Teva cordially invites you to a presentation & discussion entitled:

Management of Tardive Dyskinesia: Update for Psychiatry

Moderated by:
Cherian Karunapuzha, MD
Asst. Professor & Director of Movement Disorders Division

On
Tuesday, December 17, 2019, 6:30 PM Central

At
Eddie V's Prime Seafood
3100 West 7th Street
Fort Worth, TX 76107

Please RSVP to:
Melissa Souders at (214) 564-3024
Kerri French at (817) 629-8609

In accordance with the PhRMA Code on Interactions with Healthcare Professionals, attendance at this program is limited to healthcare professionals. Accordingly, attendance by non-clinical guests or spouses is not permitted.

2019-TEVA-US-SB-0010710

Indications and Usage
AUSTEDO® is indicated for the treatment of chorea associated with Huntington’s disease and for the treatment of tardive dyskinesia in adults.

Important Safety Information

Depression and Suicidality in Patients with Huntington’s Disease: AUSTEDO® can increase the risk of depression and suicidal thoughts and behavior (suicidality) in patients with Huntington’s disease. 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. Inform patients, their caregivers, and families of the risk of depression and suicidality and instruct them to report behaviors of concern promptly to the treating physician. Exercise caution when treating patients with a history of depression or prior suicide attempts or ideation. AUSTEDO® is contraindicated in patients who are suicidal, and in patients with untreated or inadequately treated depression.

Please see Important Safety Information continued on next page and accompanying full Prescribing Information, including Boxed Warning.
Important Safety Information (continued)

**Contraindications:** AUSTEDO® (deutetrabenazine) tablets is contraindicated in patients with Huntington’s disease who are suicidal, or have untreated or inadequately treated depression. AUSTEDO® is also contraindicated in: patients with hepatic impairment; patients taking reserpine or within 20 days of discontinuing reserpine; patients taking monoamine oxidase inhibitors (MAOIs), or within 14 days of discontinuing MAOI therapy; and patients taking tetrabenazine (Xenazine®) or valbenazine (Ingrezza®).

**Clinical Worsening and Adverse Events in Patients with Huntington’s Disease:** 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.

**QTc Prolongation:** Tetrabenazine, a closely related VMAT2 inhibitor, causes an increase in the corrected QT (QTc) interval. A clinically relevant QT prolongation may occur in some patients treated with AUSTEDO® who are CYP2D6 poor metabolizers or are co-administered a strong CYP2D6 inhibitor. Dose reduction may be necessary. The use of AUSTEDO® in combination with other drugs known to prolong QTc may result in clinically significant QT prolongations. For patients requiring AUSTEDO® doses greater than 24 mg per day who are using AUSTEDO® with other drugs known to prolong QTc, assess the QTc interval before and after increasing the dose of AUSTEDO® or the other drugs. AUSTEDO® should be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias.

**Neuroleptic Malignant Syndrome (NMS),** a potentially fatal symptom complex reported in association with drugs that reduce dopaminergic transmission, has been observed in patients receiving tetrabenazine. The risk may be increased by concomitant use of dopamine antagonists or antipsychotics. The management of NMS should include immediate discontinuation of AUSTEDO®, intensive symptomatic treatment and medical monitoring; and treatment of any concomitant serious medical problems.

**Akathisia, Agitation, and Restlessness:** AUSTEDO® may increase the risk of akathisia, agitation, and restlessness. The risk of akathisia may be increased by concomitant use of dopamine antagonists or antipsychotics. If a patient develops akathisia, the AUSTEDO® dose should be reduced; some patients may require discontinuation of therapy.

**Parkinsonism in Patients with Huntington’s Disease:** AUSTEDO® may cause parkinsonism in patients with Huntington’s disease. The risk of parkinsonism may be increased by concomitant use of dopamine antagonists or antipsychotics. If a patient develops parkinsonism, 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®. Patients should not perform activities requiring mental alertness, such as operating a motor vehicle or hazardous machinery, until they are on a maintenance dose of AUSTEDO® and know how the drug affects them. Concomitant use of alcohol or other sedating drugs may have additive effects and worsen sedation and somnolence.

**Hyperprolactinemia:** Tetrabenazine elevates serum prolactin concentrations in humans. 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:** Deutetrabenazine or its metabolites bind to melanin-containing tissues and could accumulate in these tissues over time. Prescribers should be aware of the possibility of long-term ophthalmologic effects.

Please see Important Safety Information continued on next page and accompanying full Prescribing Information, including Boxed Warning.
Important Safety Information (continued)

CYP2D6 Metabolism: In patients who are poor CYP2D6 metabolizers or are taking strong CYP2D6 inhibitors, the total daily dosage of AUSTEDO® (deutetrabenazine) tablets should not exceed 36 mg (maximum single dose of 18 mg).

Common Adverse Reactions: The most common adverse reactions for AUSTEDO® (>8% and greater than placebo) in a controlled clinical study in patients with Huntington’s disease were somnolence, diarrhea, dry mouth, and fatigue. The most common adverse reactions for AUSTEDO® (4% and greater than placebo) in controlled clinical studies in patients with tardive dyskinesia were nasopharyngitis and insomnia.

Please see accompanying full Prescribing Information, including Boxed Warning.
WARNING: DEPRESSION AND SUICIDALITY IN PATIENTS WITH HUNTINGTON'S DISEASE

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

AUSTEDO® (duloxetine tablets), for oral use

Initial U.S. Approval: 2017

HIGHLIGHTS OF PRESCRIBING INFORMATION

For patients at risk for QT prolongation, assess the QT interval before and after increasing the total dosage above 24 mg per day (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).

**DOSE FORMS AND STRENGTHS**

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

**INDICATIONS AND USAGE**

AUSTEDO is a selective serotonin reuptake inhibitor (SSRI) indicated for the treatment of:

- Major depressive disorder in adults (1)
- Generalized anxiety disorder in adults (1)
- Premenstrual dysphoric disorder in women with premenstrual dysphoria and severe premenstrual exacerbation (1)
- Obsessive-compulsive disorder in children and adolescents (6.1)

**ADVERSE REACTIONS**

Most common adverse reactions (>8% of AUSTEDO-treated patients with Huntington's disease and greater than placebo: somnolence, diarrhea, dry mouth, and fatigue (6.1). Most common adverse reactions (that occurred in 4% of AUSTEDO-treated patients with tardive dyskinesia and greater than placebo): nausea, vomiting, and diziness (6.2).

**DRUG INTERACTIONS**

Concomitant use of strong CYP2D6 inhibitors: Maximum recommended dose of AUSTEDO is 18 mg per day (18 mg twice daily) (2.5, 7.3).

Alcohol or other sedating drugs: May have additive sedation and somnolence (7.6).

**USE IN SPECIFIC POPULATIONS**

Pregnancy: Based on animal data, may cause fetal harm (6.1).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

**FULL PRESCRIBING INFORMATION: CONTENTS**

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1 INDICATIONS AND USAGE

AUSTEDO® (deutetrabenazine) is indicated for the treatment of:
- tardive dyskinesia in adults [see Clinical Studies (14.2)]

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The dose of AUSTEDO® is determined individually for each patient based on reduction of chorea or tardive dyskinesia and tolerability. When first prescribed to patients who are not being switched from tetrabenazine (a related VMAT2 inhibitor), the recommended starting dose of AUSTEDO is 8 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 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 AUSTEDO® with food [see Clinical Pharmacology (12.3)].
- Swallow AUSTEDO whole. Do not chew, crush, or break tablets.
- For patients at risk for QT prolongation, assess the QT interval before and after increasing total AUSTEDO dosage above 24 mg per day [see Warnings and Precautions (5.5) and Drug Interactions (12.2)].

2.2 Switching Patients from Tetrabenazine (XENAZINE®) to AUSTEDO

Discontinue tetrabenazine (XENAZINE®) and initiate AUSTEDO the following day. The recommended initial dosing regimen of AUSTEDO in patientsswitching from tetrabenazine (XENAZINE®) to AUSTEDO is 4 mg once daily, which may be increased at weekly intervals until a dose of 8 mg is reached.

3 Dose Forms and Strengths

AUSTEDO tablets are available in the following strengths:
- 4 mg tablets, round, blue-colored tablets, with “4” over “6” printed in black ink on one side.
- 8 mg tablets, round, blue-colored tablets, with “8” over “6” printed in black ink on one side.
- 12 mg tablets, round, beige-colored tablets, with “12” imprinted in black ink on one side.
- 16 mg tablets, round, beige-colored tablets, with “16” imprinted in black ink on one side.
- 24 mg tablets, round, beige-colored tablets, with “24” imprinted in black ink on one side.

After patients are switched to AUSTEDO®, the dose may be adjusted at weekly intervals [see Dosage and Administration (2.1)].

2.3 Dosage Adjustment with Strong CYP2D6 Inhibitors

- If patients receiving strong CYP2D6 inhibitors (e.g., quinidine, antidepresants such as paroxetine, fluoxetine, and bupropion), the total daily dosage of AUSTEDO should not exceed 36 mg (maximum single dose of 18 mg) [see Drug Interactions (7.1) and Clinical Pharmacology (12.2)].

2.4 Dosage Adjustment in Poor CYP2D6 Metabolizers

In patients who are poor CYP2D6 metabolizers, the total daily dosage of AUSTEDO should not exceed 26 mg (maximum single dose of 13 mg) [see Use in Specific Populations (8.7)].

2.5 Discontinuation and Interruption of Treatment

Treatment with AUSTEDO can be discontinued without tapering. Following treatment interruption, if AUSTEDO therapy needs to be resumed, treatment interruption of less than one week, treatment can be resumed at the previous maintenance dose without titration.

3 DOSAGE FORMS AND STRENGTHS

AUSTEDO tablets are available in the following strengths:
- The 4 mg tablets are round, blue-colored tablets, with “4” over “6” printed in black ink on one side.
- The 8 mg tablets are round, blue-colored tablets, with “8” over “6” printed in black ink on one side.
- The 12 mg tablets are round, beige-colored tablets, with “12” imprinted in black ink on one side.

4 CONTRAINDICATIONS

AUSTEDO is contraindicated in patients:
- With a history of depression or suicidal ideation or behavior [see Warnings and Precautions (5.1)].
- With hepatic impairment [see Use in Specific Populations (8.5), Clinical Pharmacology (12.3)].
- Taking ropinirole. At least 20 days should elapse after stopping ropinirole before starting AUSTEDO [see Drug Interactions (7.3)].
- Taking concomitant oestrogens (e.g., PRO-MED, PRO-NOS) AUSTEDO should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI [see Drug Interactions (7.4)].
- Taking tetrabenazine (XENAZINE®) or valbenazine [see Drug Interactions (7.7)].

5 WARNINGS AND PRECAUTIONS

5.1 Depression and Suicidality in Patients with Huntington’s Disease

Patients with Huntington’s disease are at increased risk for depression, and suicidal ideation or behavior. 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 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 AUSTEDO.

When considering the use of AUSTEDO, the risk of suicidality should be balanced against the need for treatment of chorea. All patients treated with AUSTEDO should be observed for new or worsening depression or suicidality, particularly in the treatment-emergent period. Patients treated with Huntington’s disease who express suicidal ideation should be evaluated immediately.

5.2 Clinical Worsening and Adverse Events in Patients with Huntington’s Disease

Huntington’s disease is a progressive neurodegenerative 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. Patients should be periodically re-evaluated for the need for AUSTEDO in their treatment plan.

5.3 QT Prolongation

The use of AUSTEDO has not been evaluated 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 drugs that prolong the QT 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.

5.4 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 creatine phosphokinase, myoglobinuria, rhabdomyolysis, and acute renal failure. The diagnosis of NMS can be complicated by other medical conditions (e.g., sepsis, trauma, stress, and systemic infections), and uncontrolled or untreated extrapyramidal disorders can present with similar signs and symptoms. Other important considerations in the differential diagnosis include intracranial hypertension, 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.
5.5 Akathisia, Agitation, and Restlessness

AUSTEDO may increase the risk of akathisia, agitation, and restlessness in patients with Huntington's disease and in others with clinically apparent 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, 21% of patients treated with AUSTEDO and 8% of patients on placebo experienced these events.

Patients receiving AUSTEDO should be monitored for signs and symptoms of restlessness or agitation, as these may be early 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.

5.6 Parkinsonism in Patients with Huntington's Disease

AUSTEDO may cause Parkinsonism in patients with Huntington's disease. Because rigidity can develop as part of the underlying disease process in Huntington's disease, it may be difficult to distinguish between this potential drug-induced adverse reaction and progression of the underlying disease process. Drug-induced Parkinsonism has also been reported in patients treated with other antipsychotic agents for patients with Huntington's disease. If a patient develops parkinsonism during treatment with AUSTEDO, the AUSTEDO dose should be reduced; some patients may require discontinuation of therapy.

5.7 Binding to Melanin-Containing Tissues

Serum prolactin levels were not evaluated in the AUSTEDO development program. Tetrazenate, a closely related VMAT2 inhibitor, elevates serum prolactin concentrations in humans. Following administration of 25 mg of tetrazenate 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 amniocarcinoma, 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 tetrazenate clinical 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.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Depression and Suicidality in Patients with Huntington's disease [see Warnings and Precautions (5.1)]
- QTc Prolongation [see Warnings and Precautions (5.3)]
- Neuroleptic Malignant Syndrome (NMS) [see Warnings and Precautions (5.4)]
- Akathisia, Agitation, and Restlessness [see Warnings and Precautions (5.5)]
- Sedation and Somnolence [see Warnings and Precautions (5.6)]
- Hyperprolactinemia [see Warnings and Precautions (5.8)]
- Binding to Melanin-Containing Tissues [see Warnings and Precautions (5.9)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Patients with Huntington's Disease

Study 1 was a randomized, 12-week, placebo-controlled study in patients with chorea associated with Huntington's disease. A total of 45 patients received AUSTEDO, and 45 patients received placebo. Patients ranged in age between 23 and 74 years (mean 54 years), 56% were male, and 92% were Caucasian. The most common adverse reactions occurring in greater than 8% of AUSTEDO-treated patients were somnolence, diaphoresis, dry mouth, and fatigue. Adverse reactions occurring in 4% or more of patients treated with AUSTEDO, and with a greater incidence than in patients on placebo, are summarized in Table 2.

Table 2: Adverse Reactions in Patients with Huntington’s Disease (Study 1) Experienced by at Least 4% of Patients on AUSTEDO and with a Greater Incidence than on Placebo

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>AUSTEDO (N=45)</th>
<th>Placebo (N=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Insomnia</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Anxiety</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Constipation</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

One or more adverse reactions resulted in a reduction of the dose of study medication in 7% of patients in Study 1. The most common adverse reaction resulting in a dose reduction in patients receiving AUSTEDO was dizziness (4%).

Agitation led to discontinuation in 2% of patients treated with AUSTEDO in Study 1.

Patients with Tardive Dyskinesia

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 (39%) or schizophrenia/schizoaffective disorder (53%). 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% respectively 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 Table 3.

Table 3: Adverse Reactions in 2 Placebo-Controlled Tardive Dyskinesia Studies (Study 1 and Study 2) of 12-week Treatment on AUSTEDO Reported at Least 2% of Patients and Greater than Placebo

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>AUSTEDO (N=279) (%)</th>
<th>Placebo (N=131) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Depression/Depressive disorder</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Akathisia/Agitation/Restlessness</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

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.

7 DRUG INTERACTIONS

7.1 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 tetrazenate 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 [see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)].

7.2 Drugs that Cause QTc Prolongation

Tetrazenate, a closely related VMAT2 inhibitor, may cause an increase in the corrected QT (QTc) interval. Clinically relevant QT prolongation may also occur with AUSTEDO [see Warnings and Precautions (5.3), Clinical Pharmacology (12.2)]. For patients requiring AUSTEDO doses above 24 mg per day, who are using QTc prolonging drugs known to prolong QTc, assess the QTc interval before and after increasing the dose of AUSTEDO or other medications that are known to prolong QTc. Drugs known to prolong QTc include antipsychotics (e.g., chlorpromazine, haloperidol, thioridazine, ziprasidone), antibiotics (e.g., moxifloxacin), Class IA (e.g., quinidine, procainamide), and Class III (e.g., amiodarone, sotalol) antiarrhythmic medications.

7.3 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 [see Contraindications (4)].
7.4 Monoamine Oxidase Inhibitors (MAOIs)
AUSTEDO is contraindicated in patients taking MAOIs. AUSTEDO should not be used in combination with other MAOIs, or within 14 days of discontinuing therapy with a MAOI [see Contraindications (4)].

7.5 Neuroleptic Drugs
The risk of parkinsonism, akathisia, and akinesia may be increased by concomitant use of AUSTEDO and dopamine antagonists or antipsychotics.

7.6 Alcohol or Other Sedating Drugs
Concomitant use of alcohol or other sedating drugs may have additive effects and worsening of antipsychotic side effects [see Warnings and Precautions (5.7)].

7.7 Concurrent Tetrabenazine or Valbenzine
AUSTEDO is contraindicated in patients currently taking tetrabenazine or valbenzine. AUSTEDO may be initiated the day following discontinuation of tetrabenazine [see Dosage and Administration (2.2.1)].

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy

Risk Summary
There are no adequate data on the developmental risk associated with the use of AUSTEDO in pregnant women. Administration of desipramine 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 prenatal mortality [see Data].

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.

Data

Animal Data

Oral administration of desipramine (5, 10, or 30 mg/kg/day) or tetrabenazine (30 mg/kg/day) to pregnant rats during organogenesis had no clear effect on embryofetal development. The highest dose tested was 6 times the maximum recommended human dose of 48 mg/day, on a body surface area (mg/m²) basis.

The effects of desipramine and tetrabenazine were monitored during organogenesis to rabbits and mice during pregnancy and lactation to rats have not been assessed.

Tetrabenazine had no effects on embryofetal development when administered to pregnant rabbits during the period of organogenesis at oral doses up to 60 mg/kg/day. When tetrabenazine was administered to female rats daily doses of 1, 15, and 30 mg/kg/day from the beginning of organogenesis through the lactation period, an increase in stillbirths and offspring postnatal mortality was observed at 15 and 30 mg/kg/day, and delayed pup maturation was observed at all doses.

8.2 Lactation

Risk Summary

There are no data on the presence of desipramine or its metabolites in human milk. The effects on the breastfed infant, or the effects of the drug on milk production are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for AUSTEDO and any potential adverse effects on the breastfed infant from AUSTEDO or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Genitourinary 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 in elderly patients should be guided by the same principles as those used in younger adults.

8.6 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of desipramine and its primary metabolites has not been studied; however, in a clinical study conducted with tetrabenazine, a closely related VMA2 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 [see Contraindications (4), Clinical Pharmacology (12.3)].

8.7 Poor CYP2D6 Metabolizers

Although the pharmacokinetics of desipramine and its metabolites have not been systematically evaluated in patients who do not express the drug metabolizing enzyme (CYP2D6) gene, it is likely that the exposure to desipramine and its metabolites would be increased similarly to a strong CYP2D6 inhibitor (approximately 3-fold). In patients who are CYP2D6 poor metabolizers, the daily dose of AUSTEDO should not exceed 35 mg (maximum single dose of 15 mg) [see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)].

10 OVERDOSE

Overdoses ranging from 100 mg to 1 g have been reported in the literature with tetrabenazine, a closely related VMA2 inhibitor. The following adverse reactions occurred in overdose cases: acute dystonia, orthostatic crisis, nausea and vomiting, sweating, sedation, hypotension, confusion, diarrhea, hallucinations, respirations, and coma. Treatment should consist of those general measures employed in the management of overdose with any central nervous system-acting drug. General supportive and symptomatic measures are recommended. Cardiac rhythm and vital signs should be monitored. In managing overdose, the possibility of multiple drug involvement should be considered. The physician should consider consulting a poison control center on the treatment of any overdose. Telephone numbers for certified poison control centers are listed on the American Association of Poison Control Centers website www.aapcc.org.

11 DESCRIPTION

AUSTEDO (deutetranabenzine) is a vesicular monoamine transporter 2 (VMAT2) inhibitor for oral administration. The molecular weight of deutetranabenzine is 323.46; the pKa is 6.31. Deutetranabenzine is a hydro-dimethylbenzeneurine derivative and has the following chemical name: 1-(2-(2-methylpropyl)-4,5,6,7-tetrahydro-1-benzylido-2H-thien-3-yl)-2-((2-methylpropyl)oxy)-3-(2-methylpropyl)-2H-benzo[a]quinolin-2-one. The molecular formula for deutetranabenzine is C22H23NO. Deutetranabenzine is a racemic mixture containing the following structures:

Deutetranabenzine is a white to slightly yellow crystalline powder that is sparingly soluble in water and soluble in ethanol.

AUSTEDO tablets contain 6 mg, 9 mg, or 12 mg deuterabenzine, and the following inactive ingredients: ammnonium hydroxide, black iron oxide, butylated hydroxyanisole, butylated hydroxytoluene, magnesium stearate, mannitol, microcrystalline cellulose, polyethylene glycol, polyethylene oxide, povidone, saccharin sodium, sodium stearyl fumarate, talc, titanium dioxide, and FD&C Red #40. The tablets also contain FD&C Yellow #6 lake.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanism by which deuterabenzine exerts its effects in the treatment of tardive dyskinesia and chorea in patients with Huntington's disease is unknown but is believed to be related to its effects as a reversible depletor of monoamines (such as dopamine, serotonin, noradrenergic, and histaminic) from nerve terminals. The major circulating metabolites (α-deuterabenzine [HT2E] and β-deuterabenzine) of deuterabenzine, are irreversible inhibitors of VMAT2, resulting in decreased uptake of monoamines into synaptic vesicles and depletion of monoamine stores.

12.2 Pharmacokinetics

12.2.1 Cardio Electrophysiology

The effect of a single 12-mg or 24-mg dose of AUSTEDO on the QT interval was observed in a randomized, double-blind, placebo-controlled crossover study in healthy male and female subjects with metoprolol as a positive control. At 24 mg, AUSTEDO caused an approximately 4.5 msec increase in QTc (90% CI: 2.4, 6.5 msec). Effects at higher exposures to AUSTEDO or its metabolites have not been evaluated.

12.2.2 Melanin Binding

Deutetranabenzine or its metabolites bind to melanin-containing tissues (i.e., eye, skin, hair) in pigmented rats. After a single oral dose of radiolabeled deutetranabenzine, radioactivity was still detected in eye and fur at 35 days following dosing [see Use in Specific Populations (8.5)].

12.3 Pharmacokinetics

After oral dosing up to 25 mg, plasma concentrations of deutetranabenzine are generally below the limit of detection because of the extensive hepatic metabolism of deutetranabenzine to the active deuterated dihydro metabolites (HT2E). α-HT2E and β-HT2E. Linear dose dependence of Cmax and AUC was observed for the active metabolites following single or multiple doses of deutetranabenzine (6 mg to 24 mg and 7.5 mg twice daily to 22.5 mg twice daily).

Absorption

Following oral administration of deutetranabenzine, the extent of absorption is at least 80%.

Plasma concentrations of deutetranabenzine are generally below the limit of detection after oral dosing. Peak plasma concentrations (Cmax) of deuterated α-HT2E and β-HT2E are reached within 3 to 4 hours after dosing.

Effect of Food

The effects of food on the bioavailability of AUSTEDO were studied in subjects administered a single dose with and without food. Food had no effect on the area under the plasma concentration-time curve (AUC) of α-HT2E or β-HT2E, although Cmax was increased by approximately 50% in the presence of food [see Dosage and Administration (2.1)].

Distribution

The mean volume of distribution (Vd/F) of α-HT2E and the β-HT2E metabolites of AUSTEDO are approximately 500 L and 730 L, respectively.

Results of PET-scan studies in humans show that following intravenous injection of [11C] labeled tetrabenazine or α-HT2E, radioactivity is rapidly distributed to the brain with the highest binding in the striatum and lowest binding in the cortex. The radiolabeled binding of tetrabenazine, α-HT2E, and β-HT2E was examined in human plasma for concentrations ranging from 50 to 260 ng/mL. Tetrabenazine binding ranged from 82% to 85%, α-HT2E binding ranged from 60% to 68%, and β-HT2E binding ranged from 58% to 63%.
Elimination
AUStEDo is primarily renally eliminated in the form of metabolites. The half-life of total (α+β)-HT2B from deuterated benzine is approximately 9 to 10 hours. The median clearance values (CLF) of the α-HT2B and the β-HT2B metabolites of AUStEDo are approximately 47 L/hour and 70 L/hour, respectively, in the Huntington's disease patient population.

Metabolism
In vitro experiments in human liver microsomes demonstrate that deuterated benzine is extensively biotransformed, mainly by cytochrome reductase, to its major active metabolites, α-HT2B and β-HT2B, which are subsequently metabolized primarily by CYP3A4 with minor contributions of CYP2C19 and CYP2A6, to form several minor metabolites.

Excretion
In a phase balance study in healthy subjects, 75% to 86% of the deuterated benzine dose was excreted in the urine, and fecal recovery accounted for 8% to 11% of the dose. Urinary excretion of the α-HT2B and β-HT2B metabolites from deuterated benzine each accounted for less than 10% of the administered dose. Sulfate and glucuronide conjugates of the α-HT2B and β-HT2B metabolites were also recovered in the urine. The metabolites are accounted for the majority of metabolites in the urine.

Specific Populations

Male and Female Patients

The effects of the pharmacokinetics of α-HT2B and β-HT2B of deuterated benzine in men and women have not been studied in the PK of AUStEDo.

Patients with Renal Impairment

No clinical studies have been conducted to assess the effect of renal impairment on the PK of AUStEDo.

Patients with Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of deuterated benzine and its primary metabolites has not been studied. However, in a clinical study conducted to assess the effect of hepatic impairment on the pharmacokinetics of tetrabenazine, a closely related VMA2 inhibitor, the exposure to α-HT2B and β-HT2B was up to 40% greater in patients with hepatic impairment, and the mean tetrabenazine Cmax in patients with hepatic impairment was up to 150-fold higher than in healthy subjects [see Contraindications (4), Use in Specific Populations (6.6)].

CYP2D6 Metabolizers

Although the pharmacokinetics of deuterated benzine and its metabolites have not been evaluated in patients who do not express the drug metabolism enzyme CYP2D6, it is likely that the exposure to α-HT2B and β-HT2B would be increased similarly to that seen in patients with a poor genotype CYP2D6 (approximately 3-fold) [see Dosage and Administration (2.4)], Drug Interactions (7.1)].

Drug Interactions

Deuterated benzine, α-HT2B, and β-HT2B have not been evaluated in vitro studies for induction or inhibition of CYP enzymes or interaction with P-glycoprotein. The results of preclinical studies suggest that neither tetrabenazine nor its α-HT2B and β-HT2B metabolites are likely to affect clinically relevant drug interactions.

CYP2D6 Inhibitors

In vitro studies indicate that the α-HT2B and β-HT2B metabolites of deuterated benzine are substrates for CYP2D6. The effect of CYP2D6 inhibition on the pharmacokinetics of deuterated benzine and its metabolites was studied in 24 healthy subjects following a single 22.5 mg dose of deuterated benzine given 8 days of administration of the strong CYP2D6 inhibitor paroxetine 20 mg daily. In the presence of paroxetine, systemic exposure (AUC0-∞) of α-HT2B was 1.9-fold higher and β-HT2B was 6.5-fold higher, resulting in approximately 3-fold increase in AUC0-∞ for total (α+β)-HT2B. Paroxetine decreased the clearance of α-HT2B and β-HT2B metabolites of AUStEDo with corresponding increases in mean half-life of approximately 1.5-fold and 2.7-fold, respectively. In the presence of paroxetine, Cmax of α-HT2B and β-HT2B were 1.2-fold and 2.2-fold higher, respectively. The effect of moderate or weak CYP2D6 inhibitors such as duloxetine, sertraline, and selective serotonin reuptake inhibitors (SSRIs) on the exposure of deuterated benzine and its metabolites has not been evaluated. Duloxetine AUStEDo was not evaluated for interaction with duloxetine. Duloxetine is a substrate for P-glycoprotein. A study in healthy subjects showed that tetrabenazine (25 mg twice daily for 3 days) did not affect the bioavailability of duloxetine, suggesting that at this dose, tetrabenazine does not affect P-glycoprotein in the intestinal tract. In vitro studies also do not suggest that tetrabenazine or its metabolites are P-glycoprotein inhibitors.
Figure 2: Distribution of the Change in Total Maximal Chorea Scores in Study 1.

Figure 2 shows the distribution of values for the change in Total Maximal Chorea Score in Study 1. Negative values indicate a reduction in chorea and positive numbers indicate an increase in chorea.

A patient-rated global impression of change assessed how patients rated their overall Huntington's disease symptoms. Fifty-one percent of patients treated with AUSTEDO rated their symptoms as "Much Improved" or "Very Much Improved" at the end of treatment, compared to 28% of placebo-treated patients. In a physician-rated global impression of change, 42% of patients treated with AUSTEDO rated their symptoms as "Much Improved" or "Very Much Improved" at the end of treatment compared to 13% of placebo-treated patients.

14.2 Tardive Dyskinesia

The efficacy of AUSTEDO in the treatment of tardive dyskinesia was established in two 12-week, randomized, double-blind, placebo-controlled, multi-center trials conducted in 335 adult ambulatory patients with tardive dyskinesia caused by use of dopaminergic receptor antagonists. Patients had a history of using a dopamine receptor antagonist (antipsychotics, metoclopramide) for at least 3 months (or 1 month in patients 60 years of age and older). Concurrent diagnoses included schizophrenia/schizoaffective disorder (26%) and mood disorder (33%). With respect to concurrent antipsychotic use, 54% of patients were receiving atypical antipsychotics, 12% were receiving typical antipsychotics or combination antipsychotics, and 24% were not receiving antipsychotics.

The Abnormal Involuntary Movement Scale (AIMS) was the primary efficacy measure for the assessment of tardive dyskinesia severity. The AIMS is a 12-item scale; items 1 to 7 assess the severity of involuntary movements across body regions and these items were used in each study. Each of the 7 items was scored on a 0 to 4 scale, rated as: 0-not present; 1-minimal, may be extreme normal (abnormal movements occur infrequently and/or are difficult to detect); 2-mild (abnormal movements occur infrequently and are easy to detect); 3-moderate (abnormal movements occur frequently and are easy to detect) or 4-severe (abnormal movements occur almost continuously and/or of extreme intensity). The AIMS total score (sum of items 1 to 7) could range from 0 to 28, with a decrease in score indicating improvement.

In Study 1, a 12-week, placebo-controlled, fixed-dose trial, adults with tardive dyskinesia were randomized 1:1:1:1 to 12 mg AUSTEDO, 24 mg AUSTEDO, 36 mg AUSTEDO, or placebo. Treatment duration included a 4-week dose escalation period and an 8-week maintenance period followed by a 1-week washout. The dose of AUSTEDO was started at 12 mg per day and increased at weekly intervals in 8 mg/day increments to a dose target of 12 mg, 24 mg or 36 mg per day. The population was 21 to 81 years old (mean 51 years), 49% male, and 70% Caucasian. In Study 1, the AIMS total score for patients receiving AUSTEDO demonstrated statistically significant improvement, from baseline to Week 12, of 3.3 and 3.2 units for the 36 mg and 24 mg doses, respectively, compared with 1.4 units in placebo (Study 1 Table 5).

The improvements on the AIMS total score over the course of the study are displayed in Figure 3. Data did not suggest substantial differences in efficacy across various demographic groups. The treatment response rate distribution, based on magnitude of AIMS total score from baseline to week 12, is displayed in Figure 4.

The mean changes in the AIMS total score by visit are shown in Figure 5. In Study 2, a 12-week, placebo-controlled, flexible-dose trial, adults with tardive dyskinesia (n=113) received daily doses of placebo or AUSTEDO, starting at 12 mg per day with increments allowed in 5 mg increments at 1-week intervals until satisfactory control of dyskinesia was achieved, until intolerable side effects occurred, or until a maximal dose of 48 mg per day was reached. Treatment duration included a 6-week dose titration period and a 6-week maintenance period followed by a 1-week washout. The population was 25 to 75 years old (mean 55 years), 46% male, and 70% Caucasian. Patients were titrated to an optimal dose over 6 weeks. The average dose of AUSTEDO after treatment was 36.3 mg per day. There was no evidence suggesting substantial differences in efficacy across various demographic groups. In Study 2, AIMS total score for patients receiving AUSTEDO demonstrated statistically significant improvement by 3.0 units from baseline to endpoint (Week 12), compared with 1.6 units in the placebo group with a treatment effect of -1.4 units. Table 5 summarizes the effects of AUSTEDO on tardive dyskinesia based on the AIMS.

Table 5: Improvement in AIMS Total Score in Patients Treated with AUSTEDO in Study 1 and Study 2

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Group</th>
<th>Primary Efficacy Measure: AIMS Total Score</th>
<th>Treatment Effect (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean Baseline Score (SD)</td>
<td>LS Mean Change from Baseline (SE)</td>
</tr>
<tr>
<td>Study 1</td>
<td>AUSTEDO 36 mg * (n = 55)</td>
<td>10.1 (3.21)</td>
<td>-3.3 (0.42)</td>
</tr>
<tr>
<td></td>
<td>AUSTEDO 24 mg (n = 49)</td>
<td>9.4 (2.93)</td>
<td>-3.2 (0.45)</td>
</tr>
<tr>
<td></td>
<td>AUSTEDO 12 mg (n = 60)</td>
<td>9.6 (2.40)</td>
<td>-2.1 (0.42)</td>
</tr>
<tr>
<td></td>
<td>Placebo (n = 59)</td>
<td>9.5 (2.71)</td>
<td>-1.4 (0.41)</td>
</tr>
<tr>
<td>Study 2</td>
<td>AUSTEDO (12-48 mg/day)* (n = 55)</td>
<td>9.7 (4.14)</td>
<td>-3.0 (0.45)</td>
</tr>
<tr>
<td></td>
<td>Placebo (n = 57)</td>
<td>9.6 (3.78)</td>
<td>-1.6 (0.46)</td>
</tr>
</tbody>
</table>

* Dose that was statistically significantly different from placebo after adjusting for multiplicity.

LS Mean = Least-squares mean; SD = Standard deviation; SE = Standard error; CI = 2-tailed 95% confidence interval.

Figure 2: Least Square Means of Change in AIMS Total Score from Baseline for AUSTEDO Compared to Placebo (Study 1)

**Figure 4:** Percent of Patients with Specified Magnitude of AIMS Total Score Improvement at the End of Week 12 (Study 1)

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

AUSTEDO tablets are available in the following strengths and packages:

- 6 mg: round, purple-coated tablets, with "6D" printed in black ink on one side.
- 9 mg: round, blue-coated tablets, with "9D" printed in black ink on one side.
- 12 mg: round, beige-coated tablets, with "12D" printed in black ink on one side.

Bottles of 60 tablets: NDC 68646-170-60

Bottles of 60 tablets: NDC 68646-171-60

Storage:
Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]). Protect from light and moisture.
PATIENT COUNSELING INFORMATION

Advise the patient or caregiver to read the FDA-approved patient labeling (Medication Guide).

Administration Instructions

Advise patients to take AUSTEDO with food. AUSTEDO tablets should be swallowed whole and not chewed, crushed, or broken [see Dosage and Administration (2.1)].

Risk of Depression and Suicide in Patients with Huntington's Disease

Advise patients, their caregivers, and families that AUSTEDO may increase the risk of depression, worsening depression, and suicidality, and to immediately report any symptoms to a healthcare provider [see Contraindications (4), Warnings and Precautions (5.2)].

Prolongation of the QT Interval

Inform patients to consult their physician immediately if they feel faint, less conscious, or have heart palpitations [see Warnings and Precautions (5.3)].

Advise patients to inform physicians that they are taking AUSTEDO before any new drug is taken.

Risk of Sedation and Somnolence

Advise patients that AUSTEDO may cause sedation and somnolence and may impair the ability to perform tasks that require complex motor and mental skills. Until they learn how they respond to a stable dose of AUSTEDO, patients should be careful doing activities that require them to be alert, such as driving a car or operating machinery [see Warnings and Precautions (5.7)].

Interaction with Alcohol or Other Sedating Drugs

Advise patients that alcohol or other drugs that cause sleepiness will worsen somnolence [see Drug Interactions (7.6)].

Concomitant Medications

Advise patients to notify their physician of all medications they are taking and to consult with their healthcare provider before starting any new medications because of a potential for interactions [see Contraindications (4) and Drug Interactions (7.1, 7.5)].

What is AUSTEDO?

AUSTEDO is a prescription medicine that is used to treat:

- the involuntary movements (chorea) of Huntington's disease. AUSTEDO does not cure the cause of the involuntary movements, and it does not treat other symptoms of Huntington's disease, such as problems with thinking or emotions.
- movements in the face, tongue, or other body parts that cannot be controlled (tardive dyskinesia).

It is not known if AUSTEDO is safe and effective in children.

Who should not take AUSTEDO?

Do not take AUSTEDO if you:

- have Huntington's disease and are depressed or have thoughts of suicide. See "What is the most important information I should know about AUSTEDO?"
- have liver problems.
- are taking a monoamine oxidase inhibitor (MAOI) medicine. Do not take an MAOI within 14 days after you stop taking AUSTEDO. Do not start AUSTEDO if you stopped taking an MAOI in the last 14 days. Ask your healthcare provider or pharmacist if you are not sure.
- are taking reserpine. Do not take medicines that contain reserpine (such as Serpasil and Poneez-R) with AUSTEDO. If your healthcare provider plans to switch you from taking reserpine to AUSTEDO, you must wait at least 20 days after your last dose of reserpine before you start taking AUSTEDO.
- are taking tetrabenazine (Xenazine). If your healthcare provider plans to switch you from tetrabenazine (Xenazine) to AUSTEDO, take your first dose of AUSTEDO on the day after your last dose of tetrabenazine (Xenazine).
- are taking valbenazine (Ingrezza).

Before taking AUSTEDO, tell your healthcare provider about all of your medical conditions, including if you:

- have emotional or mental problems (for example, depression, anxiety, anger, agitation, psychosis, previous suicidal thoughts or suicide attempts).
- have liver disease.
- have an irregular heart rhythm or heartbeat (QT prolongation, cardiac arrhythmia) or a heart problem called congenital long QT syndrome.
- have low levels of potassium or magnesium in your blood (hypokalemia or hypomagnesemia).
- have breast cancer or a history of breast cancer.
- are pregnant or plan to become pregnant. It is not known if AUSTEDO can harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if AUSTEDO passes into breast milk.

Tell your healthcare provider about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Taking AUSTEDO with certain other medicines may cause side effects. Do not start any new medicines while taking AUSTEDO without talking to your healthcare provider first.
How should I take AUSTEDO?
- Take AUSTEDO exactly as your healthcare provider tells you to take it.
- Take AUSTEDO by mouth and with food.
- Swallow AUSTEDO tablets whole with water. Do not chew, crush, or break AUSTEDO tablets before swallowing. If you cannot swallow AUSTEDO tablets whole, tell your healthcare provider. You may need a different medicine.
- If your dose of AUSTEDO is 12 mg or more each day, take AUSTEDO tablets 2 times a day in equal doses with food.
- Your healthcare provider will increase your dose of AUSTEDO each week for several weeks, until you and your healthcare provider find the right dose for you.
- Tell your healthcare provider if you stop taking AUSTEDO for more than 1 week. Do not take another dose until you talk to your healthcare provider.

What should I avoid while taking AUSTEDO?
Sleepiness (sedation) is a common side effect of AUSTEDO. While taking AUSTEDO, do not drive a car or operate dangerous machinery until you know how AUSTEDO affects you. Drinking alcohol and taking other drugs that may also cause sleepiness while you are taking AUSTEDO may increase any sleepiness caused by AUSTEDO.

What are the possible side effects of AUSTEDO?
AUSTEDO can cause serious side effects, including:
- Depression and suicidal thoughts or actions in people with Huntington’s disease. See “What is the most important information I should know about AUSTEDO?”
- Irregular heartbeat (QT prolongation). AUSTEDO increases your chance of having certain changes in the electrical activity in your heart. These changes can lead to a dangerous abnormal heartbeat. Taking AUSTEDO with certain medicines may increase this chance.
  - If you are at risk of QT prolongation, your healthcare provider should check your heart before and after increasing your AUSTEDO dose above 24 mg a day.
- Neuroleptic Malignant Syndrome (NMS). Call your healthcare provider right away and go to the nearest emergency room if you develop these signs and symptoms that do not have another obvious cause:
  - high fever
  - problems thinking
  - increased sweating
  - stiff muscles
  - very fast or uneven heartbeat
- Restlessness. You may get a condition where you feel a strong urge to move. This is called akathisia.
- Parkinsonism in people with Huntington’s disease. Symptoms of parkinsonism include: slight shaking, body stiffness, trouble moving, or keeping your balance.

The most common side effects of AUSTEDO in people with Huntington’s disease include:
- sleepiness (sedation)
- diarrhea
- tiredness
- dry mouth

The most common side effects of AUSTEDO in people with tardive dyskinesia include:
- inflammation of the nose and throat (nasopharyngitis)
- problems sleeping (insomnia)

These are not all the possible side effects of AUSTEDO. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store AUSTEDO?
- Store AUSTEDO tablets at room temperature, between 68°F to 77°F (20°C to 25°C).
- Keep the bottle tightly closed to protect AUSTEDO from light and moisture.

General information about the safe and effective use of AUSTEDO.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use AUSTEDO for a condition for which it was not prescribed. Do not give AUSTEDO to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for information about AUSTEDO that is written for health professionals.

What are the ingredients in AUSTEDO?
Active ingredient: deutetabenazine
Inactive ingredients: ammonium hydroxide, black iron oxide, n-butyl alcohol, butylated hydroxyanisole, butylated hydroxytoluene, magnesium stearate, mannitol, microcrystalline cellulose, polyethylene glycol, polyethylene oxide, polysorbate 80, polyvinyl alcohol, povidone, propylene glycol, shellac, talc, titanium dioxide, and FD&C blue #2 lake. The 6 mg tablets also contain FD&C red #40 lake. The 12 mg tablets also contain FD&C yellow #6 lake.

Distributed by:
Teva Pharmaceuticals USA, Inc.
North Wales, PA 19454
AUSMG-002
For more information, go to www.AUSTEDO.com or call 1-888-483-8279.

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