Deutetrabenazine (Austedo)

Classification:

Central Nervous System Agent

Pharmacology

Vesicular monoamine transporter 2 (VMAT2) is a protein that regulates the packaging and release of monoamines (dopamine, serotonin, norepinephrine, and histamine). VMAT2 inhibitors decrease monoamine uptake into the synaptic vesicles, thereby reducing neurotransmitter release into the synapse. Available reversible VMAT2 inhibitors include tetrabenazine (Xenazine), deutetrabenazine (Austedo) and valbenazine (Ingrezza). Deutetrabenazine is the deuterium substituted form of tetrabenazine. Deuterium (aka heavy hydrogen) is a hydrogen isotope that forms strong bonds with carbon which slow down deutetrabenazine's metabolism. Compared to tetrabenazine, deutetrabenazine has a longer half-life, decreased plasma fluctuations and fewer adverse effects associated with peak concentrations (somnolence, depression, insomnia, akathisia, parkinsonism). Deutetrabenazine undergoes extensive hepatic metabolism to its active deuterated metabolites--α-dihydrotetrabenazine [HTBZ] and β-HTBZ.

Black Box Warning for Depression and Suicidality in Patients with Huntington's Disease

Deutetrabenazine (Austedo) can increase the risk of depression and suicidal thoughts and behavior (suicidality) in patients with Huntington's disease. Anyone considering the use of deutetrabenazine (Austedo) must balance the risks of depression and suicidality with the clinical need for treatment of chorea. Closely monitor patients for the emergence or worsening of depression, suicidality, or unusual changes in behavior. Patients, their caregivers, and families should be informed of the risk of depression and suicidality and should be instructed to report behaviors of concern promptly to the treating physician. Particular caution should be exercised in treating patients with a history of depression or prior suicide attempts or ideation, which are increased in frequency in Huntington's disease. Deutetrabenazine (Austedo) is contraindicated in patients who are suicidal, and in patients with untreated or inadequately treated depression.

Indication

- Chorea associated with Huntington's disease
- Tardive dyskinesia

Pharmacokinetics

Pharmacokinetic Parameter	Details
Absorption	About 80% absorbed. After oral dosing, deutetrabenazine plasma concentrations are generally below the limit of detection. Peak plasma concentrations (C_{max}) of deuterated α-HTBZ and β-HTBZ reached within 3 to 4 hours. C_{max} increased approximately 50% in presence of food
Distribution	Median volume of distribution of α-HTBZ and β-HTBZ = 500 L, 730 L, respectively From PET studies, following IV injection of ^{11}C-labeled tetrabenazine, radioactivity rapidly distributed to the brain. Highest binding in the striatum, lowest binding in the cortex
Metabolism	Extensively biotransformed (carbonyl reductase) to major active metabolites-- α-dihydrotetrabenazine [HTBZ] and β-HTBZ, which are then metabolized primarily by CYP2D6, with minor contributions of CYP1A2 and CYP3A4/5, to form several minor metabolites
Excretion	Primarily renal. Half-life of total (α + β)-HTBZ = 9 to 10 hours

Dosage/Administration

The dose of deutetrabenazine (Austedo) is determined individually for each patient based on reduction of chorea or tardive dyskinesia and tolerability. The package insert contains specific dosing instructions about switching patients from tetrabenazine (Xenazine) to deutetrabenazine (Austedo). When first prescribed to patients who are not being switched from tetrabenazine, the recommended starting dose of deutetrabenazine (Austedo) is 6 mg administered orally once daily for patients with Huntington's disease and 12 mg per day (6 mg twice daily) for patients with tardive dyskinesia. The dose of deutetrabenazine (Austedo) may be increased at weekly intervals in increments of 6 mg per day to a maximum recommended daily dosage of 48 mg. Administer total daily dosages of 12 mg or above in two divided doses. Administer deutetrabenazine (Austedo) with food. Swallow deutetrabenazine (Austedo) whole. Do not chew, crush, or break tablets.

Dosage Adjustment with Strong CYP2D6 Inhibitors. In patients receiving strong CYP2D6 inhibitors (e.g., quinidine, paroxetine, fluoxetine, bupropion), the total daily dosage of deutetrabenazine (Austedo) should not exceed 36 mg (maximum single dose of 18 mg).

Dosage Adjustment in Poor CYP2D6 Metabolizers. In patients who are poor CYP2D6 metabolizers, the total daily dosage of deutetrabenazine (Austedo) should not exceed 36 mg (maximum single dose of 18 mg).

Discontinuation and Interruption of Treatment. Treatment with deutetrabenazine (Austedo) can be discontinued without tapering. Following treatment interruption of greater than one week, deutetrabenazine (Austedo) therapy should be re-titrated when resumed. For treatment interruption of less than one week, treatment can be resumed at the previous maintenance dose without titration.

Use in Special Population

Pregnancy

Risk Summary: There are no adequate data on the developmental risk associated with the use of deutetrabenazine (Austedo) in pregnant women. Administration of deutetrabenazine to rats during organogenesis produced no clear adverse effect on embryofetal development. However, administration of tetrabenazine to rats throughout pregnancy and lactation resulted in an increase in stillbirths and postnatal offspring mortality.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Lactation

Risk Summary: There are no data on the presence of deutetrabenazine or its metabolites in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for deutetrabenazine (Austedo) and any potential adverse effects on the breastfed infant from Austedo or from the underlying maternal condition.

Pediatric Use

Tourette syndrome

The safety and effectiveness of Austedo have not been established in pediatric patients for the treatment of Tourette syndrome.

Chorea associated with Huntington's disease and Tardive dyskinesia

The safety and effectiveness of Austedo have not been established in pediatric patients for the treatment of chorea associated with Huntington's disease or for the treatment of tardive dyskinesia.

Geriatric Use

Clinical studies of Austedo did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of hepatic, renal, and cardiac dysfunction, and of concomitant disease or other drug therapy.

Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of deutetrabenazine and its primary metabolites has not been studied; however, in a clinical study conducted with tetrabenazine, a closely related VMAT2 inhibitor, there was a large increase in exposure to tetrabenazine and its active metabolites in patients with hepatic impairment. The clinical significance of this increased exposure has not been assessed, but because of concerns for a greater risk for serious adverse reactions, the use of Austedo in patients with hepatic impairment is contraindicated.

Poor CYP2D6 Metabolizers

Although the pharmacokinetics of deutetrabenazine and its metabolites have not been systematically evaluated in patients who do not express the drug metabolizing enzyme, it is likely that the exposure to α-HTBZ and β-HTBZ would be increased similarly to taking a strong CYP2D6 inhibitor (approximately 3-fold). In patients who are CYP2D6 poor metabolizers, the daily dose of Austedo should not exceed 36 mg (maximum single dose of 18 mg).

Contraindication

Patients with Huntington's disease who are suicidal or have untreated or inadequately treated depression. Patients with hepatic impairment. Taking reserpine. At least 20 days should elapse after stopping reserpine before starting

deutetrabenazine (Austedo). Taking monoamine oxidase inhibitors (MAOIs). Deutetrabenazine (Austedo) should not be used in combination with an MAOI, or within 14 days of discontinuing therapy with an MAOI. Taking tetrabenazine (Xenazine) or valbenazine.

Precautions

Depression and Suicidality in Patients with Huntington's Disease

Patients with Huntington's disease are at increased risk for depression, and suicidal ideation or behaviors (suicidality). Deutetrabenazine (Austedo) may increase the risk for suicidality in patients with Huntington's disease. In a 12-week, double-blind, placebo-controlled trial, suicidal ideation was reported by 2% of patients treated with deutetrabenazine (Austedo), compared to no patients on placebo; no suicide attempts and no completed suicides were reported. Depression was reported by 4% of patients treated with deutetrabenazine (Austedo). When considering the use of deutetrabenazine (Austedo), the risk of suicidality should be balanced against the need for treatment of chorea. All patients treated with deutetrabenazine (Austedo) should be observed for new or worsening depression or suicidality. If depression or suicidality does not resolve, consider discontinuing treatment with deutetrabenazine (Austedo). Patients, their caregivers, and families should be informed of the risks of depression, worsening depression, and suicidality associated with deutetrabenazine (Austedo), and should be instructed to report behaviors of concern promptly to the treating physician. Patients with Huntington's disease who express suicidal ideation should be evaluated immediately.

Clinical Worsening and Adverse Events in Patients with Huntington's Disease

Huntington's disease is a progressive disorder characterized by changes in mood, cognition, chorea, rigidity, and functional capacity over time. VMAT2 inhibitors, including Austedo, may cause a worsening in mood, cognition, rigidity, and functional capacity. Prescribers should periodically re-evaluate the need for Austedo in their patients by assessing the effect on chorea and possible adverse effects, including sedation/somnolence, depression and suicidality, parkinsonism, akathisia, restlessness, and cognitive decline. It may be difficult to distinguish between adverse reactions and progression of the underlying disease; decreasing the dose or stopping the drug may help the clinician to distinguish between the two possibilities. In some patients, the underlying chorea itself may improve over time, decreasing the need for Austedo.

QTc Prolongation

Austedo may prolong the QT interval, but the degree of QT prolongation is not clinically significant when Austedo is administered within the recommended dosage range. Austedo should be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias. Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval.

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with drugs that reduce dopaminergic transmission. While NMS has not been observed in patients receiving Austedo, it has been observed in patients receiving tetrabenazine (a closely related VMAT2 inhibitor). Clinicians should be alerted to the signs and symptoms associated with NMS. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria, rhabdomyolysis, and acute renal failure. The diagnosis of NMS can be complicated; other serious medical illness (e.g., pneumonia, systemic infection) and untreated or inadequately treated extrapyramidal disorders can present with similar signs and symptoms. Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology. The management of NMS should include (1) immediate discontinuation of Austedo; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS. Recurrence of NMS has been reported with resumption of drug therapy. If treatment with Austedo is needed after recovery from NMS, patients should be monitored for signs of recurrence.

Akathisia, Agitation, and Restlessness

Austedo may increase the risk of akathisia, agitation, and restlessness in patients with Huntington's disease and tardive dyskinesia. In a 12-week, double-blind, placebo-controlled trial in Huntington's disease patients, akathisia, agitation, or restlessness was reported by 4% of patients treated with Austedo, compared to 2% of patients on placebo; in patients with tardive dyskinesia, 2% of patients treated with Austedo and 1% of patients on placebo experienced these events. Patients

receiving Austedo should be monitored for signs and symptoms of restlessness and agitation, as these may be indicators of developing akathisia. If a patient develops akathisia during treatment with Austedo, the Austedo dose should be reduced; some patients may require discontinuation of therapy.

Parkinsonism

Austedo may cause parkinsonism in patients with Huntington's disease or tardive dyskinesia. Parkinsonism has also been observed with other VMAT2 inhibitors. Because rigidity can develop as part of the underlying disease process in Huntington's disease, it may be difficult to distinguish between potential drug-induced parkinsonism and progression of underlying Huntington's disease. Drug-induced parkinsonism has the potential to cause more functional disability than untreated chorea for some patients with Huntington's disease. Postmarketing cases of parkinsonism in patients treated with Austedo for tardive dyskinesia have been reported. Signs and symptoms in reported cases have included bradykinesia, gait disturbances, which led to falls in some cases, and the emergence or worsening of tremor. In most cases, the development of parkinsonism occurred within the first two weeks after starting or increasing the dose of Austedo. In cases in which follow-up clinical information was available, parkinsonism was reported to resolve following discontinuation of Austedo therapy. If a patient develops parkinsonism during treatment with Austedo, the Austedo dose should be reduced; some patients may require discontinuation of therapy.

Sedation and Somnolence

Sedation is a common dose-limiting adverse reaction of Austedo. In a 12-week, double-blind, placebo-controlled trial examining patients with Huntington's disease, 11% of Austedo-treated patients reported somnolence compared with 4% of patients on placebo and 9% of Austedo-treated patients reported fatigue compared with 4% of placebo-treated patients. Patients should not perform activities requiring mental alertness to maintain the safety of themselves or others, such as operating a motor vehicle or operating hazardous machinery, until they are on a maintenance dose of Austedo and know how the drug affects them.

Hyperprolactinemia

Serum prolactin levels were not evaluated in the Austedo development program. Tetrabenazine, a closely related VMAT2 inhibitor, elevates serum prolactin concentrations in humans. Following administration of 25 mg of tetrabenazine to healthy volunteers, peak plasma prolactin levels increased 4- to 5-fold. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent in vitro, a factor of potential importance if Austedo is being considered for a patient with previously detected breast cancer. Although

amenorrhea, galactorrhea, gynecomastia, and impotence can be caused by elevated serum prolactin concentrations, the clinical significance of elevated serum prolactin concentrations for most patients is unknown. Chronic increase in serum prolactin levels (although not evaluated in the Austedo or tetrabenazine development programs) has been associated with low levels of estrogen and increased risk of osteoporosis. If there is a clinical suspicion of symptomatic hyperprolactinemia, appropriate laboratory testing should be done and consideration should be given to discontinuation of Austedo.

Binding to Melanin-Containing Tissues

Since deutetrabenazine or its metabolites bind to melanin-containing tissues, it could accumulate in these tissues over time. This raises the possibility that Austedo may cause toxicity in these tissues after extended use. Neither ophthalmologic nor microscopic examination of the eye has been conducted in the chronic toxicity studies in a pigmented species such as dogs. Ophthalmologic monitoring in humans was inadequate to exclude the possibility of injury occurring after long-term exposure. The clinical relevance of deutetrabenazine's binding to melanin-containing tissues is unknown. Although there are no specific recommendations for periodic ophthalmologic monitoring, prescribers should be aware of the possibility of long-term ophthalmologic effects.

Adverse Effects

The data described below reflect 410 tardive dyskinesia patients participating in clinical trials. Austedo was studied primarily in two 12-week, placebo-controlled trials (fixed dose, dose escalation). The population was 18 to 80 years of age and had tardive dyskinesia and had concurrent diagnoses of mood disorder (33%) or schizophrenia/schizoaffective disorder (63%). In these studies, Austedo was administered in doses ranging from 12-48 mg per day. All patients continued on previous stable regimens of antipsychotics; 71% and 14% respective atypical and typical antipsychotic medications at study entry.

The most common adverse reactions occurring in greater than 3% of Austedo-treated patients and greater than placebo were nasopharyngitis and insomnia. The adverse reactions occurring in >2% or more patients treated with Austedo (12-48 mg per day) and greater than in placebo patients in two double-blind, placebo-controlled studies in patients with tardive dyskinesia (Study 1 and Study 2) are summarized in the table below.

Adverse Reaction	Austedo n = 279 (%)	Placebo n = 131 (%)
Nasopharyngitis	4	2
Insomnia	4	1
Depression/dysthymic disorder	2	1
Akathisia/agitation/restlessness	2	1

One or more adverse reactions resulted in a reduction of the dose of study medication in 4% of Austedo treated patients and in 2% of placebo-treated patients.

Monitoring

Electrolytes; EKG (QT interval before and after dose is increased to > 24 mg/day in patients with increased risk for QTc prolongation); signs/symptoms of depression or suicidal ideation; signs and/or symptoms of NMS, restlessness and agitation

Interactions

Strong CYP2D6 Inhibitors

A reduction in Austedo dose may be necessary when adding a strong CYP2D6 inhibitor in patients maintained on a stable dose of Austedo. Concomitant use of strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, quinidine, bupropion) has been shown to increase the systemic exposure to the active dihydro-metabolites of deutetrabenazine by approximately 3-fold. The daily dose of Austedo should not exceed 36 mg per day, and the maximum single dose of Austedo should not exceed 18 mg in patients taking strong CYP2D6 inhibitors.

Reserpine

Reserpine binds irreversibly to VMAT2 and the duration of its effect is several days. Prescribers should wait for chorea or dyskinesia to reemerge before administering Austedo to help reduce the risk of overdosage and major depletion of serotonin and norepinephrine in the central nervous system. At least 20 days should elapse after stopping reserpine before starting Austedo. Austedo and reserpine should not be used concomitantly.

Monoamine Oxidase Inhibitors (MAOIs)

Austedo is contraindicated in patients taking MAOIs. Austedo should not be used in combination with an MAOI, or within 14 days of discontinuing therapy with an MAOI.

Neuroleptic Drugs

The risk of parkinsonism, NMS, and akathisia may be increased by concomitant use of Austedo and dopamine antagonists or antipsychotics.

Alcohol or Other Sedating Drugs

Concomitant use of alcohol or other sedating drugs may have additive effects and worsen sedation and somnolence.

Concomitant Tetrabenazine or Valbenazine

Austedo is contraindicated in patients currently taking tetrabenazine or valbenazine. Austedo may be initiated the day following discontinuation of tetrabenazine.

Efficacy

Aim to Reduce Movements in Tardive Dyskinesia (ARM-TD)

Methods

In a 12-week, randomized, double-blind, multicenter trial, 117 patients with moderate to severe TD received deutetrabenazine (n =58) or placebo (n = 59). Inclusion criteria included an Abnormal Involuntary Movement Scale (AIMS) score $\geq$ 6, stable psychiatric illness, and stable psychoactive medication treatment. Study subjects had a TD diagnosis for $\geq$ 3 months before screening and had been treated with dopamine receptor antagonists (DRA) for $\geq$ 3 months ($\geq$ 1 month if age $\geq$ 60 years).

Exclusion criteria included treatment with any of the following medications within 30 days: tetrabenazine, reserpine, alpha-methyl-p-tyrosine, strong anticholinergic medications, metoclopramide, dopamine agonists, levodopa, stimulants. Other exclusion criteria included treatment with botulinum toxin within three months of study initiation, presence of a neurologic condition that could confound TD assessments, serious untreated or undertreated psychiatric illness, unstable medical illness, history of active SI/behavior within 6 months, score $\geq$ 11 on the depression subscale of the Hospital Anxiety and Depression Scale (HADS), QT_c > 450 msec in men, > 460 msec in women.

At baseline, patients were stratified by use of DRA. The initial dose of deutetrabenazine was 12 mg/d (6 mg bid). For the first six weeks of the study, the

dose was titrated weekly by 6 mg/d until adequate dyskinesia control was achieved, a significant AE occurred, or the max dose (48 mg/d) was reached. Patients then entered a six-week maintenance phase followed by a one-week washout. AIMS exams were performed at weeks 2, 4, 6, 9, 12, and 13. Investigators performed EKGS at baseline and weeks 2 and 12 for all patients. Patients receiving other QT-prolonging meds also had ekgs at weeks 4, 6, and 9.

Results

Both groups had similar demographics and baseline characteristics. Roughly 70% of study subjects had been diagnosed with schizophrenia or schizoaffective disorder, 23.1% had bipolar disorder, and 25.6% had depression. Most (80.3%) were being treated with a DRA at baseline and throughout the study. At the end of the six-week dose titration phase and throughout the maintenance phase, the mean (SD) total daily dose was 38.8 (7.92) mg/d. The patient baseline characteristics by treatment group are shown in the table below.

Patient demographics	**Deutetrabenazine (n = 58)**	**Placebo (n = 59)**
Age (SD), y	55.9 (9.8)	53.3 (10.6)
Female, n (%)	29 (50.0)	32 (54.2)
White, n (%)	37 (63.8)	44 (74.6)

Clinical characteristics	**Deutetrabenazine (n = 58)**	**Placebo (n = 59)**
Duration of TD, mo	72.6 (81.7)	76.8 (82.1)
AIMS score, items 1-7 (SD)	9.6 (4.1)	9.6 (3.8)

Most common AP used at BL, n (%)	**Deutetrabenazine (n = 58)**	**Placebo (n = 59)**
Quetiapine	14 (24.1)	18 (30.5)
Risperidone	9 (15.5)	7 (11.9)

Most common AP used at BL, n (%)	Deutetrabenazine (n = 58)	Placebo (n = 59)
Olanzapine	8 (13.8)	5 (8.5)
Trazodone	9 (15.5)	10 (16.9)
Bupropion	5 (8.6)	6 (10.2)
Sertraline	6 (10.3)	4 (6.8)
Citalopram	5 (8.6)	5 (8.5)

From baseline to week 12, deutetrabenazine significantly reduced AIMS scores compared with placebo. **Least squares mean (SE) -3.0 (0.45) versus -1.6 (0.46), p = 0.019.**

The incidence of depression/depressed mood and suicidal ideation in the deutetrabenazine group was similar to or lower than that in the placebo group.

Side effect	Deutetrabenazine (n = 58), n (%)	Placebo (n = 59), n (%)
Depressed mood	1 (1.7)	0 (0.0)
Depression	0 (0.0)	1 (1.7)
Suicidal ideation	0 (0.0)	1 (1.7)
Somnolence	8 (13.8)	6 (10.2)
Insomnia	4 (6.9)	1 (1.7)
Akathisia	3 (5.2)	0 (0.0)
Anxiety	2 (3.4)	4 (6.8)

Small reductions in parkinsonism severity (Unified Parkinson's Disease Rating Scale) were observed in both groups (deutetrabenazine mean change = - 0.9 (8.09), placebo mean change = - 3.8 (7.87). There were no significant differences

in QTc interval prolongation between groups (p = 0.153). One placebo treated patient had Qtc > 500 msec.

The authors concluded that, in patients with TD, deutetrabenazine was well tolerated and significantly reduced abnormal movements.

Long-term safety and efficacy of deutetrabenazine for the treatment of TD

Fernandez and colleagues conducted a 106 week, open-label, single-arm extension study of patients who successfully completed the two, 12-week phase 3 trials (ARM-TD and AIM-TD, n = 368). Successful completion was defined as participation through week 13, compliance with study drug and procedures, and the absence of serious adverse effects.

Study subjects (n = 343) were washed out from their phase 3 study drug (deutetrabenazine [n = 232] or placebo [n = 111) for at least one week. All then started deutetrabenazine 12 mg/day (6 mg bid). For six weeks, the dose was increased weekly by 6 mg/day until adequate dyskinesia control was achieved with good tolerability. Max total daily dosage was 48 mg/day. The max dose for patients taking strong CYP2D6 inhibitors (paroxetine, fluoxetine or bupropion) was 36 mg/day.

Mean duration of deutetrabenazine treatment was 352.9 days. 76% (259/343) of patients were treated for at least 54 weeks and 20% (69/343) were treated for at least 80 weeks. Improvements in AIMS scores were noted by week 2; continued improvement was seen through Week 106 in the patients who remained in the study. The mean (SE) change in AIMS score was -4.9 (0.4) at Week 54 (n = 146), -6.3 (0.7) at Week 80 (n = 66) and -5.1 (2.0) at Week 106 (n = 8).

The most common adverse events were anxiety, somnolence and depression; most of these were mild or moderate in severity. Investigators calculated exposure-adjusted incidence rates (EAIRs) by adjusting the incidence of AEs for the duration of treatment exposure. This was done to compare adverse event frequencies in the long-term extension study with those in the short-term trials (ARM-TD and AIM-TD). EAIRs during the long-term extension study for depression, anxiety, suicidality, akathisia, somnolence, and parkinsonism were similar to or lower than those observed in the shorter studies, implying no evidence of cumulative toxicity or tolerability issues despite the longer treatment period.

Three patients had serious adverse events possibly related to deutetrabenazine: intentional overdose/suicide attempt, exacerbation of mania and exacerbation of hypomania. The patient who experienced intentional overdose and suicide attempt

had a history of depression, bipolar disorder, anxiety, and suicide attempts and was on 18 mg per day of deutetrabenazine.

6/343 (2%) of patients had a post-baseline QTc > 480 msec, 3/343 (< 1%) had a post-baseline QTc > 500 msec.

Dosage Forms/Cost

All info from GoodRX, Walgreens

Austedo 6 mg, #60 = $4,235.13

Austedo 9 mg, # 60 = $4,763.52

Austedo 12 mg, #60 = $6,348.91

Attributes	Valbenazine (Ingrezza)	Deutetrabenazine (Austedo)	Tetrabenazine (Xenazine)
Dosing	40 mg po daily-am, increase to 80 mg/day after 1 week. A dosage of 40 mg or 60 mg once daily may be considered depending on response and tolerability	6 mg po qday, increase weekly in 6 mg/day increments as tolerated to a maximum of 48 mg/day; doses > 12 mg should be divided into 2 doses	12.5-100 mg in divided doses 3 times per day
Dose adjustment	Liver impairment/strong CYP2D6/3A4 inhibitors and poor CYP2D6 metabolizers: maximum daily dose of 40 mg	Strong CYP2D6 inhibitors/poor metabolizers: maximum daily dose of 36 mg, maximum single dose of 18 mg	Strong CYP2D6 inhibitors/poor metabolizers; maximum daily dose of 50 mg, maximum single dose of 25 mg

Attributes	Valbenazine (Ingrezza)	Deutetrabenazine (Austedo)	Tetrabenazine (Xenazine)
Drug interactions	Avoid use with MAOIs and strong CYP3A4 inducers (e.g. carbamazepine, phenytoin, phenobarbital, St John's wort)	Avoid use with MAOIs; monitor QTc interval in patients taking > 24 mg/day who are also on other QTc-prolonging medications	Avoid use with MAOIs
Adverse effects	Somnolence, dry mouth, akathisia, headache, uti	Somnolence, dry mouth, akathisia, headache, anxiety, QTc prolongation (rare), depression in patients with Huntington's disease	Somnolence, fatigue, insomnia, anxiety, nausea, depression in patients with Huntington's disease
Contraindications	No contraindications but avoid in patients with impaired renal function or who are pregnant or breast-feeding	Contraindicated in patients with hepatic impairment and patients with suicidal ideation or untreated/inadequately treated depression	Contraindicated in patients with suicidal ideation or untreated/inadequately treated depression
Special information	None noted	Black box warning for increased risk of depression and suicidality in patients with Huntington's disease	Black box warning for increased risk of depression and suicidality in patients with Huntington's disease

Khorassani 2021. Comparison of VMAT2 Inhibitors. A Carlat Psychiatry Reference Table.

Summary/Conclusion

In 2017, the FDA approved the first treatments for TD in adults--valbenazine (Ingrezza) and deutetrabenazine (Austedo). In April 2018, the PEFC reviewed valbenazine (Ingrezza) and recommended that it remain non-formulary, even though the updated American Academy of Neurology (AAN) guideline (Bhidayasiri R, et al., 2018) had just declared valbenazine (Ingrezza) and deutetrabenazine

(Austedo) the first and only effective treatments (Level A recommendation) for TD. This decision was based on our system's limited resources and the fact that valbenazine's (Ingrezza) average AIMS reductions were not drastically different from those seen with non-approved treatments. In the Kinect 3 study, six weeks of treatment with valbenazine 80 mg per day reduced AIMS scores an average of 3.2 points. However, smaller, lower quality studies showed an average reduction of 2.13 points for gingko biloba and that clonazepam is probably effective in the short term (both Level B, probably effective). Studies with amantadine (Level C, possibly effective) showed average reductions of about 2 points in patients who improved while trials of controlled-release melatonin (Level U, insufficient evidence) demonstrated average reductions of 2.45 points. In April 2018, the committee approved an algorithm for the treatment of tardive dyskinesia, monitoring parameters, and a dosing table. See attached. The algorithm shows valbenazine (Ingrezza) as a last-line agent, only to be used after trials of all other treatment options.

Since the approval of the VMAT2 inhibitors in 2017, there has been a reappraisal of best practices for recognizing and managing TD. A recent consensus statement and the third edition of the APA Practice Guideline for the Treatment of Patients with Schizophrenia (2020) provide guidance on the screening, diagnosis, and treatment of TD.

In late 2017-early 2018, a group of TD experts used a modified Delphi method to develop recommendations concerning screening, diagnosis, and treatment of tardive dyskinesia. The consensus statement provides guidance on best practices including routine monitoring procedures adaptable to clinical settings, diagnosing mild cases of TD, and implementing a comprehensive strategy that incorporates patient and caregiver input, review of antipsychotic and anticholinergic medications, indications for VMAT2 inhibitors, and appropriate follow-up.

The 2020 APA Practice Guideline for the Treatment of Patients with Schizophrenia states that most patients with TD have mild symptoms but some patients' symptoms can be described as moderate or severe and that in these cases, clinicians look for other contributors to a movement disorder. This assessment would include a neurological examination, complete history of motor symptoms, past and current medications, laboratory testing. Depending on the results, additional studies might be indicated (ceruloplasmin for Wilson's disease, brain MRI, lumbar puncture). If dyskinesias have begun or increased during antipsychotic dose reduction, their course should be tracked for several months because spontaneous reductions or resolution may occur. If no contributing cause is identified and moderate to severe or disabling tardive dyskinesia persists, treatment is recommended (1B) with a reversible VMAT2 inhibitor. The guideline

also recommends that VMAT2 inhibitors be considered for patients with mild tardive dyskinesia based on TD associated impairment, effect on psychosocial functioning and patient preference.

Compared to valbenazine (Ingrezza), deutetrabenazine (Austedo) has a more complicated titration (seven versus three dosing options). Valbenazine (Ingrezza) has the advantage of once daily dosing while deutetrabenazine requires BID administration with food. Deutetrabenazine's multiple dosing options may target a wider range of VMAT2 occupancy. VMAT2 occupancies for deutetrabenazine at doses between 6 mg and 42 mg range between 51% and 92%; VMAT2 occupancies for valbenazine at doses between 40 mg and 80 mg range between 84% and 91%. Individual patients might require different degrees of VMAT2 inhibition to achieve the best balance between efficacy and tolerability and Caroff et al. recommend that if one VMAT2 inhibitor is ineffective or not tolerated, the next step is to switch to another VMAT2 inhibitor before using other agents.

Recommendation

Add both deutetrabenazine (Austedo) and valbenazine (Ingrezza) to the formulary as reserve agents. With regard to the recognition and management of TD, recommendations found in resources such as the APA guideline and Caroff et al may help clinicians identify patients who would benefit from VMAT2 inhibitor therapy.

References

1. The American Psychiatric Association (APA) Practice Guideline for the Treatment of Patients with Schizophrenia. Third Edition.
2. Austedo package insert, Teva Neuroscience, Inc. Revised 6/2021
3. Bhidayasiri R, Jitkritsadakul O, Friedman J, Fahn S. Updating the recommendations for treatment of tardive syndromes: A systematic review of new evidence and practical treatment algorithm. Journal of the Neurological Sciences 2018; 389: 67-75.
4. Caroff SN, Citrome L, Meyer J, et al. A Modified Delphi Consensus Study of the Screening, Diagnosis, and treatment of Tardive Dyskinesia. J Clin Psychiatry 2020;81(2):19cs12983
5. Fernandez H, Factor S, Hauser RA, et al. Randomized controlled trial of deutetrabenazine for tardive dyskinesia. The ARM-TD study. Neurology 2017;88:2003-2010.
6. Fernandez H, Stamler D, Davis M, et al. Long-term safety and efficacy of deutetrabenazine for the treatment of tardive dyskinesia. J Neurol Neurosurg Psychiatry 2019; 90:1317-1323.

7. "Finally, Effective Treatments for Tardive Dyskinesia", Farah Khorassani, PharmD, The Carlat Hospital Psychiatry Report, Volume 1, Number 3 & 4, April/May/June 2021.
8. Stahl, Stephen M. Comparing pharmacologic mechanism of action for the vesicular monoamine transporter 2 (VMAT2) inhibitors valbenazine and deutetrabenazine in treating tardive dyskinesia: CNS Spectrums (2018), 23, 239-247.

Prepared by:
Shiju George, RPh
Non-traditional PharmD Student
Shenandoah University

Reviewed by:
Elizabeth Kurian, PharmD
Pharmacy Director
Terrell State Hospital

Catherine Hall, PharmD, BCPP, BCACP
Clinical Pharmacist
San Antonio State Hospital