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

AUSTEDO™ (deutetrabenazine) tablets, for oral use
Initial U.S. Approval: 2017

WARNING: DEPRESSION AND SUICIDALITY
See full prescribing information for complete boxed warning.

- Increases the risk of depression and suicidal thoughts and behavior (suicidality) in patients with Huntington's disease (5.2)
- Balance risks of depression and suicidality with the clinical need for treatment of chorea when considering the use of AUSTEDO (5.2)
- Monitor patients for the emergence or worsening of depression, suicidality, or unusual changes in behavior (5.2)
- Inform patients, caregivers and families of the risk of depression and suicidality and instruct to report behaviors of concern promptly to the treating physician (5.2)
- Exercise caution when treating patients with a history of depression or prior suicide attempts or ideation (5.2)
- AUSTEDO is contraindicated in patients who are suicidal, and in patients with untreated or inadequately treated depression (4, 5.2)

INDICATIONS AND USAGE

AUSTEDO is a vesicular monoamine transporter 2 (VMAT2) inhibitor indicated for the treatment of chorea associated with Huntington's disease (1)

DOSAGE AND ADMINISTRATION

- The starting dose is 6 mg once daily. Titrate up at weekly intervals by 6 mg per day to a tolerated dose that reduces chorea, up to a maximum recommended daily dosage of 48 mg (24 mg twice daily) (2.1)
- Administer total daily dosages of 12 mg or above in two divided doses (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)

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

- Suicidal, or untreated/inadequately treated depression (4, 5.2)
- Hepatic impairment (4, 8.6, 12.3)
- Taking MAOIs, reserpine, or tetrabenazine (XENAZINE®) (4, 7.2, 7.3, 7.7)

WARNINGS AND PRECAUTIONS

- Neuroleptic Malignant Syndrome (NMS): Discontinue if this occurs (5.3, 7.4)
- Akathisia, agitation, restlessness, and parkinsonism: Reduce dose or discontinue if this occurs (5.4, 5.5)
- Sedation/somnolence: May impair the patient's ability to drive or operate complex machinery (5.6)

ADVERSE REACTIONS

Most common adverse reactions (>8% of AUSTEDO-treated patients and greater than placebo) were: somnolence, diarrhea, dry mouth, and fatigue (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals at 1-888-483-8279 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Concomitant use of strong CYP2D6 inhibitors: Maximum recommended dose of AUSTEDO is 36 mg per day (18 mg twice daily) (2.3, 7.1)
- Alcohol or other sedating drugs: May have additive sedation and somnolence (7.5)

USE IN SPECIFIC POPULATIONS

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 4/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: DEPRESSION AND SUICIDALITY

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 must balance the risks of depression and suicidality with the clinical need for treatment of chorea. Closely monitor patients for the emergence or worsening of depression, suicidality, or unusual changes in behavior. Patients, their caregivers, and families should be informed of the risk of depression and suicidality and should be instructed to report behaviors of concern promptly to the treating physician.

Particular caution should be exercised in treating patients with a history of depression or prior suicide attempts or ideation, which are increased in frequency in Huntington's disease. AUSTEDO is contraindicated in patients who are suicidal, and in patients with untreated or inadequately treated depression *[see Contraindications (4) and Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

AUSTEDO™ is indicated for the treatment of chorea associated with Huntington's disease.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The dose of AUSTEDO is determined individually for each patient based on reduction of chorea 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 6 mg administered orally once daily.

- 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.

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 patients switching from tetrabenazine (XENAZINE®) to AUSTEDO is shown in Table 1.

Table 1. Recommended Initial Dosing Regimen when Switching from Tetrabenazine (XENAZINE®) to AUSTEDO

Current tetrabenazine daily dosage	Initial regimen of AUSTEDO
12.5 mg	6 mg once daily
25 mg	6 mg twice daily
37.5 mg	9 mg twice daily
50 mg	12 mg twice daily
62.5 mg	15 mg twice daily
75 mg	18 mg twice daily
87.5 mg	21 mg twice daily
100 mg	24 mg twice daily

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

In patients receiving strong CYP2D6 inhibitors (e.g., quinidine, antidepressants 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 (12.3)]*.

2.4 Dosage Adjustment in Poor CYP2D6 Metabolizers

In patients who are poor CYP2D6 metabolizers, the total daily dosage of AUSTEDO should not exceed 36 mg (maximum single dose of 18 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 of greater than one week, AUSTEDO therapy should be re-titrated when resumed. For treatment interruption of less than one week, treatment can be resumed at the previous maintenance dose without titration.

3 DOSAGE FORMS AND STRENGTHS

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 is contraindicated in patients:

- Who are suicidal, or in patients with untreated or inadequately treated depression *[see Warnings and Precautions (5.2)]*.
- With hepatic impairment *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.
- Taking monoamine oxidase inhibitors (MAOIs). 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 reserpine. At least 20 days should elapse after stopping reserpine before starting AUSTEDO *[see Drug Interactions (7.2)]*.
- Taking tetrabenazine (XENAZINE®) *[see Drug Interactions (7.7)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Clinical Worsening and Adverse Events

Huntington's disease is a progressive disorder characterized by changes in mood, cognition, chorea, rigidity, and functional capacity over time. VMAT2 inhibitors, including AUSTEDO, may cause a worsening in mood, cognition, rigidity, and functional capacity.

Prescribers should periodically re-evaluate the need for AUSTEDO in their patients by assessing the effect on chorea and possible adverse effects, including sedation/somnolence, depression and suicidality, parkinsonism, akathisia, restlessness, and cognitive decline. It may be difficult to distinguish between adverse reactions and progression of the underlying disease; decreasing the dose or stopping the drug may help the clinician to distinguish between the two possibilities. In some patients, the underlying chorea itself may improve over time, decreasing the need for AUSTEDO.

5.2 Depression and Suicidality

Patients with Huntington's disease are at increased risk for depression, and suicidal ideation or behaviors (suicidality). 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. If depression or suicidality does not resolve, consider discontinuing treatment with AUSTEDO.

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

5.3 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 *[see Drug Interactions (7.4)]*. While NMS has not been observed in patients receiving AUSTEDO, it has been observed in patients receiving tetrabenazine (a closely related VMAT2 inhibitor). Clinicians should be alerted to the signs and symptoms associated with NMS. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria, rhabdomyolysis, and acute renal failure. The diagnosis of NMS can be complicated; other serious medical illness (e.g., pneumonia, systemic infection) and untreated or inadequately treated extrapyramidal disorders can present with similar signs and symptoms. Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include (1) immediate discontinuation of AUSTEDO; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

Recurrence of NMS has been reported with resumption of drug therapy. If treatment with AUSTEDO is needed after recovery from NMS, patients should be monitored for signs of recurrence.

5.4 Akathisia, Agitation, and Restlessness

AUSTEDO may increase the risk of akathisia, agitation, and restlessness in patients with Huntington's disease. In a 12-week, double-blind, placebo-controlled trial, akathisia, agitation, or restlessness was reported by 4% of patients treated with AUSTEDO, compared to 2% of patients on placebo.

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

5.5 Parkinsonism

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 the potential to cause more functional disability than untreated chorea for some patients with Huntington's

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