

INTRODUCTION

- Huntington disease (HD) is a progressive neurodegenerative disorder characterized by motor dysfunction, cognitive decline, and neuropsychiatric disturbances (*Coppen and Roos 2017*).
 - Motor dysfunction in HD may include involuntary movements (eg, chorea, dystonia, and tics) and voluntary movements (eg, bradykinesia, apraxia, and motor impersistence) (*Austedo dossier 2017, Coppen and Roos 2017*).
 - Choreic movements are rapid and unpredictable contractions of the facial muscles, trunk, and extremities which vary in frequency, intensity, and amplitude (*Austedo dossier 2017, Suchowersky 2016a*).
 - Chorea is a defining symptom at the time of diagnosis and typically develops early in the clinical onset of HD. Symptoms may gradually worsen over time and plateau or decline in late stages (*Armstrong and Miyasaki 2012, Suchowersky 2016a*).
 - Dystonia is characterized by sustained or intermittent muscle contractions which lead to abnormal posture of the trunk and extremities. It is more commonly observed in advanced disease stages (*Coppen and Roos 2017*).
 - Motor function slowly deteriorates as HD progresses, and chorea may eventually be replaced by bradykinesia and parkinsonism in advanced stages of the disease (*Suchowersky 2016a, Suchowersky 2016b*).
- HD affects an estimated 1 in 7300 individuals (approximately 43,000 people) in the United States. It is a rare and fatal autosomal dominant genetic disorder associated with onset in early adulthood and death within 20 years of symptom onset. The prevalence of chorea is estimated to be 50% in patients with new-onset HD (*Austedo dossier 2017, Austedo FDA Summary Review 2017*).
- Since there are no curative or disease-modifying therapies available for HD, the focus of treatment is on symptom management and supportive care to optimize quality of life (*Suchowersky 2016b*).
 - The most commonly prescribed medications in HD are neuroleptics and antidepressants. Neuroleptics are traditionally used off-label in HD to treat psychiatric symptoms (eg, agitation, psychosis) and suppress chorea. While there is an abundance of clinical experience with neuroleptics in reducing chorea, there is a lack of robust evidence from clinical trials supporting their use (*Armstrong and Miyasaki 2012, Suchowersky 2016b*).
 - Prior to the approval of deutetrabenazine, tetrabenazine was the only product FDA-approved for the treatment of chorea due to HD. Both tetrabenazine and deutetrabenazine are vesicular monoamine transporter 2 (VMAT2) inhibitors.
 - Deutetrabenazine is a chemically modified form of tetrabenazine with deuterium substituted for hydrogen at specific positions. Deuterium is a naturally occurring heavy isotope of hydrogen which creates stronger bonds that extend the half-life of deutetrabenazine. Compared to tetrabenazine, deutetrabenazine reaches comparable systemic exposure with smaller doses, longer treatment intervals, and lower peak concentrations (*Austedo dossier 2017, Coppen and Roos 2017*).
 - Many clinicians utilize neuroleptics (eg, olanzapine, risperidone) in the first-line setting for chorea associated with HD due to additional benefits in sleep dysfunction, mood disturbances, and weight maintenance. For patients with HD, neuropsychiatric symptoms typically have a greater impact on quality of life and functional disability than the motor or cognitive symptoms of the disease (*Austedo dossier 2017, Coppen and Roos 2017*).
- Tardive dyskinesia (TD) is a movement disorder resulting from exposure to dopamine receptor antagonists (DRAs), including typical and atypical antipsychotics, antiemetics, and metoclopramide. Approximately 20% to 50% of patients receiving antipsychotics develop TD (*Fernandez et al 2017*).
 - TD is characterized by rapid, repetitive, stereotypic movements mostly involving the oral, buccal, and lingual area. Movements may include tongue thrusting, lip smacking or pursing, grimacing and chewing movements, piano-playing finger movements, trunk and pelvic thrusting, flexion/extension of the ankles or toes, irregular respirations, and various vocalizations (*Muller et al 2015, Rana et al 2013*).
 - Ingrezza (valbenazine), another VMAT2 inhibitor, was the first drug FDA-approved for TD in April 2017 (*Drugs@FDA 2017*). Deutetrabenazine received approval for this indication in August 2017.

- Advantages of valbenazine over deutetrabenazine include once-daily dosing (vs. twice daily dosing) and the absence of a boxed warning for depression and suicidality in patients with HD. Of note, valbenazine has not been studied in patients with HD (*Ingrezza prescribing information 2017*).
- Prior to the approval of valbenazine and deutetrabenazine, guidelines suggested clonazepam, amantadine, and tetrabenazine were likely effective when used off-label for TD (*Bhidayasiri et al 2013*). The guidelines have yet to be updated to include the FDA-approved treatment options for TD.
- While deutetrabenazine has been designated a new molecular entity and an orphan drug, it was approved through the 505(b)(2) pathway with tetrabenazine as the Reference Listed Drug (RLD) (*Austedo FDA Summary Review 2017*).
 - The FDA issued a Complete Response Letter (CRL) for deutetrabenazine on May 27, 2016, which cited inadequate pharmacology studies identifying all major human metabolites of deutetrabenazine. The manufacturer was required to demonstrate that all major metabolites of deutetrabenazine were the same as those of tetrabenazine in order to bridge the nonclinical studies conducted for the RLD (*Austedo FDA Summary Review 2017*).
- Medispan class: Psychotherapeutic and Neurological Agents – Misc.; Movement Disorder

INDICATIONS

- Deutetrabenazine is indicated for chorea associated with HD and for TD in adults (*Austedo prescribing information 2017*).
- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Huntington Disease (HD)

- The approval of deutetrabenazine was supported by the First-Time Use of Austedo in HD (First-HD) study conducted by the Huntington Study Group (HSG). The Phase 3, double-blind, multicenter, randomized controlled trial compared deutetrabenazine with placebo for 12 weeks, followed by a 1-week washout in 90 adults with HD (*HSG 2016*).
 - The study included patients with a Unified Huntington's Disease Rating Scale (UHDRS) total maximal chorea (TMC) score of at least 8 at baseline and a UHDRS total functional capacity score of at least 5 at screening.
 - The UHDRS is a widely accepted scale that has undergone extensive reliability and validity testing in HD. The TMC score ranges from 0 to 28, with higher scores indicating more severe chorea (*Coppen and Roos 2017, Geschwind and Paras 2016*).
 - Patients with untreated psychiatric illness, history of suicidal thoughts, prolonged QT interval, hepatic impairment, renal impairment, and dysphagia were excluded from the trial.
 - The primary endpoint was the change from baseline in UHDRS-TMC score; results for efficacy endpoints are summarized in **Table** below.
 - The placebo-adjusted mean change from baseline in TMC with deutetrabenazine was -2.5 points (95% confidence interval [CI], -3.7 to -1.3; $p < 0.001$).
 - In the deutetrabenazine group, the mean TMC scores improved by -4.4 points from 12.1 (95% CI, 11.2 to 12.9) to 7.7 (95% CI, 6.5 to 8.9) over 12 weeks. In the placebo group, mean TMC scores improved by -1.9 points from 13.2 (95% CI, 12.2 to 14.3) to 11.3 (95% CI, 10.0 to 12.5).
 - Four secondary endpoints were assessed hierarchically in the following order: Patient Global Impression of Change (PGIC), Clinical Global Impression of Change (CGIC), 36-Item Short Form (SF-36) physical functioning subscale score, and Berg Balance Test (BBT). For the PGIC and CGIC, treatment success was defined as an answer of "much" or "very much" improved overall HD symptoms at Week 12.
 - The proportion of patients who reported treatment success on the PGIC was 31.1% greater with deutetrabenazine than placebo ($p = 0.002$).
 - The proportion of clinicians who reported treatment success on the CGIC was 28.9% greater with deutetrabenazine than placebo ($p = 0.002$).
 - The placebo-adjusted improvement in the SF-36 physical functioning subscale was 4.34 points with deutetrabenazine ($p = 0.03$).
 - BBT improvement observed with deutetrabenazine did not achieve statistical significance over placebo ($p = 0.14$).

- Additional pre-specified efficacy endpoints included the change in UHDRS total motor score (TMS) and the percentage change in TMC score. The TMS assesses all of the motor symptoms of HD (eg, chorea, dystonia, rigidity, bradykinesia), with higher scores indicating more severe motor impairment (*Austedo dossier 2017*).
 - The placebo-adjusted mean change from baseline in TMS with deutetrabenazine was -4.0 points (95% CI, -6.5 to -1.5; p = 0.002).
 - The placebo-adjusted percentage change from baseline in TMC with deutetrabenazine was -21% (95% CI, -30% to -11%; p < 0.001).
- In the First-HD study, the incidence of overall, psychiatric, and nervous system treatment-emergent adverse events (TEAEs) was similar between the deutetrabenazine and placebo groups.
 - While AEs were generally mild to moderate, AEs resulted in dose reductions for 3 patients (6.7%) in each group. Serious AEs resulted in drug suspension for 1 patient (2.2%) in each group.
 - Somnolence and diarrhea were reported more frequently with deutetrabenazine than with placebo.

Table 1. First-HD Study Efficacy Results

Endpoint	DTBZ (n=45)	Placebo (n=45)	Difference (95% CI)	p-value
Primary Endpoint				
TMC Score*, LS mean (95% CI)	-4.4 (-5.3 to -3.6)	-1.9 (-2.8 to -1.1)	-2.5 (-3.7 to -1.3)	< 0.001
Secondary Endpoints				
PGIC Treatment Success†, n (%)	23 (51)	9 (20)	31.1 (12.4 to 49.8)	0.002
CGIC Treatment Success†, n (%)	19 (42)	6 (13)	28.9 (11.4 to 46.4)	0.002
SF-36 Physical Functioning Score*, LS mean (95% CI)	0.7 (-2.0 to 3.4)	-3.6 (-6.4 to -0.8)	4.3 (0.4 to 8.3)	0.03
BBT Score*, LS Mean (95% CI)	2.2 (1.3 to 3.1)	1.3 (0.4 to 2.2)	1.0 (-0.3 to 2.3)	0.14
Additional Pre-Specified Endpoints				
UHDRS TMS*, LS Mean (95% CI)	-7.4 (-9.1 to -5.6)	-3.4 (-5.1 to -1.6)	-4.0 (-6.5 to -1.5)	0.002
TMC % Change*, LS Mean (95% CI)	-37 (-44 to -30)	-16 (-23 to -9)	-21 (-30 to -11)	< 0.001

Abbreviations: BBT, Berg Balance Test; CGIC, Clinical Global Impression of Change; CI, confidence interval; DTBZ, deutetrabenazine; LS, least squares; PGIC, Patient Global Impression of Change; TMC, total maximal chorea; TMS, total motor score; UHDRS, Unified Huntington Disease Rating Scale

*Change from baseline to end of maintenance therapy

†Treatment success at Week 12 was defined as “much improved” or “very much improved”

- The ongoing Alternatives for Reducing Chorea in HD (ARC-HD) study is a Phase 3, open-label, multicenter, long-term trial which evaluates the safety and efficacy of deutetrabenazine in 112 patients in 2 cohorts (*Austedo dossier 2017, Stamler 2016*).
 - The rollover cohort includes 75 patients from the First-HD study who underwent washout of deutetrabenazine or placebo. The switch cohort includes 37 patients previously on tetrabenazine who were switched overnight to deutetrabenazine at approximately half their previous tetrabenazine dose.
 - According to interim analyses, patients in the switch cohort demonstrated improved TMC from baseline with deutetrabenazine 8 weeks following conversion (-2.06 points; p = 0.0006). Improvements in TMC from baseline were also observed in the rollover cohort at Week 2 (-1.9; p < 0.0001; n = 58) and maintained through Week 28 (-4.4; p = 0.0055; n = 14). Common TEAEs included somnolence, falls, depression, and insomnia.

Tardive Dyskinesia (TD)

- The safety and efficacy of deutetrabenazine was established in the ARM-TD and AIM-TD trials, which were 12-week double-blind, placebo-controlled, multicenter, randomized controlled trials. Both studies evaluated the change from baseline in items 1 to 7 of the Abnormal Involuntary Movement Scale (AIMS) score as the primary efficacy endpoint. The AIMS total score ranges from 0 to 28, and a decreased score indicates improvement (*Anderson et al 2017, Fernandez et al 2017*).
 - The Phase 2/3 ARM-TD study randomized 117 adults with moderate to severe TD to receive deutetrabenazine titrated to an optimal dose or placebo. The mean dose of deutetrabenazine at the end of titration was 38.8 mg/day.

Data as of September 11, 2017 KAL/JD

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Significant reductions in TD were observed in patients who received deutetrabenazine compared to placebo (Fernandez *et al* 2017).

- The LS mean AIMS score improved by -3.0 points in the deutetrabenazine group vs. -1.6 points in the placebo group (treatment difference -1.4; 95% CI, -2.6 to -0.2; p = 0.019).
 - Secondary endpoints included proportion of patients who experienced treatment success at week 12 on the CGIC and PGIC. Although CGIC and PGIC results were numerically higher for the deutetrabenazine group, the difference was not statistically significant.
 - The rates of AEs were similar between the deutetrabenazine and placebo groups, including depression and suicidal ideation.
- The Phase 3 AIM-TD study randomized 298 adults with TD to receive 1 of 3 fixed doses of deutetrabenazine (12, 24, or 36 mg/day) or placebo. Significant reductions in TD were observed in patients who received 24 or 36 mg of deutetrabenazine per day (Anderson *et al* 2017).
- The LS mean AIMS score improved by -3.3, -3.2, -2.1, and -1.4 points in the deutetrabenazine 36 mg/day, 24 mg/day, 12 mg/day, and placebo groups, respectively. The treatment difference was -1.9 points (95% CI, -3.09 to -0.79; p = 0.001) with deutetrabenazine 36 mg/day, -1.8 points (95% CI, -3.00 to -0.63; p = 0.003) with deutetrabenazine 24 mg/day, and -0.7 points (95% CI, -1.84 to 0.42; p = 0.217) with deutetrabenazine 12 mg/day.
 - The overall rate of AEs was similar between groups (51%, 44%, 49%, and 47% for deutetrabenazine 36 mg/day, 24 mg/day, 12 mg/day, and placebo, respectively).
 - Rates of depression, depressed mood, and suicidal ideation were low in all treatment arms; no dose-response relationship was detected.

CLINICAL GUIDELINES

Huntington Disease (HD)

- **American Academy of Neurology (AAN):** Pharmacologic treatment of chorea in HD (Armstrong and Miyasaki 2012)
 - Whether chorea requires treatment should be an individualized decision for providers and their patients with HD.
 - While some studies reported that improving chorea decreases disability or increases quality of life, other studies failed to show an association between chorea and functional decline in HD.
 - The impact of chorea on quality of life should be weighed against other issues, including mood disturbance, cognitive decline, AEs, and polypharmacy risks.
 - For HD chorea which requires pharmacological management, tetrabenazine (up to 100 mg/day), amantadine (300 to 400 mg/day), or riluzole (200 mg/day) are recommended.
 - Tetrabenazine likely provides very important antichoreic benefits, and riluzole 200 mg/day likely provides moderate benefits. The degree of benefit is unknown for amantadine.
 - Patients on tetrabenazine should be monitored for parkinsonism and depression/suicidality while patients on riluzole should be monitored for elevated liver enzymes.
 - Nabilone may be used for modest decreases in HD chorea, but there is insufficient evidence to recommend long-term use, particularly given concerns for abuse potential.
 - While neuroleptic agents (eg, clozapine) may be reasonable options with a historical suggestion of antichoreic benefit, formal recommendations are not provided due to a lack of studies with sufficient sample sizes and validated outcome measures.
 - The guideline has not been updated since the FDA approval of deutetrabenazine.

Tardive Dyskinesia (TD)

- **American Academy of Neurology (AAN):** Treatment of tardive syndromes (Bhidayasiri *et al* 2013)
 - Recommendations for tardive syndromes are summarized in Table 2 below.
 - The guideline has not been updated since the FDA approval of deutetrabenazine.

Table 2. Guideline Recommendations for Tardive Syndromes

Level of evidence	Recommendation
Level A (Recommendation must be done; high confidence in the evidence with high benefit and low risk)	None

<p>Level B (Recommendation should be done based on benefit/risk profile)</p>	<p>Recommended:</p> <ul style="list-style-type: none"> • Ginkgo biloba extract (EGb-761) for schizophrenia only • Clonazepam, for short-term use <p>Not recommended:</p> <ul style="list-style-type: none"> • Diltiazem
<p>Level C (Recommendation may or might be done; lowest recommendation level considered useful within the scope of practice)</p>	<p>Recommended:</p> <ul style="list-style-type: none"> • Amantadine for short-term use • Tetrabenazine <p>Not recommended:</p> <ul style="list-style-type: none"> • Galantamine
<p>Level U (Available evidence is insufficient to support or refute efficacy of an intervention)</p>	<ul style="list-style-type: none"> • Withdrawal of dopamine receptor blocking agents (DRBAs) • Switching from typical to atypical antipsychotics • Acetazolamide plus thiamine • Typical antipsychotics • Atypical antipsychotics • Electroconvulsive therapy • Reserpine or α-methyldopa • Bromocriptine • Anticholinergic agents (other than galantamine) • Biperiden discontinuation • Antioxidants (vitamin E, vitamin B6, melatonin, selegiline, yi-gan san) • Baclofen • Levetiracetam • Nifedipine • Buspirone • Botulinum toxin • Pallidal deep-brain stimulation

SAFETY SUMMARY

• Contraindications

- Deutetrabenazine is contraindicated in the following populations:
 - Patients with HD who are suicidal or have untreated or inadequately treated depression
 - Patients with hepatic impairment
 - Patients concurrently on monoamine oxidase inhibitors (MAOIs) or who have discontinued MAOI therapy within 14 days
 - Patients concurrently on reserpine or who have discontinued reserpine therapy within 20 days
 - Patients concurrently on tetrabenazine or valbenazine

• Warnings/precautions

- **Boxed warning:** Depression and suicidality in patients with HD
 - Patients with HD have a greater risk of depression and suicidality. Treatment with deutetrabenazine may further increase this risk in patients with HD.
 - In the First-HD study, suicidal ideation was reported by 2% of patients treated with deutetrabenazine, compared to no patients on placebo. Depression was reported by 4% of patients treated with deutetrabenazine.

- Patients on deutetrabenazine should be closely monitored for worsening depression, suicidal thoughts, or unusual changes in behavior.
- Additional key warnings and precautions for deutetrabenazine include:
 - Clinical worsening (eg, decline in mood, cognition, rigidity, and functional capacity) and AEs (eg, sedation, depression, parkinsonism, akathisia, restlessness, cognitive decline) in patients with HD
 - The effect of deutetrabenazine on chorea should be periodically weighed against possible AEs to determine whether continued therapy is necessary. The underlying chorea may improve over the course of the disease, decreasing the need for pharmacologic therapy.
 - Neuroleptic malignant syndrome (NMS) in patients with HD and TD
 - NMS is a potentially fatal syndrome associated with hyperpyrexia, muscle rigidity, altered mental status, and autonomic instability. While NMS has not been observed with deutetrabenazine, it has been observed with its RLD, tetrabenazine. Deutetrabenazine should be discontinued immediately if NMS occurs.
 - Akathisia, agitation, and restlessness in patients with HD and TD
 - In the First-HD study, akathisia, agitation, or restlessness was reported by 4% of patients treated with deutetrabenazine and 2% of patients on placebo. In patients with TD, 2% of patients treated with deutetrabenazine and 1% of patients on placebo experienced these events.
 - Parkinsonism in patients with HD
 - Patients with HD often develop rigidity as part of their underlying disease progression. Drug-induced parkinsonism may cause more functional impairment than untreated chorea. Patients who develop parkinsonism during treatment with deutetrabenazine should reduce their dosage.
 - Sedation and somnolence
 - Sedation is a common dose-limiting AE with deutetrabenazine. In the First-HD study, 11% of patients treated with deutetrabenazine reported somnolence compared with 4% of patients on placebo.
 - QTc prolongation
- **Adverse effects**
 - The most common AEs (incidence > 8% and greater than placebo) with deutetrabenazine in the First-HD study included somnolence, diarrhea, dry mouth, and fatigue.
 - The most common AEs (incidence > 3% and greater than placebo) with deutetrabenazine in the TD studies included nasopharyngitis and insomnia.
- **Drug Interactions**
 - Deutetrabenazine is contraindicated in patients taking MAOIs, reserpine, tetrabenazine, or valbenazine.
 - Strong cytochrome P450 (CYP) 2D6 inhibitors increase the systemic exposure to metabolites of deutetrabenazine.
 - Concurrent use of tetrabenazines with neuroleptic drugs (ie, dopamine antagonists, antipsychotics) may increase risk for parkinsonism, NMS, and akathisia.
 - Concomitant use of deutetrabenazine with other drugs that are known to cause QT prolongation should be avoided.

DOSING AND ADMINISTRATION

- The dose of deutetrabenazine is determined individually for each patient based on reduction of chorea or TD and tolerability.

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Austedo (deutetrabenazine)	Tablets	Oral	Twice daily	Initial daily dose: 6 mg (HD) or 12 mg (TD) Maximum daily dose: 48 mg Titrated at weekly intervals by 6 mg per day Administer with food

See the current prescribing information for full details

CONCLUSION

- Deutetrabenazine represents an additional oral therapeutic option for patients with TD or chorea associated with HD.

- For HD chorea, deutetrabenazine is comparable in safety and efficacy to its RLD, tetrabenazine. The use of both products in HD is limited by dose-related AEs (eg, somnolence, parkinsonism) and a boxed warning for depression and suicidality in a population that is already at a significantly increased risk.
 - Alternatives to tetrabenazine and deutetrabenazine include neuroleptics, which are more commonly used in clinical practice for HD. In addition to suppressing chorea, neuroleptics treat neuropsychiatric symptoms associated with HD.
- For TD, valbenazine is an alternative with the same mechanism of action and a convenient once-daily dosing schedule compared to twice-daily deutetrabenazine.

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