatment (ARC-HD) in HD patients[6] • In TD patients up to 145 weeks of treatment, exposure-adjusted incidence rates (EAIRs) of AEs were comparable to or lower than those observed with short-term Austedo and placebo treatment. [17]
RIM-TD[17]	• Ongoing 3-year Open-Label Extension study to evaluate the long-term safety and efficacy of Austedo in patients with TD. • As of July 2018, 78 participants completed the study. Interim analysis up to week 145. • Change in AIMS score from baseline decreased over time in patients remaining in the study. Mean (SE) change in AIM score from baseline was -7.0 (0.57) at week 145. • Three-quarters of all patients experienced a ≥50% improvement in AIMS score. >80% of patients were a treatment success based on the CGIC score.
ARC-HD[6]	• 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 98 patients completed 54 weeks of Austedo treatment. • The EAIRs of patients reporting any AEs, serious AEs and AEs leading to withdrawal were similar

	between the rollover and switch cohorts. EAIRs were smiliar to the rates observed in the Austedo and placebo groups in First-HD. • At Week 54, Total Maximal Chorea Score (TMC) was reduced by 4.1 and 3.0 units in the Rollover and Switch cohorts, respectively.
On-going clinical development	• The safety and efficacy of Austedo is currently being investigated in Tourette Syndrome patients in 3 phase III randomized controlled trials. (NCT03452943, NCT03571256, NCT03567291) • 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	• Due to the relative lack of FDA approved treatments available to treat tardive dyskinesia or chorea in Huntington's Disease, I ask the members of the committee to consider the data that I have presented and allow for TD and HD patients to continue to have access to Austedo.
	References: 1. Austedo [package insert] North Wales, PA:Teva Pharmaceuticals USA, Inc; July 2019.. 2. Anderson KE et al. Deutetrabenazine for treatment of involuntary movements in patients with tardive dyskinesia (AIM-TD): a double-blind, randomised, placebo-controlled, phase 3 trial.Lancet Psychiatry. 2017 Aug;4(8):595-604 3. Anderson KE, et al. Deutetrabenazine for the treatment of tardive dyskinesia: results from an open-label, long-term study. Poster presented at: The American Psychiatric Association 2017 Annual Meeting; May 20-14, 2017; San Diego, CA. P7-009. 4. Teva Media Latest News http://www.tevapharm.com/news/teva_announces_fda_approval_of_austedo_deutetrabenazine_tablets_for_the_treatment_of_chorea_associated_with_huntington_s_disease_04_17.aspx Published April 3, 2017. Accessed May 8, 2017. 5. 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 6. Frank S et al. The long-term safety of deutetrabenazine for chorea in Huntington Disease: updated safety results from the ARC-HD trial. Poster presented at: The International Congress of Parkinson's Disease and Movement Disorders; June 4-8, 2017; Vancouver, BC. 7. Teva Data on File as of February 2018; Data provided by Teva Shared Solutions via IQVIA. N=1641. 8. Fernandez HH et al.Randomized controlled trial of deutetrabenazine for tardive dyskinesia: The ARM-TD study.Neurology. 2017 May 23;88(21):2003-2010 9. Kouzam HR. Identification and management of tardive dyskinesia: A case series and literature review. Postgrad Med. J. 2015;127(7):726-37. 10. Lerner PP et al. Tardive dyskinesia (syndrome): Current concept and modern approaches to its management. Psychiatry Clin Neurosci. 2015;69(6):321-34. 11. Waln O et al. An update on tardive dyskinesia: from phenomenology to treatment. Tremor Other Hyperkinet Mov (N.Y.). 2013;3. 12. Jankovic, et al.Chorea associated with Huntington's disease: to treat or not to treat? 2014;29:1414-1418 13. Auspex Pharmaceuticals Inc. Securities and Exchange Commission Form S-1 Registration Statement. 2013. 14. Fernandez et al. Int Congress Parkinson's Dis and Mov Disord [Abstract #412]. 2017. 15. Fernandez et al. Int Congress Parkinson's Dis and Mov Disord [Abstract #404]. 2017 16. Fernandez et al. Int Congress Parkinson's Dis and Mov Disord [Abstract #407]. 2017 17. Hauser H et al. Long-Term Treatment With Deutetrabenazine Is Associated With Continued Improvement in Tardive Dyskinesia (TD): Results From an Open-Label Extension Study. Presented at The American Academy of Neurology 2019 Annual Meeting. May 4–10, 2019, Philadelphia, Pennsylvania, USA 18. Teva Data on File, based on CMS utilization data 2Q2018-1Q2019.