



## **Vesicular Monoamine Transporter Type 2 Inhibitors: deutetrabenazine (Austedo<sup>®</sup>, Austedo<sup>®</sup> XR), tetrabenazine (Xenazine<sup>®</sup>), valbenazine (Ingrezza<sup>™</sup>)**

**Policy #** 00304

**Original Effective Date:** 08/17/2011

**Current Effective Date:** 08/14/2023

*Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.*

### **When Services May Be Eligible for Coverage**

*Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:*

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

### **Tardive Dyskinesia**

Based on review of available data, the Company may consider deutetrabenazine (Austedo<sup>®</sup>, Austedo<sup>®</sup> XR)<sup>†</sup> or valbenazine (Ingrezza<sup>™</sup>)<sup>‡</sup> for the treatment of tardive dyskinesia to be **eligible for coverage**.\*\*

### **Patient Selection Criteria**

Coverage eligibility for the use of deutetrabenazine (Austedo, Austedo XR) or valbenazine (Ingrezza) for the treatment of patients with tardive dyskinesia will be considered when ALL of the following criteria are met:

- Patient has a documented diagnosis of tardive dyskinesia confirmed by ALL of the following:
  - Has involuntary athetoid or choreiform movements; AND
  - Has a history of treatment with a dopamine receptor blocking agent (e.g. metoclopramide, haloperidol, chlorpromazine, etc); AND
  - Has experienced symptoms for longer than 8 weeks; AND
- Patient is  $\geq 18$  years of age; AND
- If Austedo or Austedo XR is requested, the patient has tried and failed (e.g. intolerance or inadequate response) Ingrezza for at least 8 weeks.

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*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary\*\* if not met.)*

### **Chorea Associated with Huntington's disease**

Based on review of available data, the Company may consider deutetrabenazine (Austedo, Austedo XR), generic tetrabenazine, or brand tetrabenazine (Xenazine<sup>®</sup>)<sup>‡</sup> for the treatment of chorea associated with Huntington's disease to be **eligible for coverage**.\*\*

#### **Patient Selection Criteria**

Coverage eligibility for the use of deutetrabenazine (Austedo, Austedo XR), generic tetrabenazine, or brand tetrabenazine (Xenazine) for the treatment of patients with chorea associated with Huntington's disease will be considered when the following criterion is met:

- Patient has a documented diagnosis of chorea associated with Huntington's disease

### **When Services Are Considered Not Medically Necessary**

Based on review of available data, the Company considers the use of deutetrabenazine (Austedo, Austedo XR) for tardive dyskinesia when valbenazine (Ingrezza) has not been tried and failed for at least 8 weeks to be **not medically necessary**.\*\*

### **When Services Are Considered Investigational**

*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Company considers the use of valbenazine (Ingrezza) for any indication other than tardive dyskinesia, deutetrabenazine (Austedo, Austedo XR) for any indication other than tardive dyskinesia or chorea associated with Huntington's disease, or tetrabenazine (Xenazine) for any indication other than chorea associated with Huntington's disease to be **investigational**.\*

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## **Background/Overview**

Deutetrabenazine (Austedo, Austedo XR), tetrabenazine (Xenazine), and valbenazine (Ingrezza) are all reversible inhibitors of the vesicular monoamine 2 transporter (VMAT2) which regulates monoamine uptake from the cytoplasm to the synaptic vesicle for storage and release. Inhibition of this transporter results in decreased uptake of monoamines into synaptic vesicles and depletion of monoamine stores. Tetrabenazine also exhibits weak in vitro binding to the D2 receptor. Although the exact mechanism for benefit is unknown, all of these agents have demonstrated some efficacy in reducing tardive dyskinesia and Austedo and Xenazine have demonstrated efficacy in reducing chorea associated with Huntington's Disease.

Xenazine is the oldest available agent in this class and is indicated only for the treatment of chorea associated with Huntington's Disease (HD). However, it has been used off-label for the treatment of tardive dyskinesia. It is supplied as 12.5 mg and 25 mg tablets. Individualization of dose with careful weekly titration is required along with genetic testing for CYP2D6 mutation if the dose exceeds 50 mg per day. Austedo is the deuterated form of Xenazine and is therefore more resistant to metabolism by CYP2D6 than Xenazine. It is available as 6, 9, and 12 mg immediate release tablets as well as 6, 12, and 24 mg extended release tablets and should be dosed to response with increases of 6 mg per week to a maximum dose of 48 mg per day. Recommended dosing for patients switching between Xenazine and Austedo is provided in the Austedo package insert.

Both Austedo and Xenazine have a black box warning for increased risk of depression and suicidality, but Austedo's warning is limited to patients with HD. Both drugs are also associated with QTc prolongation and should not be combined with other QTc prolonging agents.

Ingrezza lacks the black box warning, possibly due to not being studied in patients with HD who are at a higher risk for suicidality and depression. It is indicated for the treatment of adults with tardive dyskinesia at a dose of 40, 60, or 80 mg once daily depending on patient characteristics.

## **Tardive Dyskinesia**

Tardive dyskinesia is a hyperkinetic movement disorder that can occur with delayed onset after use of dopamine receptor blocking agents such as the antipsychotic drugs and the antiemetic, metoclopramide. Diagnosis of tardive dyskinesia can be made using the Diagnostic and Statistical

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Manual of Mental Disorders, 5<sup>th</sup> edition (DSM-5) criteria and symptom severity and progression can be measured with the Abnormal Involuntary Movement Scale (AIMS) or Clinical Global Impressions (CGI) scale. DSM-5 criteria for diagnosis of tardive dyskinesia include involuntary athetoid or choreiform movements generally of the tongue, lower face and jaw, and extremities (but sometimes involving the pharyngeal diaphragmatic, or trunk muscles) developing in association with the use of a neuroleptic medication for at least a few months. Symptoms lasting less than 4-8 weeks are considered withdrawal-emergent dyskinesia instead of tardive dyskinesia.

The only treatments recommended with level B evidence in the 2013 American Academy of Neurology (AAN) guidelines on tardive symptoms are clonazepam and ginkgo biloba. At the time of guideline publication, each of these agents had one class I study demonstrating efficacy. The guidelines suggest that amantadine and tetrabenazine (Xenazine) might be considered as treatment (evidence Level C), but that data are insufficient to support or refute treatment by withdrawing causative agents or switching from typical to atypical dopamine receptor blocking agents. However, many clinicians recommend discontinuation of the offending drug or switching from a first to a second generation antipsychotic prior to adding other pharmacologic agents. The AAN guidelines were published before Ingrezza or Austedo received approval from the FDA and thus do not provide recommendations regarding them.

### **Huntington's Disease**

HD is a devastating neurodegenerative disease that causes progressive movement disorders, cognitive dysfunction, and behavioral changes and is ultimately a fatal condition. Chorea, characterized by excessive involuntary and repetitive movements, is the most common symptom, affecting approximately 90% of HD patients. These movements are the most visible and dangerous manifestations of HD and interfere with patients' abilities to perform activities of daily living, including dressing, bathing, and caring for themselves. It is estimated that approximately 30,000 people are affected in the United States.

Austedo and Xenazine are the only two drugs currently labeled to treat chorea associated with HD, but they have not been compared head-to-head in a clinical trial. Based on a review of the pivotal trials of each drug, Austedo and Xenazine appear to have similar efficacy. It is unknown if either agent has an advantage with regard to adverse events, but both contain the same warnings and

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precautions and require dose adjustment when administered with CYP2D6 inhibitors or to patients who are CYP2D6 poor metabolizers.

## **FDA or Other Governmental Regulatory Approval**

### **U.S. Food and Drug Administration (FDA)**

Austedo and Austedo XR are indicated for the treatment of chorea associated with HD and for tardive dyskinesia in adults. There is a boxed warning for depression and suicidality in patients with HD.

Ingrezza is indicated for the treatment of adults with tardive dyskinesia.

Xenazine was approved in 2008 for the treatment of chorea associated with HD. There is a boxed warning indicating the risk of depression as well as suicidal thoughts and behavior in patients with HD and the use of Xenazine.

## **Rationale/Source**

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

### **Austedo**

Austedo was approved for treatment of chorea associated with HD based on a randomized, double-blind, placebo-controlled trial in 90 ambulatory patients. These patients were treated for 12 weeks including an 8 week dose titration period and 4 week maintenance period followed by a 1 week washout. The primary efficacy endpoint was the Total Maximal Chorea Score which comes from the Unified Huntington's Disease Rating Scale. The score ranges from 0 to 28 with 0 being no chorea. After 12 weeks, the total maximal chorea scores for patients receiving Austedo improved by approximately 4.4 units compared to approximately 1.9 units in the placebo group ( $p < 0.0001$ ). After the 1 week washout period, the Total Maximal Chorea scores had returned to baseline. In addition

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to the primary endpoint, the Austedo group also had significantly higher scores on both patient and physician-rated global impression of change scales.

Austedo was approved for treatment of tardive dyskinesia based on two 12 week, randomized, double-blind, placebo controlled trials in 335 ambulatory patients with tardive dyskinesia caused by use of dopamine receptor antagonists. Efficacy was measured using the AIMS, a 12-item scale used to assess the severity of involuntary movements. The total score ranges from 0 to 28 with a decrease in score indicating improvement. In study 1, the patients were randomized 1:1:1:1 to 12 mg Austedo, 24 mg Austedo, 36 mg Austedo, or placebo. The AIMS total score from baseline to week 12 was significantly lower in the 36 mg and 24 mg arms (3.3 and 3.2 units respectively) than the placebo arm (1.4 units). In study 2, the patients either received placebo or Austedo started at 12 mg per day and increased to satisfactory control of dyskinesia or intolerable side effects or to a maximal dose of 48 mg per day. The average dosage of Austedo was 38.3 mg per day. The AIMS score decreased statistically significantly more in the Austedo group (3 units) than the placebo group (1.6 units).

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.

### **Ingrezza**

Ingrezza was approved based on a randomized, double-blind, placebo-controlled trial conducted in 234 patients with moderate to severe tardive dyskinesia as determined by clinical observation. Individuals at significant risk for suicidal or violent behavior and individuals with unstable psychiatric symptoms were excluded. Patients were randomized to receive 40 mg of Ingrezza, 80 mg of Ingrezza, or placebo. At the end of week 6, subjects initially assigned to placebo were re-randomized to receive Ingrezza 40 mg or 80 mg. Subjects initially randomized to Ingrezza continued Ingrezza at their randomized dose. Follow-up was continued through week 48 on the assigned drug, followed by a 4-week period off-drug.

Efficacy was assessed using the AIMS score. The change from baseline in the AIMS total dyskinesia score in the 80 mg Ingrezza group was statistically significantly different from the change in placebo group (-3.2 vs -0.1). Following discontinuation of Ingrezza, the mean AIMS dyskinesia total score appeared to return toward baseline.

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## **Xenazine**

Xenazine was approved primarily based on a randomized, double-blind, placebo-controlled multicenter trial conducted in ambulatory patients with a diagnosis of HD. The participants were diagnosed with HD based on family history, neurological exam, and genetic testing. Treatment duration was 12 weeks including a 7-week dose titration period and a 5-week maintenance period followed by a 1-week washout. The dose of Xenazine was started at 12.5 mg/day and titrated upward at weekly intervals in 12.5 mg increments until satisfactory control of chorea was achieved, until intolerable side effects occurred, or until a maximal dose of 100 mg per day was reached.

The primary efficacy endpoint was the Total Chorea Score, an item of the Unified Huntington's Disease Rating Scale. On this scale, chorea is rated from 0-4 (with 0 representing no chorea) for 7 different parts of the body. The total score ranges from 0 to 28.

Total Chorea Scores for subjects in the drug group declined by an estimated 5.0 units during maintenance therapy (average of Week 9 and Week 12 scores versus baseline), compared to an estimated 1.5 units in the placebo group. The treatment effect of 3.5 units was highly statistically significant. At the Week 13 follow-up, the Total Chorea Scores of subjects receiving Xenazine returned to baseline.

## **References**

1. Austedo, Austedo XR [package insert]. Teva. North Wales, PA. Updated February 2023.
2. Ingrezza [package insert]. Neurocrine. San Diego, CA. Updated April 2021
3. Tetrabenazine. [package insert]. Ingenus Pharmaceuticals. Fairfield, NJ. Updated March 2017
4. Bhidayasiri R, Fahn S, Weiner WJ, Gronseth GS, Sullivan KL, Zesiewicz TA. Evidence-based guideline: treatment of tardive syndromes. *Neurology*. 2013;81(5):463-469.
5. Tarsy D. Tardive dyskinesia: prevention and treatment. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. <http://www.uptodate.com>.

## **Policy History**

Original Effective Date: 08/17/2011

Current Effective Date: 08/14/2023

08/04/2011 Medical Policy Committee review

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08/17/2011	Medical Policy Implementation Committee approval. New policy.
08/02/2012	Medical Policy Committee review
08/15/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/19/2013	Coding updated
08/01/2013	Medical Policy Committee review
08/21/2013	Medical Policy Implementation Committee approval. Reworded the patient selection criteria, however there is no coverage change. Rearranged the background section. Made a few wording changes to the rationale/source section.
08/07/2014	Medical Policy Committee review
08/20/2014	Medical Policy Implementation Committee approval. No change to coverage.
08/06/2015	Medical Policy Committee review
08/19/2015	Medical Policy Implementation Committee approval. No change to coverage.
08/04/2016	Medical Policy Committee review
08/17/2016	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
08/03/2017	Medical Policy Committee review
08/23/2017	Medical Policy Implementation Committee approval. No change to coverage.
01/04/2018	Medical Policy Committee review
01/17/2018	Medical Policy Implementation Committee approval. Added Austedo and Ingrezza to policy with relevant background information.
01/10/2019	Medical Policy Committee review
01/23/2019	Medical Policy Implementation Committee approval. No change to coverage.
01/03/2020	Medical Policy Committee review
01/08/2020	Medical Policy Implementation Committee approval. No change to coverage.
01/07/2021	Medical Policy Committee review
01/13/2021	Medical Policy Implementation Committee approval. No change to coverage.
07/01/2021	Medical Policy Committee review
07/14/2021	Medical Policy Implementation Committee approval. Updated coverage criteria to remove step through alternative treatment options for Ingrezza. Updated background information to reflect addition of 60 mg dose of Ingrezza.
07/07/2022	Medical Policy Committee review
07/13/2022	Medical Policy Implementation Committee approval. No change to coverage

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07/06/2023 Medical Policy Committee review

07/12/2023 Medical Policy Implementation Committee approval. Added new extended release Austedo XR dosage form throughout the policy.

Next Scheduled Review Date: 07/2024

\*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
  1. Consultation with technology evaluation center(s);
  2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
  3. Reference to federal regulations.

\*\*Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services

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at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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**NOTICE:** If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

**NOTICE:** Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

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