AUSTEDO® (deutetrabenazine) tablets, for oral use

1 INDICATIONS AND USAGE

WARNING: DEPRESSION AND SUICIDALITY IN PATIENTS WITH HUNTINGTON’S DISEASE

- Increases the risk of depression and suicidal thoughts and behavior (suicidal ideation) in patients with Huntington’s disease (5.1)
- Balance risks of depression and suicidality with the clinical need for treatment of chorea when considering the use of AUSTEDO XR or AUSTEDO (5.1)
- Monitor patients for the emergence or worsening of depression, suicidality, or unusual changes in behavior (5.1)
- Inform patients, caregivers, and families of the risk of depression and suicidality and instruct to report behaviors of concern promptly to the treating physician (5.1)
- Exercise caution when treating patients with a history of depression or prior suicide attempts or ideation (5.1)
- AUSTEDO XR and AUSTEDO are contraindicated in patients who are suicidal, and in patients with untreated or inadequately treated depression (4, 5.1)

2 DOSAGE AND ADMINISTRATION

- Starting Dosage: 12 mg once daily (6 mg per day) as a single daily dose (2.1)
- Administer AUSTEDO with food and administer total daily dosages of 12 mg or above in two divided doses (2.1)
- Titrate at weekly intervals by 6 mg per day based on reduction of chorea or tardive dyskinesia, and tolerability, up to a maximum recommended daily dosage of 48 mg (2.1)
- Administer AUSTEDO with food and administer total daily dosages of 12 mg or above in two divided doses (2.1)

2.1 Dosing Information

2.2 Switching Patients from Tetrabenazine to AUSTEDO XR or AUSTEDO

2.3 Dosage Adjustment with Strong CYP2D6 Inhibitors

2.4 Dosage Adjustment in Poor CYP2D6 Metabolizers

2.5 Discontinuation and Interruption of Treatment

3 DOSAGE FORMS AND STRENGTHS

AUSTEDO XR (deutetrabenazine) extended-release tablets, for oral use

- Tablets: 6 mg, 12 mg, and 24 mg
- Extended-release tablets: 6 mg, 9 mg, and 12 mg

AUSTEDO® XR (deutetrabenazine) extended-release tablets

- Tablets: 6 mg, 12 mg, and 24 mg

4 CONTRAINDICATIONS

- AUSTEDO XR and AUSTEDO are vesicular monoamine transporter 2 (VMAT2) inhibitors indicated safely and effectively. See full prescribing information for AUSTEDO XR and AUSTEDO.
- These highlights do not include all the information needed to use AUSTEDO XR or AUSTEDO

5 WARNINGS AND PRECAUTIONS

5.1 Depression and Suicidality

- Suicidal, or untreated/inadequately treated depression in patients with Huntington’s disease (4, 5.1)
- Hepatic impairment (4, 5.6)
- Taking reserpine, MAOIs, tetrabenazine, or valbenazine (4, 7.2, 7.3, 7.6)

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

5.3 QTc Prolongation

- QT Prolongation: Avoid use in patients with congenital long QT syndrome or with arrhythmias associated with a prolonged QT interval (5.3)

5.4 Neuroleptic Malignant Syndrome (NMS)

- Neuroleptic Malignant Syndrome (NMS): Discontinue if this occurs (5-4)
- Akathisia, agitation, restlessness, and Parkinsonism: Reduce dose or discontinue if this occurs (5.5, 5.6)

5.5 Alcohol or Other Sedating Drugs

- Sedation/somnolence: May impair the patient’s ability to drive or operate complex machinery (5.7)

5.6 Parkinsonism

- Use in patients with Parkinson’s disease (5.6)

5.7 Sedation and Somnolence

- Use in patients with sedation/somnolence (5.7)

5.8 Hyperprolactinemia

- Use in patients with hyperprolactinemia (5.8)

5.9 Binding to Melanin-Containing Tissues

- Use in patients with binding to melanin-containing tissues (5.9)

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

- 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)

6.2 Tardive Dyskinesia

- Most common adverse reactions (that occurred in 4% of AUSTEDO-treated patients with tardive dyskinesia and greater than placebo): nasopharyngitis and insomnia (6.1)

6.3 Chorea Associated with Huntington's Disease

7 DRUG INTERACTIONS

7.1 Strong CYP2D6 Inhibitors

7.2 Reserpine

7.3 Monoamine Oxidase Inhibitors (MAOIs)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

- Pregnancy: Based on animal data, may cause fetal harm (8.1)

8.2 Lactation

- Lactation: Use in patients who are breastfeeding (8.2)

8.3 Pediatric Use

- Pediatric Use: Use in patients with pediatric use (8.3)

8.4 Geriatric Use

- Use in patients with geriatric use (8.4)

8.5 Concomitant Use

- Use in patients with concomitant use (8.5)

9 OVERDOSAGE

- Overdosage: Based on animal data, may cause fetal harm (9.1)

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

10.2 Pharmacodynamics

10.3 Pharmacokinetics

11 DESCRIPTION

11.1 AUSTEDO XR

11.2 AUSTEDO

12 CLINICAL STUDIES

12.1 Chorea Associated with Huntington’s Disease

12.2 Tardive Dyskinesia

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 HOW SUPPLIED/STORAGE AND HANDLING

15 PATIENT COUNSELING INFORMATION

16 USE IN SPECIFIC POPULATIONS

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.
AUSTEDO® XR (deutetrabenazine) extended-release tablets

AUSTEDO® (deutetrabenazine) tablets

FULL PRESCRIBING INFORMATION

WARNING: DEPRESSION AND SUICIDALITY IN PATIENTS WITH HUNTINGTON’S DISEASE

AUSTEDO XR and AUSTEDO can increase the risk of depression and suicidal thoughts and behavior (suicidality) in patients with Huntington’s disease. Anyone considering the use of AUSTEDO XR or AUSTEDO must balance the risks of depression and suicidality with the clinical need for treatment of chorea. Close monitoring 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. AUSTEDO XR and AUSTEDO are contraindicated in patients who are suicidal, and in patients with untreated or inadequately treated depression [see Contraindications (4) and Warnings and Precautions (5.1)].

1 INDICATIONS AND USAGE

AUSTEDO XR and AUSTEDO are indicated in adults for the treatment of:
• chorea associated with Huntington’s disease [see Clinical Studies (14.1)]
• tardive dyskinesia [see Clinical Studies (14.2)]

2 DOSE ADMINISTRATION

2.1 Dosing Information

The dose of AUSTEDO XR and AUSTEDO is determined individually for each patient based on reduction of chorea and/or tardive dyskinesia and tolerability. Table 1 displays the recommended dosage and important administration instructions of AUSTEDO XR and AUSTEDO when first prescribed to patients who are not being switched from tetrabenazine (a related VMAT2 inhibitor).

Table 1: Recommended Dosage and Important Administration Instructions for AUSTEDO XR and AUSTEDO

<table>
<thead>
<tr>
<th>AUSTEDO XR extended-release tablet</th>
<th>AUSTEDO tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommended Starting Dosage</strong></td>
<td></td>
</tr>
<tr>
<td>12 mg once daily (12 mg per day)</td>
<td>6 mg twice daily (12 mg per day)</td>
</tr>
<tr>
<td><strong>Recommended Dose Titration</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Important Administration Instructions</strong></td>
<td></td>
</tr>
<tr>
<td>• Administer AUSTEDO XR with or without food [see Clinical Pharmacology (12.3)].</td>
<td>• Administer AUSTEDO with food [see Clinical Pharmacology (12.3)].</td>
</tr>
<tr>
<td>• Swallow AUSTEDO XR whole, Do not chew, crush, or break tablets.</td>
<td>• Swallow AUSTEDO whole, Do not chew, crush, or break tablets.</td>
</tr>
<tr>
<td>• Administer AUSTEDO XR once daily.</td>
<td>• Administer AUSTEDO total daily dosages of 12 mg or above in two divided doses.</td>
</tr>
</tbody>
</table>

Swapping Between AUSTEDO and AUSTEDO XR

When switching between AUSTEDO tablets (twice daily) and AUSTEDO XR extended-release tablets (once daily), switch to the same total daily dosage.

2.2 Switching Patients from Tetrabenazine to AUSTEDO XR or AUSTEDO

Discontinue tetrabenazine and initiate AUSTEDO XR or AUSTEDO the following day. The recommended initial dosing regimen of AUSTEDO XR or AUSTEDO in patients switching from tetrabenazine to AUSTEDO XR or AUSTEDO is shown in Table 2.

Table 2: Recommended Initial Dosing Regimen when Switching from Tetrabenazine to AUSTEDO XR or AUSTEDO

<table>
<thead>
<tr>
<th>Current tetrabenazine daily dosage</th>
<th>Initial regimen of AUSTEDO XR extended-release tablet</th>
<th>Initial regimen of AUSTEDO tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.5 mg</td>
<td>6 mg once daily</td>
<td>6 mg once daily</td>
</tr>
<tr>
<td>25 mg</td>
<td>12 mg once daily</td>
<td>6 mg twice daily</td>
</tr>
<tr>
<td>31.25 mg</td>
<td>18 mg once daily</td>
<td>9 mg twice daily</td>
</tr>
<tr>
<td>50 mg</td>
<td>24 mg once daily</td>
<td>12 mg twice daily</td>
</tr>
<tr>
<td>62.5 mg</td>
<td>30 mg once daily</td>
<td>15 mg twice daily</td>
</tr>
<tr>
<td>75 mg</td>
<td>36 mg once daily</td>
<td>18 mg twice daily</td>
</tr>
<tr>
<td>87.5 mg</td>
<td>42 mg once daily</td>
<td>21 mg twice daily</td>
</tr>
<tr>
<td>100 mg</td>
<td>48 mg once daily</td>
<td>24 mg twice daily</td>
</tr>
</tbody>
</table>

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

2.3 Dosage Adjustment with Strong CYP2D6 Inhibitors

In patients receiving strong CYP2D6 inhibitors, the total daily dosage of AUSTEDO XR or AUSTEDO should not exceed 36 mg [see Drug Interactions (7.2)].

2.4 Dosage Adjustment in Poor CYP2D6 Metabolizers

In patients who are poor CYP2D6 metabolizers, the total daily dosage of AUSTEDO XR or AUSTEDO should not exceed 36 mg [see Use in Specific Populations (8.7)].

AUSTEDO XR extended-release tablets are available in the following strengths:
• The 6 mg extended-release tablets are round, grey-coated tablets, with “06” printed in black ink on one side.
• The 12 mg extended-release tablets are round, blue-coated tablets, with “Q12” printed in black ink on one side.
• The 24 mg extended-release tablets are round, purple-coated tablets, with “Q24” printed in black ink on one side.

AUSTEDO tablets are available in the following strengths:
• The 6 mg tablets are round, purple-coated tablets, with “SD” over “6” printed in black ink on one side.
• The 9 mg tablets are round, blue-coated tablets, with “SD” over “9” printed in black ink on one side.
• The 12 mg tablets are round, beige-coated tablets, with “SD” over “12” printed in black ink on one side.

4 CONTRAINDICATIONS

AUSTEDO XR and AUSTEDO are contraindicated in patients:
• With Huntington’s disease who are suicidal, or have untreated or inadequately treated depression [see Warnings and Precautions (5.1)].
• With hepatic impairment [see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)].
• Taking resepine. At least 20 days should elapse after stopping resepine before starting AUSTEDO XR or AUSTEDO [see Drug Interactions (7.2)].
• Taking monoamine oxidase inhibitors (MAOIs). AUSTEDO XR and AUSTEDO should not be used in combination with an MAOI, or within 14 days of discontinuing therapy with an MAOI [see Drug Interactions (7.3)].
• Taking tetrahydrobiopterin, 5-MTHF, 5-hydroxytryptophan, or L-tryptophan [see Drug Interactions (7.3)].

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 behaviors (suicidality). AUSTEDO XR and 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 XR or AUSTEDO, the risk of suicidality should be balanced against the need for treatment of chorea. All patients treated with AUSTEDO XR or AUSTEDO should be observed for new or worsening depression or suicidality. If depression or suicidality does not resolve, consider discontinuing treatment with AUSTEDO XR or AUSTEDO.

Patients, their caregivers, and families should be informed of the risks of depression, worsening depression, and suicidality associated with AUSTEDO XR and AUSTEDO, and should be instructed to report behaviors of concern promptly to the treating physician. Patients with Huntington’s disease who express suicidal ideas should be evaluated immediately.

5.2 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 XR and AUSTEDO, may cause a worsening in mood, cognition, rigidity, and functional capacity.

Prescribers should periodically re-evaluate the need for AUSTEDO XR or 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 XR or AUSTEDO.

5.3 QTc Prolongation

AUSTEDO XR and AUSTEDO may prolong the QT interval, but the degree of QT prolongation is not clinically significant when AUSTEDO XR or AUSTEDO is administered within the recommended dosage range [see Clinical Pharmacology (12.2)].

AUSTEDO XR and 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 points and/or sudden death in association with the use of 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 XR or 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 elevated blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevation of enzymes (e.g., transaminases, 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.

AUSTEDO® (deutetrabenazine) tablets
The management of NMS should include (1) immediate discontinuation of AUSTEDO XR and 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 XR or AUSTEDO is needed after recovery from NMS, patients should be monitored for signs of recurrence.

5.5 Akathisia, Agitation, and Restlessness
AUSTEDO XR and 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 patients with Huntington’s disease, 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 XR or 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 XR or AUSTEDO, the AUSTEDO XR or AUSTEDO dose should be reduced; some patients may require discontinuation of therapy.

5.6 Parkinsonism
AUSTEDO XR and 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 the disease-dependent 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 XR or AUSTEDO, the AUSTEDO XR or AUSTEDO dose should be reduced; some patients may require discontinuation of therapy.

5.7 Sedation and Somnolence
Sedation is a common dose-limiting adverse reaction of AUSTEDO XR and 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 XR or AUSTEDO and know how the drug affects them.

5.8 Hyperprolactinemia
Serum prolactin levels were not evaluated in the AUSTEDO XR and AUSTEDO development program. Tetrabenazine, an unrelated 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 that are prolactin-dependent in vitro, a factor of potential importance if AUSTEDO XR or AUSTEDO is being considered for a patient with previously detected breast cancer. Although reports of 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 XR or AUSTEDO, or tetrabenazine development programs) has been associated with low levels of estrogen and an 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 XR and AUSTEDO.

5.9 Binding to Melanin-Containing Tissues
Since tetrabenazine or its metabolites bind to melanin-containing tissues, it could accumulate in these tissues over time. This raises the possibility that AUSTEDO XR and 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 occurring after long-term exposure.

The clinical relevance of tetrabenazine’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 [see Clinical Pharmacology (12.3)].

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)]
- Citalopram 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)]
- Parkinsonism [see Warnings and Precautions (5.6)]
- Sedation and Somnolence [see Warnings and Precautions (5.7)]
- 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.

The studies described below were conducted with AUSTEDO XR tablets; adverse reactions with AUSTEDO XR extended-release tablets are expected to be similar to AUSTEDO tablets.

Patients with Huntington’s Disease

Study 1 [see Clinical Studies (14.3)] was a randomized, 12-week, placebo-controlled study in patients with chorea associated with Huntington’s disease. A total of 45 patients received placebo and 45 patients received placebo. Patients ranged in age between 23 and 76 years (mean 54 years); 66% were male, and 92% were Caucasian. The most common adverse reactions occurring in greater than 8% of AUSTEDO-treated patients were somnolence, diarrhea, 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 3.

Table 3: 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>%</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>9</td>
<td>0</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>
<tr>
<td>Contusion</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 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) [see Clinical Studies (14.2)]. 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% 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 4.

Table 4: Adverse Reactions in 2 Placebo-Controlled Tardive Dyskinesia Studies (Study 1 and Study 2) of 12-week Treatment on AUSTEDO Reported in at Least 2% of Patients and Greater than Placebo

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>AUSTEDO (N = 129) (%)</th>
<th>Placebo (N = 133) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Depression/Dysthmic 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 XR or AUSTEDO may be necessary when using a strong CYP2D6 inhibitor in patients maintained on a stable dose of AUSTEDO XR or AUSTEDO. Concomitant use of strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, quinidine, bupropion) has been shown to increase the systemic exposure to the active dihydrometabolites of deutetrabenazine by approximately 3-fold. The daily dose of AUSTEDO XR or AUSTEDO should not exceed 36 mg per day in patients taking strong CYP2D6 inhibitors [see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)].

7.2 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 XR or 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 XR or AUSTEDO. AUSTEDO XR and AUSTEDO should not be used concomitantly with reserpine [see Contraindications (4)].

7.3 Monoamine Oxidase Inhibitors (MAOIs)

AUSTEDO XR and AUSTEDO are contraindicated in patients taking MAOIs. AUSTEDO XR and AUSTEDO should not be used in combination with an MAOI, or within 14 days of discontinuing therapy with an MAOI [see Contraindications (4)].
Deutetrabenazine is a white to slightly yellow crystalline powder that is sparingly soluble in water and soluble in ethanol.

AUSTEDO XR extended-release tablets contain 6 mg, 12 mg, or 24 mg deutetrabenazine, and the following inactive ingredients: ammonium hydroxide, black iron oxide, butyl alcohol, butylated hydroxyanisole, butylated hydroxytoluene, cellulose acetate, hydroxypropyl cellulose, hypromellose, isopropyl alcohol, magnesium stearate, polyethylene glycol, polyethylene glycol 3350, polyethylene oxide, propylene glycol, propylene glycol, shellac, sodium chloride, talc, titanium dioxide, FD&C blue #2 lake, and FD&C red #40 lake. The 6 mg and 12 mg extended-release tablets also contain FD&C yellow #6 lake.

AUSTEDO tablets contain 6 mg, 9 mg, or 12 mg deutetrabenazine, and the following inactive ingredients: ammonium hydroxide, black iron oxide, butyl alcohol, butylated hydroxyanisole, butylated hydroxytoluene, magnesium stearate, mannitol, microcrystalline cellulose, polyethylene glycol, polyethylene oxide, polysorbate 80, propylene glycol, propylene glycol, shellac, tcalc, 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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanism by which deutetrabenazine 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 effect as a reversible depletor of monoamines (such as dopamine, serotonin, norepinephrine, and histamine) from nerve terminals. The major circulating metabolites (α- and β-hexahydro-9,10-di(methoxy-d3)-3-(2-methylpropyl)-2H-benzo[a]quinolizin-2-one) are metabolized in the liver and excreted in urine.

12.2 Pharmacodynamics

Cardiac Electrophysiology

At the maximum recommended dose, AUSTEDO XR and AUSTEDO do not prolong the QT interval to any clinically relevant extent. An exposure-response analysis on QTC prolongation from a study in extensive or intermediate (EM) and poor CYP2D6 metabolizers (PM) showed that a clinically-relevant effect can be excluded at exposures following single doses of 24 and 48 mg of AUSTEDO.

12.3 Melanin Binding

Deutetrabenazine or its metabolites bind to melanin-containing tissues (i.e., eye, skin, fur) in pigmented rats. After a single oral dose of radiolabeled deutetrabenazine, radioactivity was still detected in eye and fur at 35 days following dosing.
Intake of approximately 3-fold [see Dosage and Administration (2.4)]

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

Absorption

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

Peak plasma concentrations (Cmax) of deutetrabenazine, deuterated α-HTBZ, and β-HTBZ are reached within approximately 3 hours, followed by sustained plateaus for several hours allowing for a 24-hour dosing interval.

Deutetrabenazine is absorbed following oral administration and is rapidly distributed to the brain, with the highest binding in the striatum and lowest binding in the cortex.

The in vitro protein binding of tetrabenazine, α-HTBZ, and β-HTBZ was examined in human plasma for concentrations ranging from 50 to 200 ng/mL. Tetrabenazine binding ranged from 82% to 85%, α-HTBZ binding ranged from 60% to 68%, and β-HTBZ binding ranged from 59% to 63%.

Elimination of α-HTBZ and β-HTBZ metabolites is primarily renal, with 70% to 80% excreted in the urine and 10% to 20% excreted in the feces.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Mutagenesis

Impairment of Fertility

The efficacy of AUSTEDO as a treatment for chorea associated with Huntington’s disease was established primarily in Study 1, a randomized, double-blind, placebo-controlled, multi-center trial conducted in 90 ambulatory patients with manifest chorea associated with Huntington’s disease. The diagnosis of Huntington’s disease was based on family history, neurological exam, and genetic testing. Treatment duration was 12 weeks, including an 8-week dose titration period and a 4-week maintenance period, followed by a 1-week washout. Patients were not blinded to discontinuation.

Chorea Associated with Huntington’s Disease

The efficacy of AUSTEDO as a treatment for chorea associated with Huntington’s disease was established primarily in Study 1, a randomized, double-blind, placebo-controlled, multi-center trial conducted in 90 ambulatory patients with manifest chorea associated with Huntington’s disease. The diagnosis of Huntington’s disease was based on family history, neurological exam, and genetic testing. Treatment duration was 12 weeks, including an 8-week dose titration period and a 4-week maintenance period, followed by a 1-week washout. Patients were not blinded to discontinuation.

AUSTEDO XR (deutetrabenazine) extended-release tablets

AUSTEDO® (deutetrabenazine) tablets

12.3 Pharmacokinetics

After oral dosing, plasma concentrations of deutetrabenazine are low compared to that of the active deuterated metabolites because of the extensive hepatic metabolism of deutetrabenazine.

AUSTEDO XR

The effects of food on the bioavailability of AUSTEDO XR were studied in subjects administered a single dose with or without food. Food had no effect on Cmax or AUC of deutetrabenazine, α-HTBZ or β-HTBZ [see Dosage and Administration (2.1)].

AUSTEDO

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

Distribution

The median volume of distribution (Vd/F) of the α-HTBZ, and the β-HTBZ metabolites of deutetrabenazine are approximately 500 L and 730 L, respectively.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Mutagenesis

Impairment of Fertility

The elimination half-life and clearance of AUSTEDO XR are similar to that of AUSTEDO.

65 L/hour and 200 L/hour, respectively, for a 70 kg HD or TD patient with functional CYP2D6 metabolism in the fed state.

The elimination half-life and clearance of AUSTEDO XR are similar to that of AUSTEDO.

Metabolism

In vivo experiments in human liver microsomes demonstrate that deutetrabenazine is extensively biotransformed, mainly by carbonyl reductase, to its major active metabolites, α-HTBZ and β-HTBZ, which are subsequently metabolized primarily by CYP2D6.

In vitro experiments in human liver microsomes show that following intravenous injection of 11C-labeled α-HTBZ, radioactivity is rapidly distributed to the brain, with the highest binding in the striatum and lowest binding in the cortex.

The half-life of the active deuterated α-HTBZ, β-HTBZ, and total (α+β)HTBZ metabolites is approximately 12 hours, 75 hours, and 9 to 11 hours, respectively.

The clearance volume (CL/F) of the α-HTBZ, and β-HTBZ metabolites of deutetrabenazine are approximately 65 L/hour and 200 L/hour, respectively, for a 70 kg HD or TD patient with functional CYP2D6 metabolism in the fed state.

In a mass balance study in 6 healthy subjects, 75% to 86% of the deutetrabenazine dose was excreted in the urine, and fecal recovery accounted for 8% to 11% of the dose. Urinary excretion of the α-HTBZ and β-HTBZ metabolites from deutetrabenazine each accounted for less than 5% of the dose, and fecal excretion accounted for 8% to 11% of the dose. Urinary excretion of the α-HTBZ and β-HTBZ metabolites from deutetrabenazine each accounted for less than 5% of the dose, and fecal excretion accounted for 8% to 11% of the dose.

Excretion

In a mass balance study in 6 healthy subjects, 75% to 86% of the deutetrabenazine dose was excreted in the urine, and fecal recovery accounted for 8% to 11% of the dose. Urinary excretion of the α-HTBZ and β-HTBZ metabolites from deutetrabenazine each accounted for less than 5% of the dose, and fecal excretion accounted for 8% to 11% of the dose.

Specific Populations

Male and Female Patients

There is no apparent effect of gender on the pharmacokinetics of α-HTBZ and β-HTBZ metabolites of deutetrabenazine.

Patients with Renal Impairment

No clinical studies have been conducted to assess the effect of renal impairment on the PK of deutetrabenazine and its primary metabolites.

Patients with 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 to assess the effect of hepatic impairment on the pharmacokinetics of tetrabenazine, a closely related VMA22 inhibitor, the exposure to α-HTBZ and β-HTBZ was up to 40% greater in patients with hepatic impairment, and the mean tetrabenazine Cmax in patients with hepatic impairment was up to 190-fold higher than in healthy subjects [see Contraindications (4), Use in Specific Populations (8.6)].

Drug Interactions

Although the pharmacokinetics of deutetrabenazine and its metabolites have not been systematically evaluated in patients who do not express the drug metabolizing enzyme CYP2D6, it is likely that the exposure to α-HTBZ and β-HTBZ would be increased similarly to taking strong CYP2D6 inhibitors (approximately 3-fold) [see Dosage and Administration (2.4)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Mutagenesis

Impairment of Fertility

The effects of deutetrabenazine on fertility have not been evaluated. Oral administration of deutetrabenazine (doses of 5, 10, or 30 mg/kg/day) to female rats for 3 months resulted in estrous cycle disruption at all doses; the lowest dose tested was similar to the maximum recommended human dose (48 mg/day) on a body surface area (mg/m²) basis.

Oral administration of tetrabenazine (doses of 5, 15, or 30 mg/kg/day) to female rats prior to and throughout mating with untreated females did not affect the bioavailability of tetrabenazine, 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.

14 CLINICAL STUDIES

The studies described below establish effectiveness for Huntington’s disease and tardive dyskinesia were conducted with AUSTEDO tablets. The efficacy of AUSTEDO XR is based on a relative bioavailability study comparing AUSTEDO XR tablets administered once daily and AUSTEDO tablets administered twice daily [see Clinical Pharmacology (12.3)].

14.1 Chorea Associated with Huntington’s Disease

The efficacy of AUSTEDO as a treatment for chorea associated with Huntington’s disease was established primarily in Study 1, a randomized, double-blind, placebo-controlled, multi-center trial conducted in 90 ambulatory patients with manifest chorea associated with Huntington’s disease. The diagnosis of Huntington’s disease was based on family history, neurological exam, and genetic testing. Treatment duration was 12 weeks, including an 8-week dose titration period and a 4-week maintenance period, followed by a 1-week washout. Patients were not blinded to discontinuation.

AUSTEDO was started at 6 mg per day and titrated upward, at weekly intervals, in 6 mg increments until satisfactory treatment of chorea was achieved, tolerable side effects occurred, or until a maximal dose of 48 mg per day was reached. The primary efficacy endpoint was the Total Maximal Chorea Score, an item of the Unified Huntington’s Disease Rating Scale (UHDRS). On this scale, chorea is rated from 0 to 4 (with 0 representing no chorea) for 7 different parts of the body. The total score ranges from 0 to 28.

Of the 90 patients enrolled, 87 patients completed the study. The mean age was 54 (range 23 to 74). Patients were 56% male and 52% Caucasian. The mean dose after titration was 40 mg per day. Table 5 and Figure 1 summarize the effects of AUSTEDO on chorea based on the Total Maximal Chorea Score. Total Maximal Chorea Scores for patients receiving AUSTEDO improved by approximately 4 A4 units from baseline to the maintenance period (average of Week 9 and Week 12), compared to approximately 13 units in the placebo group. The treatment effect of -2.5 units was statistically significant (p<0.0001).

The Maintenance Endpoint is the mean of the Total Maximal Chorea Scores for the Week 9 and Week 12 visits. At the Week 13 follow-up visit (1 week after discontinuation of the study medication), the Total Maximal Chorea Scores of patients who had received AUSTEDO returned to baseline (Figure 1).
**AUSTEDO**® XR (deutetrabenazine) extended-release tablets

**AUSTEDO**® (deutetrabenazine) tablets

Table 5: Change from Baseline to Maintenance Therapy in Total Maximal Chorea (TMC)* Score in Patients with Huntington's Disease Treated with AUSTEDO in Study 1

<table>
<thead>
<tr>
<th>Motor Endpoint</th>
<th>AUSTEDO N=45</th>
<th>Placebo N=45</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in Total Chorea Score* from Baseline to Maintenance Therapy*</td>
<td>-4.4</td>
<td>-1.9</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*TMC is a subscale of the Unified Huntington's Disease Rating Scale (UHDRS)

**AUSTEDO® (deutetrabenazine) tablets**

**AUSTEDO® XR (deutetrabenazine) extended-release tablets**

The mean changes in the AIMS total score by visit are shown 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 3. 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 increases allowed in 6-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), 48% male, and 79% Caucasian. Patients were titrated to an optimal dose over 6 weeks. The average dose of AUSTEDO after treatment was 38.3 mg per day. There was no evidence suggesting a treatment effect of -1.4 units. Figure 4 summarizes the effects of AUSTEDO on tardive dyskinesia based on the AIMS.

Table 6: Improvement in AIMS Total Score in Patients Treated with AUSTEDO in Study 1 and Study 2

<table>
<thead>
<tr>
<th>Study Treatment Group</th>
<th>Primary Efficacy Measure: AIMS Total Score</th>
<th>Mean Baseline Score (SD)</th>
<th>LS Mean Change from Baseline (SE)</th>
<th>Treatment Effect (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUSTEDO 36 mg*</td>
<td></td>
<td>10.1 (2.21)</td>
<td>-3.3 (0.42)</td>
<td>-1.9 (-3.09, -0.79)</td>
</tr>
<tr>
<td>AUSTEDO 24 mg</td>
<td></td>
<td>9.4 (2.53)</td>
<td>-3.2 (0.45)</td>
<td>-1.8 (-3.00, -0.63)</td>
</tr>
<tr>
<td>AUSTEDO 12 mg</td>
<td></td>
<td>9.6 (2.40)</td>
<td>-2.1 (0.42)</td>
<td>-0.7 (-1.84, 0.42)</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td>9.5 (2.71)</td>
<td>-1.4 (0.41)</td>
<td></td>
</tr>
<tr>
<td><strong>Study 2</strong></td>
<td></td>
<td>9.7 (4.14)</td>
<td>-3.0 (0.45)</td>
<td>-1.4 (-2.6, -0.2)</td>
</tr>
<tr>
<td>AUSTEDO (12-48 mg/day)*</td>
<td></td>
<td>9.6 (3.78)</td>
<td>-1.6 (0.46)</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td>9.6 (3.78)</td>
<td>-1.6 (0.46)</td>
<td></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-sided 95% confidence interval.

**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 20% of placebo-treated patients. In a physician-rated clinical global impression of change, physicians rated 42% percent of patients treated with AUSTEDO as "Much Improved" or "Very Much Improved" at the end of treatment compared to 13% of placebo-treated patients.

**Tardive Dyskinesia**

The efficacy of AUSTEDO in the treatment for 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 dopamine 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 (62%) and mood disorder (33%). With respect to concurrent antipsychotic use, 64% of patients were receiving atypical antipsychotics, 12% were receiving typical 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 this 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 thus 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 6 mg/day increments to a dose target of 12 mg, 24 mg or 36 mg per day. The population (n=222) was 21 to 81 years old (mean 57 years), 48% male, and 79% 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 arms, respectively, compared with 1.4 units in placebo (Study 1 in Table 6). 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.
16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

AUSTEDO tablets are supplied in the following configurations:

<table>
<thead>
<tr>
<th>Strength</th>
<th>Description</th>
<th>Package Configuration</th>
<th>NDC Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 mg</td>
<td>Round, grey-coated tablets, with “Q6” printed in black ink on one side</td>
<td>Bottle with child-resistant cap / 30 count</td>
<td>68546-470-56</td>
</tr>
<tr>
<td>12 mg</td>
<td>Round, blue-coated tablets, with “Q12” printed in black ink on one side</td>
<td>Bottle with child-resistant cap / 30 count</td>
<td>68546-471-56</td>
</tr>
<tr>
<td>24 mg</td>
<td>Round, purple-coated tablets, with “Q24” printed in black ink on one side</td>
<td>Bottle with child-resistant cap / 30 count</td>
<td>68546-472-56</td>
</tr>
</tbody>
</table>

AUSTEDO XR Patient Titration Kits are supplied in the following configurations:

<table>
<thead>
<tr>
<th>4-Week Patient Titration Kit</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 mg</td>
</tr>
<tr>
<td>Round, grey-coated tablets, with “Q6” printed in black ink on one side</td>
</tr>
<tr>
<td>Bottle with child-resistant cap / 42 count</td>
</tr>
</tbody>
</table>

AUSTEDO tablets are supplied in the following configurations:

<table>
<thead>
<tr>
<th>Strength</th>
<th>Description</th>
<th>Package Configuration</th>
<th>NDC Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 mg</td>
<td>Round, purple-coated tablets, with “SD” over “6” printed in black ink on one side</td>
<td>Bottle with child-resistant cap / 60 count</td>
<td>68546-710-60</td>
</tr>
<tr>
<td>9 mg</td>
<td>Round, blue-coated tablets, with “SD” over “9” printed in black ink on one side</td>
<td>Bottle with child-resistant cap / 60 count</td>
<td>68546-711-60</td>
</tr>
<tr>
<td>12 mg</td>
<td>Round, beige-coated tablets, with “SD” over “12” printed in black ink on one side</td>
<td>Bottle with child-resistant cap / 60 count</td>
<td>68546-712-60</td>
</tr>
</tbody>
</table>

AUSTEDO XR U.S. Patent Nos: 8,524,733; 9,550,780; 10,959,996; 11,357,772; 11,311,488; 11,564,917

Dispense with Medication Guide available at: www.tevausa.com/medguides

17 PATIENT COUNSELING INFORMATION

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

Administration Instructions

Inform patients that swallowing AUSTEDO XR or AUSTEDO whole and not to chew, crush, or break AUSTEDO XR or AUSTEDO [see Dosage and Administration (2.1)].

AUSTEDO XR

Advise patients to take AUSTEDO XR with or without food in one-daily doses.

AUSTEDO

Advise patients to take AUSTEDO with food. Advise patients to take daily dosages of 12 mg or higher in two divided doses (twice daily).

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

Advise patients, their caregivers, and families that AUSTEDO XR and 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 (5.1)].

Prolongation of the QTc Interval

Inform patients to consult their physician immediately if they feel faint, lose consciousness, or have heart palpitations [see Warnings and Precautions (5.2)]. Advise patients to inform their physicians if they are taking AUSTEDO XR or AUSTEDO before any new drug is taken.

Parkinsonism

Inform patients that AUSTEDO XR and AUSTEDO may cause Parkinson-like symptoms, which could be severe. Advise patients to consult their healthcare provider if they experience slight shaking, body stiffness, trouble moving, trouble keeping their balance, or falls [see Warnings and Precautions (5.3)].

Risk of Sedation and Somnolence

Advise patients that AUSTEDO XR and 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 XR or 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 (5.4)].
Who should not take AUSTEDO XR or AUSTEDO?

Do not take AUSTEDO XR or AUSTEDO if you:

- have Huntington’s disease and are depressed or have thoughts of suicide.
- are taking tetrabenazine. If your healthcare provider plans to switch you from tetrabenazine to AUSTEDO XR or AUSTEDO, take your first dose of AUSTEDO XR or AUSTEDO on the day after your last dose of tetrabenazine.
- are taking valbenazine.

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

- have emotional or mental problems (for example, depression, nervousness, 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 XR or AUSTEDO can harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if AUSTEDO XR or 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 XR or AUSTEDO with other medicines may cause side effects. Do not start any new medicines while taking AUSTEDO XR or AUSTEDO without talking to your healthcare provider first.

How should I take AUSTEDO XR or AUSTEDO?

- Take AUSTEDO XR or AUSTEDO exactly as your healthcare provider tells you to take it.
- If you take AUSTEDO XR, take your dose by mouth one time each day, with or without food.
- If you take AUSTEDO, take your dose by mouth and with food. If your dose of AUSTEDO is 12 mg or more each day, take AUSTEDO tablets 2 times a day in equal doses.
- Swallow AUSTEDO XR or AUSTEDO tablets whole with water. Do not chew, crush, or break AUSTEDO XR or AUSTEDO tablets before swallowing. If you cannot swallow AUSTEDO XR or AUSTEDO tablets whole, tell your healthcare provider. You may need a different medicine.
- Your healthcare provider may increase your dose of AUSTEDO XR or 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 XR or 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 XR or AUSTEDO?

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

What are the possible side effects of AUSTEDO XR and AUSTEDO? AUSTEDO XR and 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 XR and AUSTEDO?”
- Irregular heartbeat (QT prolongation). AUSTEDO XR and 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 XR or AUSTEDO with certain medicines may increase this chance.
- 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
  - very fast or uneven heartbeat
  - increased sweating
  - Restlessness. You may get a condition where you feel a strong urge to move. This is called akathisia.
  - Parkinsonism. Symptoms of parkinsonism include: slight shaking, body stiffness, trouble moving, trouble keeping your balance, or falls.

How to store AUSTEDO XR and AUSTEDO?

Store AUSTEDO XR and AUSTEDO tablets at room temperature between 68°F to 77°F (20°C to 25°C).

Keep the bottle tightly closed to protect AUSTEDO XR and AUSTEDO from light and moisture.

Keep AUSTEDO XR and AUSTEDO and all medicines out of the reach of children.

General information about the safe and effective use of AUSTEDO XR and AUSTEDO.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use AUSTEDO XR or AUSTEDO for a condition for which it was not prescribed. Do not give AUSTEDO XR or 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 XR and AUSTEDO that is written for health professionals.

What are the ingredients in AUSTEDO XR and AUSTEDO? AUSTEDO XR:

Active ingredient: deutetrabenazine

Inactive ingredients: ammonium hydroxide, black iron oxide, butyl alcohol, butylated hydroxyanisole, butylated hydroxytoluene, cellulose acetate, hydroxypropyl cellulose, hypromellose, isopropyl alcohol, magnesium stearate, polyethylene glycol, polyethylene glycol 3350, polyethylene oxide, polyvinyl alcohol, propylene glycol, shellac, sodium chloride, talc, titanium dioxide, FD&C blue #2 lake, and FD&C red #40 lake. The 6 mg and 12 mg extended-release tablets also contain FD&C yellow #6 lake.
AUSTEDO® XR (deutetrabenazine) extended-release tablets
AUSTEDO® (deutetrabenazine) tablets

**AUSTEDO:**

**Active ingredient:** deutetrabenazine

**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.

Manufactured for:

**Teva Neuroscience, Inc.**
Parsippany, NJ 07054
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AUSMG-008

For more information, go to www.AUSTEDO.com or call 1-888-483-8279.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Revised: February 2023

AUSTEDO® XR (deutetrabenazine) extended-release tablets
AUSTEDO® (deutetrabenazine) tablets