Drug Monograph

Drug/Drug Class:	**Austedo® (deutetrabenazine) coated tablet/ Huntington's Disease**
Prepared for:	MO HealthNet
Prepared by:	Conduent Heritage

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Austedo® is available in a coated tablet in strengths of 6 mg, 9 mg, or 12 mg of deutetrabenazine. Distributed by: Teva Pharmaceuticals USA, Inc., North Wales, PA 19454
Summary of Findings:	Austedo® was evaluated in 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. The primary endpoint was the Total Maximal Chorea Score, an item of the Unified Huntington's Disease Rating Scale. The total score ranges from 0 to 28 with 28 being the worse. Patients receiving Austedo® saw a decrease of 4.4 units on the scale vs. only 1.9 units for patients receiving placebo. After a 1 week washout period, the Total Maximal Chorea Score of patients receiving Austedo® returned to normal.
Status Recommendation:	☒ Prior Authorization (PA) Required ☐ Open Access ☐ Clinical Edit ☐ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Preferred Agent ☒ Appropriate Indications ☐ Non-Preferred Agent

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [2]

Chorea is the most visible feature of Huntington's disease, a genetic disorder affecting the brain. 9 out of 10 people with Huntington's will develop chorea at some point as their illness progresses. The most characteristic initial physical symptoms are jerky, random, and uncontrollable movements. Chorea may be initially exhibited as general restlessness, small unintentionally initiated or incomplete motions, or lack of coordination. The clear appearance of symptoms such as rigidity, writhing motions or abnormal posturing appear as the disorder progresses. Psychomotor functions become increasingly impaired, such that any action that requires muscle control is affected. Common consequences are physical instability, abnormal facial expression, and difficulties chewing, swallowing, and speaking.

Dosage Form(s) [1]

Austedo® is available in a coated tablet in strengths of 6 mg, 9 mg, or 12 mg of deutetrabenazine.

Manufacturer [1]

Distributed by: Teva Pharmaceuticals USA, Inc., North Wales, PA 19454

Indication(s) [1]

Austedo® is indicated for the treatment of chorea associated with Huntington's disease and for tardive dyskinesia in adults.

Clinical Efficacy [1] (mechanism of action/pharmacology, comparative efficacy)

Austedo® is a vesicular monoamine transporter 2 (VMAT2) inhibitor. The precise mechanism by which Austedo® exerts its anti-chorea effects is unknown but is believed to be related to its effect as a reversible depletory of monoamines (such as dopamine, serotonin, norepinephrine, and histamine) from nerve terminals.

Pharmacokinetics:

	Austedo®
Distribution	500 to 730 L
Elimination	Primarily Renal in the form of metabolites
Half-Life	9 to 10 hours
Excretion	75 to 86% urine 8 to 11% feces

Austedo® treatment for 12 weeks resulted in a statistically significant improved in Total Maximal Chorea Scores when compared to placebo.

Study 1 – Chorea associated with Huntington's Disease

STUDY DESIGN	Randomized, double-blind, placebo-controlled, multi-center trial (N=90).
INCLUSION CRITERIA	Ambulatory patients with manifest chorea associated with Huntington's disease.
EXCLUSION CRITERIA	Not specified
TREATMENT REGIMEN	Treatment duration was 12 weeks, including an 8 week dose titration period and a 4 week maintenance period, followed by a 1 week washout. 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, intolerable side effect occurred, or until a maximal dose of 48 mg was reached.
RESULTS	Total Maximal Chorea Scores for patients receiving Austedo® improved by approximately 4.4 units from baseline to the maintenance period, compared to approximately 1.9 units in the placebo group. 51% 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 patient rated global impression of change. Likewise, in a physician rated clinical 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.
SAFETY	Not specified.

Study 2 – Tardive Dyskinesia

STUDY DESIGN	Randomized, double-blind, placebo-controlled, multi-center trials (n=222)
INCLUSION CRITERIA	History of using a dopamine receptor antagonist for at least 3 months (or 1 month in patients 60 years of age and older) with a diagnosis of tardive dyskinesia
EXCLUSION CRITERIA	Not specified

TREATMENT REGIMEN	Patients were randomized 1:1:1:1 to 12 mg Austedo, 24 mg Austedo, 36 mg Austedo, or placebo. Treatment duration included a 4 week escalation period and an 8 week maintenance period followed by a 1 week washout. Patients were 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.
RESULTS	The primary efficacy measure for the assessment of tardive dyskinesia severity was the Abnormal Involuntary Movement Scale (AIMS). 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 to 1.4 units in placebo.
SAFETY	Not specified.

Contraindications [(1)]

- Patients who are suicidal, or in patients with untreated or inadequately treated depression
- With hepatic impairment
- Taking monamine oxidase inhibitors. Austedo® should not be used in combination with a MAOI, or within 14 days of discontinuing therapy with a MAOI.
- Taking reserpine. At least 20 days should elapse after stopping reserpine before starting Austedo®
- Taking tetrabenazine

Warnings and Precautions [(1)]

- 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.
- Patients with Huntington's disease are at increased risk for depression, and suicidal ideation or behaviors. Austedo® may increase the risk for suicidality in patients with Huntington's disease.
- A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with drugs that reduce dopaminergic transmission.
- Austedo® may increase the risk of akathisia, agitation, and restlessness in patients with Huntington's disease.
- Austedo® may cause parkinsonism in patients with Huntington's disease.
- Sedation is a common dose-limiting adverse reaction of Austedo®.
- 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.
- Serum prolactin levels were not evaluated in the Austedo® development program. Tetrabenazine, a closely related VMAT2 inhibitor, elevates serum prolactin concentrations

in humans.
- Since deutetrabenazine or its metabolites bind to melanin-containing tissues, it could accumulate in these tissues over time.

Adverse Effects [1]

Most common, ≥ 4 %	Austedo® (n=45)	Placebo (n=45)
Somnolence	11%	4%
Diarrhea	9%	0%
Dry mouth	9%	7%
Fatigue	9%	4%
Urinary tract infection	7%	2%
Insomnia	7%	4%
Anxiety	4%	2%
Constipation	4%	2%
Contusion	4%	2%

Drug Interactions [1]

- Strong CYP2D6 Inhibitors; e.g. paroxetine, fluoxetine, quinidine, bupropion
- Reserpine
- MAOI's
- Neuroleptic drugs
- Alcohol or other sedating drugs
- Drugs that cause QTc prolongation
- Tetrabenazine

Dosage and Administration [1]

The dose of Austedo® is determined individually for each patient based on reduction of chorea or tardive dyskinesia and tolerability. The recommended starting dose is 6 mg administered orally once daily. The dose 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 with food. Do not chew, crush, or break tablets.

Cost

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	COST/ TABLET*
Deutetrabenazine	Austedo	Teva	6 mg tablet	$55.34
			9 mg tablet	$62.26
			12 mg tablet	83.02
Tetrabenazine	Xenazine	Lundbeck	12.5 mg tablet	$69.34
			25 mg tablet	$138.69

*Maximum Allowable Cost

Conclusion

Austedo® is a vesicular monamine transporter 2 inhibitor. It is indicated for the treatment of chorea associated with Huntington's disease and for tardive dyskinesia in adults. In its clinical trial for Chorea, treatment with Austedo® resulted in a statistically significant increase in Total Maximal Chorea Score, an item of the Unified Huntington's Disease Rating Scale, when compared with placebo. Austedo® does come with a Black Box Warning that states: Austedo® can increase the risk of depression and suicidal thoughts and behavior (suicidality) in patients with Huntington's disease.

The efficacy of Austedo® for tardive dyskinesia was established in two 12 week, randomized, double-blind, placebo-controlled, multi-center trials. Treatment with Austedo® 24 mg and 36 mg resulted in 3, 3.2, and 3.3 reductions in the Abnormal Involuntary Movement Scale (AIMS) total score compared to only 1.4 and 1.6 reductions in those receiving placebo.

Recommendation

The MO HealthNet Division recommends prior authorization status for this product.

References

1. Austedo. Retrieved 8/18/2017 and 9/14/2017 from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=7ea3c60a-45c7-44cc-afc2-d87fa53993c0
2. HD Chorea Symptoms. Retrieved 8/18/2017 from: http://www.xenazineusa.com/hd-chorea-symptoms

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