BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

AUSTEDO™ (deutetrabenazine) oral
INGREZZA™ (valbenazine) oral
Tetrabenazine oral
XENAZINE® (tetrabenazine) oral
Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

- **Criteria for initial therapy:** Austedo (deutetrabenazine), Austedo XR (deutetrabenazine), Ingrezza (valbenazine), generic tetrabenazine, Xenazine (tetrabenazine), and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Psychiatrist or Neurologist.

  2. Individual is 18 years of age or older

3. Individual has a confirmed diagnosis of **ONE** of the following:
    a. Chorea associated with Huntington's disease

    b. Tardive dyskinesia

4. **ONE** of the following:
    a. **For Huntington's disease chorea:**
        i. Failure, contraindication per FDA label, intolerance, or is not a candidate for **tetrabenazine (generic)** and either **aripiprazole, olanzapine, or risperidone**
    b. **For tardive dyskinesia:**
        i. Discontinue offending drug if clinically appropriate
        ii. Switch from a first to a second-generation antipsychotic drug if clinically appropriate
        iii. Failure, contraindication per FDA label, intolerance, or is not a candidate for clonazepam **OR** amantadine
        iv. For localized forms of severe tardive dystonia (e.g., cervical dystonia, blepharospasm), failure, contraindication per FDA label, intolerance, or is not a candidate for botulinum toxin injections
        v. Failure, contraindication per FDA label, intolerance, or is not a candidate for **tetrabenazine**

5. **For brand Xenazine (tetrabenazine)**: Individual has documented failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for **generic tetrabenazine** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

6. **For brands Austedo, Austedo XR, or Ingrezza if available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

7. There are **NO** FDA-label contraindications for Austedo, Austedo XR, tetrabenazine, and Xenazine:
    a. Suicidal, or untreated/inadequately treated depression in an individual with Huntington's disease
    b. Hepatic impairment
    c. Use with reserpine or within 20 days of stopping reserpine
    d. Use with MAOIs or within 14 days of stopping MAOI
    e. Use with another vesicle monoamine transporter type 2 (VMAT-2) inhibitor (e.g., tetrabenazine (Xenazine or generic), or Ingrezza (valbenazine) or deutetrabenazine (Austedo or Austedo XR)

8. Individual does not have congenital long QT syndrome, or a history of cardiac arrhythmias associated with QT prolongation

9. There are no significant interacting drugs:
    a. **For Ingrezza**:
        i. Use with MAOIs (e.g., isocarboxazid, phenelzine, selegiline) or within 14 days of stopping MAOI

ii. Use with strong CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's wort)

b. **For tetrabenazine (brand Xenazine and generic)**:
   i. Use with other drugs that prolong QTc antipsychotic medications (e.g., chlorpromazine, haloperidol, thioridazine, ziprasidone), antibiotics (e.g., moxifloxacin), Class 1A (e.g., quinidine, procainamide) and Class III (e.g., amiodarone, sotalol) antiarrhythmic medications or any other medications known to prolong the QTc interval

Initial approval duration:
6 months: For tardive dyskinesia and tics due to Tourette's syndrome
6 months: For chorea due to Huntington's disease

- **Criteria for continuation of coverage (renewal request):** Austedo (deutetrabenazine), Austedo XR (deutetrabenazine), Ingrezza (valbenazine,) generic tetrabenazine, Xenazine (tetrabenazine), and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Psychiatrist or a Neurologist

2. Individual's condition has responded while on therapy with response defined as the following:
   a. **For Huntington's Disease**: There is documented reduction in chorea
   b. **For tardive dyskinesia**: There is documentation of improvement in symptoms compared to baseline such as:
      i. Protruding and twisting movements of the tongue
      ii. Pouting, puckering, or smacking movements of the lips
      iii. Retraction of the corners of the mouth
      iv. Bulging of the cheeks
      v. Chewing movements
      vi. Blepharospasm
      vii. Twisting, spreading, and "piano-playing" finger movements
      viii. Tapping foot movements
      ix. Dystonic extensor postures of the toes

3. The indication for use is one that requires a longer duration than the usual 3 months such as use for tardive dyskinesia

4. Individual has been adherent with the medication

5. **For brand Xenazine (tetrabenazine)**: Individual has documented failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for **generic tetrabenazine** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

6. **For brands Austedo, Austedo XR, or Ingrezza <u>if available</u>**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

7. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use such as:
    a. Contraindications as listed in the criteria for initial therapy section
    b. Significant adverse effect such as:
        i. QT prolongation
        ii. Neuroleptic malignant syndrome
        iii. Akathisia, agitation, restlessness, and parkinsonism in individual with Huntington's disease and tardive dyskinesia, that does not resolve with dose adjustment
        iv. Emerging or worsening of depression, suicidality, or unusual changes in behavior in individual with Huntington's
        v. Symptomatic hyperprolactinemia

8. Individual does not have congenital long QT syndrome, or a history of cardiac arrhythmias associated with QT prolongation

9. There are no significant interacting drugs:
    a. **For <u>Ingrezza</u>**:
        i. Use with MAOIs (e.g., isocarboxazid, phenelzine, selegiline) or within 14 days of stopping MAOI
        ii. Use with strong CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's wort)
    b. **For tetrabenazine (brand Xenazine and generic)**:
        i. Use with other drugs that prolong QTc antipsychotic medications (e.g., chlorpromazine, haloperidol, thioridazine, ziprasidone), antibiotics (e.g., moxifloxacin), Class 1A (e.g., quinidine, procainamide) and Class III (e.g., amiodarone, sotalol) antiarrhythmic medications or any other medications known to prolong the QTc interval

<u>Renewal duration</u>: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

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INGREZZA™ (valbenazine) oral
Tetrabenazine oral
XENAZINE® (tetrabenazine) oral
Generic Equivalent (if available)

Description:

Austedo (deutetrabenazine), Austedo XR (deutetrabenazine extended release), tetrabenazine (brand Xenazine and generic), and Ingrezza (valbenazine) are indicated for the treatment of chorea associated with Huntington's disease (HD). The mechanism of the anti-chorea action is unknown, but it is believed to be related to depletion of monoamines from nerve terminals. Austedo (deutetrabenazine), Austedo XR (deutetrabenazine extended release), and Ingrezza (valbenazine) are indicated for the treatment of adults with tardive dyskinesia (TD). The mechanism of action of deutetrabenazine and valbenazine in the treatment of TD is unknown but is thought to be due to regulation of monoamine uptake from the cytoplasm into the synaptic vesicle for storage and release.

Deutetrabenazine, tetrabenazine, and valbenazine are reversible inhibitors of the vesicle monoamine transporter type 2 (VMAT-2). They inhibit uptake of the neurotransmitter's serotonin, norepinephrine, histamine, and, especially, dopamine into the granular vesicles of presynaptic neurons and ultimately lead to depletion of monoamine stores. Dopamine is a chemical that communicates between certain nerve cells in the brain. In patients with HD, this system is overactive and results in the abnormal movements of chorea. The pathophysiology of TD remains poorly understood, but it is believed to be the result of chronic blockade of dopamine receptors, particularly D2 and possibly D3, by dopamine receptor blocking agents (DRBA). In addition to dopamine, other neurotransmitter receptors may be important, especially 5-hydroxytryptamine 2 (5-HT2) receptors that modulate motor activity. One of the most prominent theories about TD pathogenesis is that chronic exposure to the neuroleptics results in D2 receptor upregulation with postsynaptic dopamine receptor super-sensitivity.

HD is a rare, inherited neurological disorder affecting about 1 in 10,000 people in the United States. The disease results from degeneration and deterioration of brain cells. The deterioration causes uncontrolled movements (chorea), cognitive decline, and psychiatric/behavioral changes. Cognitive symptoms include confusion on time and place, loss of judgment, memory loss, and personality changes. Movement problems include restless leg, fidgeting, facial movements, head turning to shift eye position, jerking of arms, legs, face and other body parts, speech problems, slow uncontrolled movements, swallowing problems, and unsteady gait. As chorea worsens the individual is at risk for falls. Due to swallowing difficulties, HD individuals also have difficulty in maintaining nutrition leading to further declines in functional capacity.

Chorea is an abnormal involuntary movement caused by overactivity of the neurotransmitter dopamine in the areas of the brain that control movement. It is characterized by brief, irregular contractions that are not repetitive or rhythmic, but appear to flow from one muscle to the next. The full spectrum of motor impairment in HD includes eye movement abnormalities, Parkinsonian features and dystonia, myoclonus, tics, ataxia, dysarthria, dysphagia, spasticity with hyperreflexia and extensor plantar responses.

The underlying pathology and neurochemical bases of HD are complex and not fully understood. It is thought that dopamine and glutamate transmission and their interaction with receptors at various sites in the brain are affected.

A recent guideline on the treatment of HD published in 2012 from the American Academy of Neurology (AAN) stated that amantadine, tetrabenazine, or riluzole (although its effect is dose dependent) may be used for chorea. Nabilone may have a weak or a slight effect on chorea, but long-term information is lacking. Data on use of

clozapine, other neuroleptics, or donepezil were not sufficient to make a recommendation for or against their use in the management of chorea. Evidence from four small, randomized, double-blind, placebo-controlled trials is conflicting for amantadine. However, based upon results from two of these trials, guidelines from the American Academy of Neurology conclude that amantadine is likely effective in decreasing HD chorea, though the degree of benefit is unknown.

Tardive dyskinesia (TD) is one of the most well-known types of tardive syndromes (TDS). TD is estimated to affect 500,000 people in the United States. TDS are movement disorders that affect voluntary muscles. In TDS, abnormal body movements occur, and these movements cannot be controlled voluntarily. Classic TD usually involves random rhythmic involuntary movements of the face; affecting the tongue, lips, or jaw where abnormal movement of the jaw is seen as a chewing motion and facial grimacing. Other affected body parts include the hands, arms, legs, fingers, toes, or hips. TDS includes other types of abnormal movements besides TD and includes tardive akathisia, tardive dystonia, tardive myoclonus, tardive tremor, and tardive tics (also known as tardive tourettism).

TD results from chronic (three or more months) exposure to DRBA, some neuroleptics or antipsychotics (typical and atypical agents), tricyclic antidepressants (amoxapine), and antiemetics or other medications used for gastrointestinal disorders (promethazine and metoclopramide). Not all individuals who are using DRBA go on to develop TD. Factors that may contribute to the development of TD include duration of treatment, type of DRBA used, age, alcohol use or use of other substances of abuse, HIV/AIDS, and female gender. The diagnosis of TD is based on the patient's history of exposure to DRBA, characteristic clinical presentation, and exclusion or other conditions such as includes Huntington's disease.

In 2013 the American Academy of Neurology evidence-based guideline on the treatment of TDS stated that clonazepam or ginkgo biloba probably improves TDS, and both should be considered as treatment. The guideline also stated that amantadine and tetrabenazine might be considered as treatment for TDS.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Resources:

Austedo (deutetrabenazine) tab and Austedo XR (deutetrabenazine) extended-release tab product information, revised by Teva Neuroscience, Inc. 07-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 21, 2024.

Ingrezza (valbenazine) cap product information, revised by Neurocrine Biosciences, Inc. 04-2024.Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 21, 2024.

Xenazine (tetrabenazine) tab product information, revised by Lundbeck Pharmaceuticals, LLC. 11-2019. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 21, 2024.

Tetrabenazine tab product information, revised by Apotex Corp.. 10-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 21, 2024.

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Liang TW. Tardive dyskinesia: Prevention, treatment, and prognosis. In: UpToDate, Hurtig HI, Marder S, Eichler AF (Eds), UpToDate, Waltham MA.: UpToDate Inc. http://uptodate.com. Literature current through November 2024. Topic last updated June 12, 2023. Accessed December 23, 2024.