tetrabenazine (Xenazine®); deutetrabenazine (Austedo™); valbenazine (Ingrezza™)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO157

Description

Tetrabenazine (Xenazine), deutetrabenazine (Austedo) and valbenazine (Ingrezza) 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 (Tardive dyskinesia): Three months
- Initial (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	30 tablets/30 days
	9 mg		
	12 mg		120 tablets/30 days
valbenazine (Ingrezza)	40 mg	Tardive Dyskinesia	30 capsules/30 days; 4-week Initiation Pack
	80 mg		

Initial Evaluation

I. Tetrabenazine (Xenazine), deutetrabenazine (Austedo) and valbenazine (Ingrezza) 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)], monoamine oxidase inhibitor (MAOI) [e.g. isocarboxazid (Marplan®), phenelzine, tranylcypromine, reserpine]; **AND**
   D. A diagnosis of one of the following:
      1. **Chorea associated with Huntington's disease**; **AND**
         i. Prior treatment with at least one standard-of-care therapy for the treatment of chorea (e.g. amantadine , olanzapine, risperidone, aripiprazole, riluzole, haloperidol, fluphenazine) has been ineffective, unless all are contraindicated or not tolerated; **AND**
         ii. Member has been tested and genotyped to determine if they are poor metabolizers (PMs) or extensive metabolizers (EMs) by their ability to express the drug metabolizing enzyme, CYP2D6 (see quantity limit table based on metabolizer status); **AND**
         iii. *For deutetrabenazine (Austedo) only:* Treatment with generic tetrabenazine has been ineffective, contraindicated or not tolerated; **AND**
         iv. *For Tetrabenazine (Xenazine) only***:** Treatment with generic tetrabenazine and deutetrabenazine (Austedo) has been ineffective, contraindicated or not tolerated; **OR**
      2. [*For generic tetrabenazine, valbenazine (Ingrezza) and deutetrabenazine (Austedo) only*] **Tardive dyskinesia**; **AND**
         i. At least one of the following treatment approaches was ineffective, unless all are contraindicated, not tolerated, or put psychiatric stability at risk:
            a. Switching from a first-generation neuroleptic (e.g. fluphenazine, haloperidol, loxapine, perphenazine, trifluoperazine) to a second-generation neuroleptic (e.g. clozapine, risperidone, olanzapine, quetiapine]; **OR**
            b. Member has history of discontinuation or dose modification of the offending medication; **OR**
            c. Member has been trialed on at least one standard therapy (e.g tetrabenazine, amantadine, benztropine, benzodiazepine) for symptomatic treatment of tardive dyskinesia; **AND**
         ii. *For valbenazine (Ingrezza) only:* Treatment with generic tetrabenazine has been ineffective, contraindicated or not tolerated; **AND**
         iii. *For deutetrabenazine (Austedo) only*: Treatment with generic tetrabenazine and valbenazine (Ingrezza) has been ineffective, contraindicated or not tolerated

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

III. Valbenazine (Ingrezza) is considered investigational when used for all other conditions, including but not limited to:
   A. Chorea associated with Huntington's disease
   B. 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 in pediatric patients has not been established.
II. Tetrabenazine (Xenazine), deutetrabenazine (Austedo), and valbenazine (Ingrezza) need to be prescribed by a neurologist or psychiatrist considering the serious 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) 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) should not be used in combination with an MAOI.
IV. The American Academy of Neurology (AAN) recommends the use of tetrabenazine (Xenazine), amantadine, or riluzole when medication therapy for chorea is warranted. 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.
V. No sufficient evidence was found to show superiority of one agent over the other.
VI. 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.

VII. 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.

VIII. 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.

IX. 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)
      i. 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).
      ii. 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)
      i. Valbenazine (Ingrezza) 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) did not meet the pre-specified primary endpoint of change from baseline between the placebo valbenazine (Ingrezza) 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) to suppress tics in pediatric patients.

ii. Although valbenazine (Ingrezza) is being studied for the treatment of Tourette's syndrome, there is currently no published evidence supporting its safety or efficacy in this setting.

II. Chorea associated with Huntington's disease

A. Valbenazine (Ingrezza) is currently being investigated for use in Chorea associated with Huntington's disease in a Phase 3, randomized, double-blind, placebo-controlled study to assess the efficacy, safety, and tolerability of valbenazine for the treatment of chorea associated with Huntington's disease.

References

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12. A Pilot Study Of SD-809 (Deutetrabenazine) In Moderate To Severe Tourette Syndrome, ClinicalTrials.gov Identifier: NCT02674321, https://clinicaltrials.gov/ct2/show/NCT02674321?term=deutetrabenazine&draw=2&rank=4
13. A Randomized, Double-blind, Placebo-controlled Study of TEV-50717 (Deutetrabenazine) for the Treatment of Tourette Syndrome in Children and Adolescents, ClinicalTrials.gov Identifier: NCT03452943, https://clinicaltrials.gov/ct2/show/NCT03452943?term=deutetrabenazine&draw=2&rank=7
14. Safety and Efficacy of NBI-98854 (valbenazine) in Pediatric Subjects With Tourette Syndrome, ClinicalTrials.gov Identifier: NCT03530293, https://clinicaltrials.gov/ct2/show/NCT03530293?term=valbenazine&draw=2&rank=7

Policy Implementation/Update:

Date Created	December 2019
Date Effective	December 2019
Last Updated	December 2019
Last Reviewed	05/2017, 06/2017, 08/2019, 09/2017 , 12/2019

Action and Summary of Changes	Date
• 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