Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO157

Description

Tetrabenazine (Xenazine), deutetrabenazine (Austedo) and valbenazine (Ingrezza/Ingrezza Sprinkle) are reversible vesicular monoamine transporter 2 (VMAT2) inhibitors that act by regulating monoamine uptake from the cytoplasm to the synaptic vesicle. Its mechanism of action in Tardive dyskinesia or chorea-reduction is unknown.

Length of Authorization

- Initial:
  - i. Tardive dyskinesia: Six months
  - ii. Chorea associated with Huntington's disease: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
tetrabenazine (Xenazine)	12.5 mg	Chorea associated with Huntington's disease	60 tablets/30 days
	25 mg		
	25 mg	Chorea associated with Huntington's disease, genotyped *extensive* and *intermediate metabolizers*	120 tablets/30 days
generic tetrabenazine	12.5 mg	Chorea associated with Huntington's disease	60 tablets/30 days
	25 mg		
	25 mg	Chorea associated with Huntington's disease, genotyped *extensive* and *intermediate metabolizers*	120 tablets/30 days
deutetrabenazine (Austedo)	6 mg	Tardive dyskinesia in adults; Chorea associated with Huntington's disease	210 tablets/30 days
	9 mg		60 tablets/30 days
	12 mg		120 tablets/30 days
deutetrabenazine (Austedo XR)	6mg, 12mg, 24mg titration tab kit	Tardive dyskinesia in adults; Chorea associated with Huntington's disease	42 tablets/28 days
	6 mg		210 tablets/30 days
	12 mg		90 tablets/30 days
	24 mg		60 tablets/30 days
	30 mg		30 tablets/30 days
	36 mg		30 tablets/30 days

	42 mg		30 tablets/30 days
	48 mg		30 tablets/30 days
valbenazine (Ingrezza)	40 mg	Tardive dyskinesia; Chorea associated with Huntington's disease	30 capsules/30 days; 4-week Initiation Pack
	60 mg		
	80 mg		
valbenazine (Ingrezza Sprinkle)	40 mg	Tardive dyskinesia; Chorea associated with Huntington's disease	30 capsules/30 days
	60 mg		
	80 mg		

Initial Evaluation

I. **Tetrabenazine (Xenazine), deutetrabenazine (Austedo) and valbenazine (Ingrezza/Ingrezza Sprinkle)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a neurologist or psychiatrist; **AND**
   C. Medication will not be used in combination with another VMAT2 inhibitor [e.g. tetrabenazine (Xenazine), deutetrabenazine (Austedo) valbenazine (Ingrezza/Ingrezza Sprinkle)], monoamine oxidase inhibitor (MAOI) [e.g. isocarboxazid (Marplan®), phenelzine, tranylcypromine, reserpine]; **AND**
   D. Provider attestation that member does not have uncontrolled symptoms of depression, agitation, psychosis, or increased risk of suicidality; **OR**
      1. Provider attestation that the potential benefit of treatment with VMAT2-I outweighs the risk of depression or suicidality; **AND**
   E. A diagnosis of one of the following:
      1. **Chorea associated with Huntington's disease**; **AND**
         i. For BRAND tetrabenazine (Xenazine) or generic tetrabenazine:
            a. Provider attestation that doses exceeding 50mg per day are to be reserved for extensive and intermediate metabolizers (see quantity limit table based on metabolizer status); **AND**
               i. If request is for BRAND tetrabenazine (Xenazine), treatment with generic tetrabenazine, deutetrabenazine (Austedo), and valbenazine (Ingrezza/Ingrezza Sprinkle) has been ineffective, contraindicated or not tolerated; **OR**
      2. **Tardive dyskinesia**; **AND**
         i. The request is for generic tetrabenazine, valbenazine (Ingrezza/Ingrezza Sprinkle) and deutetrabenazine (Austedo); **AND**
         ii. Member has failed to respond to a change or is unable to switch current antidopaminergic therapy

II. Tetrabenazine (Xenazine), deutetrabenazine (Austedo), and Valbenazine (Ingrezza/Ingrezza Sprinkle) are considered investigational when used for all other conditions, including but not limited to:
   A. Tourette's syndrome

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms.

Supporting Evidence

I. Safety and effectiveness of VMAT2 inhibitors have not been established in pediatric patients.
II. Agents in this policy are required to be prescribed by or in consultation with a neurologist or psychiatrist considering the seriousness of adverse effects (depression and suicidality, cognitive decline, Parkinsonism, dysphagia, sedation/somnolence, akathisia, restlessness, and disability), complexity of the disease state, and dosing of the medication.
III. Concomitant use of tetrabenazine (Xenazine), deutetrabenazine (Austedo), and valbenazine (Ingrezza/Ingrezza Sprinkle) with MAOIs may increase the concentration of monoamine neurotransmitters in synapses, potentially leading to increased risk of adverse reactions such as serotonin syndrome, or attenuated treatment effect. Tetrabenazine (Xenazine), deutetrabenazine (Austedo), and valbenazine (Ingrezza/Ingrezza Sprinkle) should not be used in combination with an MAOI.
IV. The International Guidelines for the Treatment of Huntington's Disease recommend tetrabenazine (VMAT2-I) as first line for chorea management except for patients who have, "not well-managed depression or suicidal thoughts" due to the side effects of the drug class. In patients with psychiatric disorders or personality/behavioral disorders that increase suicide risk, the guidelines recommend the use of 2nd generation neuroleptics. Treatment with a single agent is preferred due to the risk of additional adverse effects. Additionally, compendia cites comorbid depression, agitation, and/or psychosis as criteria for determining whether a VMAT2-I is appropriate based on patient comorbidities.
V. Per the Physician's Guide to the Management of Huntington's Disease 3rd edition, providers often treat chorea with neuroleptics (e.g., aripiprazole, haloperidol, fluphenazine, risperidone, olanzapine) based on clinical experience and due to safety concerns associated with VMAT2-inhibitors, namely: decreased cognition and mood, increased suicidality and depression. Studies

of the anti-choreic effects of neuroleptics were excluded from the AAN guideline review due to criteria set forth; however, the AAN acknowledges neuroleptics are commonly used in clinical practice to treat chorea and recommends additional study in recognition of this use. In consideration of the Boxed Warnings and adverse effects associated with this class, a trial of therapy often considered in standards-of-care is reasonable.

VI. KINECT-HD was a phase 3, randomized, double-blind, placebo-controlled trial which studied valbenazine (Ingrezza/Ingrezza Sprinkle) vs placebo for 12 weeks. The trial included 125 participants (valbenazine n=64, placebo n=61) with a moderate level of disease advancement per UHDRS TFC (Total Functional Capacity) scores for Huntington's chorea. The primary endpoint of the study was assessing the mean change in UHDRS-TMC (Unified Huntington's Disease Rating Scale –Total Maximal Chorea) from baseline to the end of the study at week 12. The results demonstrated a statistically and clinically significant improvement in the primary endpoint for valbenazine vs placebo (-4.6 vs 1.4, difference -3.2, 95% CI –4.4 to –2.0, p<0.0001). The secondary endpoints included Clinical Global Impression of Change (CGI-C) and Patient Global Impression of Change (PCI-C) at week 12, and mean changes from baseline to week 12 in short-form Quality of Life in Neurological (NeuroQoL) Disorders Upper Extremity and Lower Extremity Function T-scores. By week 12, there was a statistically significant difference in the CGI-C and PGI-C scores compared to baseline (p=-.0007, p=0.0062). However, the new secondary measures within the study (NeuroQoL) indicated no statistically significant change when compared to placebo (p=0.3304). In terms of safety, the results listed no worsening of anxiety, depression, akathisia, parkinsonism, or new reports of suicidal ideation.

VII. No sufficient evidence was found to show superiority of one agent over the other.

VIII. When clinically appropriate, the two main strategies of pharmacotherapy in patients who are showing signs of tardive dyskinesia include discontinuation of the offending drug and switching from a first- to a second-generation antipsychotic drug because second generation neuroleptics have a lower risk of TD.

IX. Additional pharmacologic options [e.g. benzodiazepines, anticholinergic drugs (trihexyphenidyl, benztropine)] have been used in clinical practice for many years. AAN states use of benzodiazepines and tetrabenazine (Xenazine) as standard of care treatments is based on weak clinical evidence but it has been standard of care. According to the 2012 AAN guidelines, amantadine or riluzole could be other agents prescribed for chorea management (Level B).

X. There is a lack of head-to-head trials and scientific evidence to show superiority of one medication over the other. There is history of use with tetrabenazine in tardive dyskinesia.

XI. For patients with a diagnosis of TD, additional pharmacologic interventions include the use of benzodiazepines, botulinum toxin injections, or tetrabenazine (Xenazine) to control symptoms of TD, paradoxically, resuming treatment with antipsychotic drugs in order to suppress TD.

Investigational or Not Medically Necessary Uses

I. Tourette's syndrome
   A. Tetrabenazine (Xenazine)
      A. VMAT2 inhibitors currently available in the United States include deutetrabenazine and valbenazine. Although both are being investigated in the treatment of TS, they, like tetrabenazine (Xenazine), are not yet approved by the US Food and Drug Administration (FDA).
      B. There is insufficient evidence to support the use of tetrabenazine (generic, Xenazine) for the treatment of other movement disorders, including, but not limited to dystonic tremor, or Tourette's syndrome.
   B. Deutetrabenazine (Austedo)
      i. Deutetrabenazine (Austedo) is currently being investigated for use in Tourette's syndrome in:
         a. A Pilot Study Of SD-809 (Deutetrabenazine) In Moderate To Severe Tourette Syndrome
         b. A Randomized, Double-blind, Placebo-controlled Study of TEV-50717 (Deutetrabenazine) for the Treatment of Tourette Syndrome in Children and Adolescents
      ii. Although deutetrabenazine (Austedo) is being studied for the treatment of Tourette's syndrome, there is currently no published evidence supporting its safety or efficacy in this setting.
   C. Valbenazine (Ingrezza/Ingrezza Sprinkle)
      i. Valbenazine (Ingrezza/Ingrezza Sprinkle) is currently being investigated for use in Tourette's syndrome; however, initial studies have not demonstrated efficacy for this condition.
         a. In a phase 2 trial in pediatric patients with tics associated with Tourette's syndrome, valbenazine (Ingrezza/Ingrezza Sprinkle) did not meet the pre-specified primary endpoint of change from baseline between the placebo valbenazine (Ingrezza/Ingrezza Sprinkle) in the Yale Global Tic Severity Scale (YGTSS) at week six in the intent-to-treat population.
         b. Based on the above results, a second phase 2 trial will aim to evaluate a higher dose of valbenazine (Ingrezza/Ingrezza Sprinkle) to suppress tics in pediatric patients.
      ii. Although valbenazine (Ingrezza/Ingrezza Sprinkle) is being studied for the treatment of Tourette's syndrome, there is currently no published evidence supporting its safety or efficacy in this setting.

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Added 30mg, 36mg, 42mg, and 48mg Austedo XR tablets to table	06/2024
Added 60mg Ingrezza sprinkles to table	05/2024
Added Huntington's chorea indication for valbenazine (Ingrezza). Removed the step through generic tetrabenazine. Updated initial authorization for Tardive Dyskinesia indication to 6 months following standard authorization.	12/2023
Adding Austedo XR titration tablet kit	07/2023
Added Austedo XR to QL table	04/2023
Updated QL for 6mg and 9mg Austedo tablets; updated formatting	01/2023

• Updated criteria to policy format and combined separate polices into one • Generic tetrabenazine added to tardive dyskinesia criteria • For deutetrabenazine (Austedo) only: Treatment with generic tetrabenazine and valbenazine (Ingrezza) has been ineffective, contraindicated or not tolerated • Medication will not be used in combination with another VMAT2 inhibitor , monoamine oxidase inhibitor (MAOI) [e.g. isocarboxazid (Marplan®), phenelzine, tranylcypromine, reserpine], it is contraindicated	12/2019
Added Tardive Dyskinesia indication for deutetrabenazine (Austedo™)	09/2017
Updated question 5 for valbenazine (Ingrezza™) based on P&T recommendations	08/2017
Previous Reviews	05/2017; 06/2017; 09/2017; 08/2019; 12/2019;