Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCNEU010.0824	**NEUROMUSCULAR DRUGS** **VMAT2 INHIBITORS** See Appendix A for medications covered by policy
Effective Date: 10/1/2024	**Review/Revised Date**: 04/09, 04/11, 10/11, 08/12, 12/13, 08/14, 08/15, 07/16, 07/17, 07/18, 07/19, 06/20, 06/21, 06/22, 07/23, 12/23, 06/24 (JCN)
Original Effective Date: 04/09	**P&T Committee Meeting Date**: 02/09, 04/09, 04/10, 04/11, 10/11, 08/12, 12/13, 08/14, 08/15, 08/16, 08/17, 08/18, 08/19, 08/20, 08/21, 08/22, 08/23, 12/23, 08/24
Approved by: Oregon Region Pharmacy and Therapeutics Committee	

SCOPE:
Providence Health Plan and Providence Health Assurance as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit. Other medically accepted uses may be approved according to the clinical criteria outlined in the below policy.

REQUIRED MEDICAL INFORMATION:

1. **For chorea associated with Huntington disease:**
    a. Initiation of therapy requires all the following must be met:
        i. Diagnosis of Huntington Disease confirmed by all the following:
            1) DNA testing showing CAG expansion of 36 or higher, **AND**
            2) Family history (if known), **AND**
            3) Classic presentation (choreiform movements, psychiatric problems, and dementia), **AND**
        ii. Documentation that chorea is causing functional impairment, **AND**
        iii. For deutetrabenazine (Austedo® and Austedo® XR) and valbenazine (Ingrezza®/ Ingrezza® Sprinkle): Documented trial (of at least eight weeks) and failure or intolerance to tetrabenazine.
    b. For reauthorization: Documented benefit of therapy, as evidence by improved function through reduction in choreiform movements.
2. **For Tardive Dyskinesia**
    a. For initiation of therapy, all the following criteria must be met:
        i. Diagnosis of tardive dyskinesia secondary to therapy with a dopamine receptor blocking agent (e.g. first or second generation antipsychotics, metoclopramide), **AND**

ii. Documentation of moderate to severe tardive dyskinesia that is causing functional impairment, defined as an Abnormal Involuntary Movement Scale (AIMS) score of 3 or 4 on any one of items 1 through 9 (see supplemental information) OR tardive dyskinesia that is interfering with activities of daily living (ADLs), **AND**
iii. For deutetrabenazine (Austedo® and Austedo® XR) and valbenazine (Ingrezza®/ Ingrezza® Sprinkle): Documented trial (of at least eight weeks) and failure or intolerance of tetrabenazine.

b. For reauthorization: Documentation of positive clinical response to therapy, as demonstrated by improved function or activities of daily living (ADLs), or a decrease in AIMS score

EXCLUSION CRITERIA: Use in combination with monoamine oxidase inhibitors or other VMAT2 inhibitors

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS:
Must be prescribed by, or in consultation with, a neurologist or psychiatrist

COVERAGE DURATION:
Initial prior authorization will be approved for three months. First reauthorization will be approved for one year. Second reauthorization will be approved until no longer eligible with the plan, subject to formulary or benefit changes.

QUANTITY LIMITS:
Deutetrabenazine (Austedo®) 6 mg and 12 mg tablet: four per day
Deutetrabenazine (Austedo®) 9 mg tablet: five per day
Deutetrabenazine (Austedo® XR): one tablet per day
Valbenazine (Ingrezza® and Ingrezza Sprinkle®): 40 mg, 60mg and 80 mg capsule: one per day
Tetrabenazine (Xenazine®) 12.5 mg and 25 mg tablet: four per day

---

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCNEU010	NEUROMUSCULAR DRUGS VMAT2 INHIBITORS See Appendix A for medications covered by policy

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:

Tetrabenazine (Xenazine®), valbenazine (Ingrezza®) and deutetrabenazine (Austedo® and Austedo® XR) reversibly inhibit the human vesicular monoamine transporter type 2 (VMAT2) resulting in decreased uptake of monoamines (such as dopamine, serotonin, norepinephrine, and histamine) into synaptic vesicles and depletion of monoamine stores.

The cause of chorea (rapid, involuntary, non-repetitive or arrhythmic movement involving the face, trunk, and limbs) associated with Huntington Disease is not fully understood but is thought to involve an imbalance of monoamine neurotransmitters, including dopamine, in the brain. Tetrabenazine and deutetrabenazine do not cure the cause of chorea and do not treat other symptoms of Huntington's disease, such as problems with thinking or emotions.

Tardive dyskinesia (TD) is a movement disorder resulting from exposure to dopamine receptor antagonists (DRAs) including typical and atypical antipsychotics, antiemetics, and metoclopramide. The pathophysiology of TD is unknown, but upregulation and sensitization of D2 receptors after blockade may be contributory.

DSM-V Definition of TD: Involuntary athetoid or choreiform movements (lasting at least a few weeks) 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 may develop after a shorter period of medication use in older people.

FDA APPROVED INDICATIONS:

- Tetrabenazine (Xenazine®): Treatment of chorea associated with Huntington disease
- Deutetrabenazine (Austedo® and Austedo® XR): Treatment of chorea associated with Huntington disease and tardive dyskinesia in adults
- Valbenazine (Ingrezza®): Treatment of chorea associated with Huntington disease and tardive dyskinesia in adults

POSITION STATEMENT:

Huntington Disease:

- Huntington Disease is a progressive neurological disorder which may cause changes in mood, cognition, chorea, rigidity, and functional capacity over time.
- Tetrabenazine (Xenazine®), deutetrabenazine (Austedo® and Austedo® XR), and valbenazine (Ingrezza®) are all FDA approved for the treatment of chorea associated with Huntington disease.

Tardive dyskinesia:

- All dopamine receptor-blocking agents have the potential to cause TD. First- and second-generation antipsychotic drugs and metoclopramide are most common culprits. Rate of TD with first generation antipsychotics is 4-8% per year and thought to be about three times higher than that with second generation antipsychotics.[19] Some risk factors include age greater than 55 years, female, presence of a mood disorder, intellectual disability, central nervous system injury and past or current akathisia.[19]
- Structure evaluation tools for tardive dyskinesia can be used to identify TD, determine likely etiologies, monitor changes and determine effects of treatments. Two available scales include the Abnormal Involuntary Movement scale (AIMS) and the Dyskinesia Identification System Condensed User Scale (DISCUS).[19]
- The American Psychiatric Association (APA) practice guideline (2020) for the treatment of patients with schizophrenia (third edition) discusses VMAT2 medications for tardive dyskinesia:[19]
    - APA recommends that patients who have moderate to severe or disabling tardive dyskinesia associated with antipsychotic therapy be treated with a reversible inhibitor of the vesicular monoamine transporter 2 (VMAT2) [moderate level of evidence indicating benefits of the intervention clearly outweigh harms]
    - Recommend deutetrabenazine or valbenazine over tetrabenazine due to greater published evidence for those agents
- The American Academy of Neurology last updated their Guidelines for the Treatment of Tardive Syndromes in 2013 (reaffirmed 2019) prior to the FDA approval of Austedo® and Ingrezza®. The following agents have weak to moderate evidence and might be useful in the treatment of Tardive Syndromes:
    - Amantadine (Weak evidence)
        - Amantadine reduced TDS when used conjointly with a neuroleptic during the first 7 weeks (1 Class II study, 2 Class III studies). Amantadine with neuroleptics may be considered to treat TDS for short-term use (Level C).
    - Tetrabenazine (Weak evidence)
        - Tetrabenazine (TBZ) possibly reduces TDS symptoms (2 consistent Class III studies). TBZ possibly reduces TDS symptoms (2 consistent Class III studies). TBZ may be considered in treating TDS (Level C).

  - Ginkgo biloba (Moderate evidence)
    - Ginkgo biloba (EGb-761) is probably useful in TDS treatment (1 Class I study), but data are limited to inpatients with schizophrenia (Level B)
  - Clonazepam (Moderate Evidence)
    - Based on 1 Class I study, clonazepam is probably effective in decreasing TDD symptoms short-term (approximately 3 months) and should be considered for short-term TDD treatment (Level B).
- Valbenazine (Ingrezza®) was studied in one short-term (6 weeks), randomized, placebo-controlled clinical trial in patients with moderate-to-severe dopamine receptor blocker-induced tardive dyskinesia.
  - Primary endpoint: Change from baseline to week 6 in the Abnormal Involuntary Movement Scale (AIMS) dyskinesia score for the valbenazine 80 mg/day group compared to placebo
  - Key secondary endpoints:
    - Clinical Global Impression-Tardive Dyskinesia (CGI-TD) mean score at week 6
    - Percentage of subjects classified as AIMS responders (a reduction in ≥50% from baseline dyskinesia score) at week 6
  - Results:
    - Primary endpoint: Statistically significant
    - Secondary endpoints:
      - CGI-TD: no significant differences noted
      - Higher proportion of responders in valbenazine 80 mg/day group compared to placebo
  - Overall, the clinical significance of the results is unclear, as the trial had significant limitations (such as short duration, placebo-controlled, manufacturer involved in study design, analysis and publication)
- Deutetrabenazine (Austedo®) was studied in two small placebo-controlled studies in patients with tardive dyskinesia
  - In both trials deutetrabenazine was superior to placebo for reduction of AIMS score. However, it was only compared to placebo rather than alternative therapies for treating TD, so it is difficult to evaluate comparative safety and efficacy.
  - Additionally, despite improvements on AIMS score, treatment with deutetrabenazine did not result in improvement on Clinical Global Impression of Change (CGIC) scores.
  - The efficacy of Austedo® XR is based on a relative bioavailability study comparing Austedo® XR tablets given once daily and Austedo® tablets given twice daily.
- The Institute for Clinical and Economic Review report assessing VMAT2 inhibitors for treatment of tardive dyskinesia had the following conclusion:

- "The clinical benefits associated with valbenazine and deutetrabenazine will lead to increased quality-adjusted life expectancy over no specific treatment for TD symptoms (i.e., placebo). At current pricing levels, however, the estimate lifetime cost-effectiveness of these agents far exceeds commonly-cited cost-effectiveness thresholds."

Safety and other considerations:

- The prescribing information for Xenazine® and Austedo® includes a black box warning about an increased risk of depression and suicidal thoughts and behaviors in patients with Huntington Disease.
  - Close observation for the emergence of worsening of depression, suicidality, or unusual changes in behavior should accompany therapy.
  - The patient, caregivers, and families should be informed of the risk of depression and suicidality and report behaviors of concern to the treating physician.
  - Particular caution should be exercised in treating patients with a history of depression or prior suicide attempts or ideation, which are increased in frequency in Huntington Disease.
  - Xenazine® and Austedo® are contraindicated in patients who are actively suicidal, and in patients with untreated or inadequately treated depression.
- Neuroleptic Malignant Syndrome (NMS) is a potentially fatal symptom complex that has been reported in association with Xenazine®.
- Xenazine® is metabolized primarily by CYP2D6 in the liver.
  - Use caution when combining with CYP2D6 Inhibitors (i.e. fluoxetine, paroxetine, quinidine); dosage reductions may be necessary
  - If doses of >50mg per day are required, patients should be tested for the CYP2D6 gene to determine whether they are poor metabolizers (PMs) or extensive or intermediate metabolizers (EMs or IMs).
    - PMs should be limited to no more than 50mgs per day.
    - IMs or EMs should be limited to no more than 100mgs per day.
- The safety and efficacy of VMAT2 inhibitors in children have not been established.
- Valbenazine was studied in a Phase 2 trial for Tourette's Syndrome, which did not meet the primary endpoint. Other studies are ongoing for this indication.
- The current evidence available for VMAT2 inhibitors for conditions other than the FDA approved indications is of low quality and does not provide strong support for their use.

Supplemental Information:

Medications associated with Tardive Dyskinesia:

Centrally Acting Dopamine Receptor Blocking Agents: chlorpromazine, fluphenazine, perphenazine, thioridazine, thiothixene, trifluoperazine, chlorpromazine, perphenazine, prochlorperazine, promethazine, thiethylperazine, amoxapine, haloperidol, droperidol, metoclopramide, trimethobenzamide, loxapine, pimozide, aripiprazole, brexpiprazole, asenapine, cariprazine, clozapine, quetiapine, iloperidone, lurasidone, ziprasidone, olanzapine, paliperidone, risperidone

Abnormal Involuntary Movement Scale (AIMS)
The AIMS is a 12-item clinician-rated scale to assess severity of dyskinesias (specifically, orofacial movements and extremity and truncal movements) in patients taking neuroleptic medications. Items 1-10 are rated on a 5 point anchored scale. Items 1-4 assess orofacial movements, items 5-7 assess extremity and truncal movements, items 8-10 deal with global severity and items 11-12 are yes-no questions concerning problems with teeth and/or denture, because such problems can lead to a mistaken diagnosis of dyskinesia. The AIMS dyskinesia total score (sum of items 1 to 7) could range from 0 to 28, with a decrease in score indicating improvement.

Public Health Service
Alcohol, Drug Abuse, and Mental Health Administration
National Institute of Mental Health

KEY: 0 = None
1 = Minimal, may be extreme normal
2 = Mild
3 = Moderate
4 = Severe

NAME: _____
DATE: _____
Prescribing practitioner: _____

MOVEMENT RATINGS: Rate highest severity observed. Rate movements that occur upon activation one less than those observed spontaneously. Circle movement as well as code number that applies.		RATER Date
Facial and oral movements	1. **Muscles of facial expression** eg, movements of forehead, eyebrows, periorbital area, cheeks, including frowning, blinking, smiling, grimacing	0 1 2 3 4
	2. **Lips and perioral area** eg, puckering, pouting, smacking	0 1 2 3 4
	3. **Jaw** eg, biting, clenching, chewing, mouth opening, lateral movement	0 1 2 3 4
	4. **Tongue** Rate only increases in movement both in and out of mouth. NOT inability to sustain movement. Darting in and out of mouth.	0 1 2 3 4
Extremity movements	5. **Upper (arms, wrists, hands, fingers)** Include choreic movements (ie, rapid, objectively purposeless, irregular, spontaneous) athetoid movements (ie, slow, irregular, complex, serpentine). DO NOT INCLUDE TREMOR (ie, repetitive, regular, rhythmic).	0 1 2 3 4
	6. **Lower (legs, knees, ankles, toes)** eg, lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot	0 1 2 3 4
Trunk movements	7. **Neck, shoulders, hips** eg, rocking, twisting, squirming, pelvic gyrations	0 1 2 3 4
Global judgments	8. **Severity** of abnormal movements overall	0 1 2 3 4
	9. **Incapacitation due to abnormal movements**	0 1 2 3 4
	10. **Patient's awareness of abnormal movements** Rate only patient's report - No awareness 0 - Aware, no distress 1 - Aware, mild distress 2 - Aware, moderate distress 3 - Aware, severe distress 4	0 1 2 3 4
Dental status	11. **Current problems with teeth and/or dentures?**	No Yes
	12. **Are dentures usually worn?**	No Yes
	13. **Edentia?**	No Yes
	14. **Do movements disappear in sleep?**	No Yes

REFERENCE/RESOURCES:

1. Marshall FJ, Walker F, et al. Tetrabenazine as antichorea therapy in Huntington disease. *Neurology*. 2006;66:366-372.
2. Xenazine® package insert. Deerfield, IL;Lundbeck, 2019 Nov

3. Tetrabenazine. In: Facts and Comparisons: Clin-eguide [internet database]. St. Louis, MO: Wolters Kluwer Health, Inc., Updated periodically.
4. Tetrabenazine. In: DRUGDEX© System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically.
5. Murphy TK, Lewin AB, Storch EA, Stock S, American Academy of Child and Adolescent Psychiatry (AACAP) Committee on Quality Issues (CQI). Practice parameter for the assessment and treatment of children and adolescents with tic disorders. J Am Acad Child Adolesc Psychiatry. 2013 Dec;52(12):1341-59.
6. Pringsheim T, Doja A, Gorman D, et al. Guidelines for the Evidence-Based Treatment of Tic Disorders: Pharmacotherapy. Canadian Journal of Psychiatry 2012; 57(3): 133–143.
7. Roessner V, Plessen KJ, Rothenberger A, et al. European clinical guidelines for Tourette syndrome and other tic disorders. Part II: pharmacological treatment. European Child & Adolescent Psychiatry. 2011;20(4):173-196. doi:10.1007/s00787-011-0163-7.
8. Bhidayasiri R, Fahn S, Weiner WJ, Gronseth GS, Sullivan KL, Zesiewicz TA. Evidence-based guideline: treatment of tardive syndromes: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2013 Jul 30;81(5):463-9.
9. Chen J, Ondo W, Dashtipour K, Swope D. Tetrabenazine for the Treatment of Hyperkinetic Movement Disorders: A Review of the Literature. Clin Ther. 2012 July 34 (7): 1482-1504
10. Fernandez HH, Factor SA, Hauser RA, et al. Randomized controlled trial of deutetrabenazine for tardive dyskinesia: the ARM-TD study. Neurology. 2017; 88(21):2003-2010.
11. Institute for Clinical and Economic Review. Tardive Dyskinesia: Final Evidence Report and Meeting Summary. https://icer-review.org/material/td-final-report/. Accessed: July 18, 2018
12. Soares-Weiser K, Rathbone J, Ogawa Y, Shinohara K, Bergman H. Miscellaneous treatments for antipsychotic-induced tardive dyskinesia. Cochrane Database Syst Rev. 2018;3:CD000208.
13. Guy W. ECDEU Assessment Manual for Psychopharmacology: Revised (DHEW Publication number ADM 76-338). Rockville,MD, US Department of Health, Education and Welfare, Public Health Service, Alcohol, Drug Abuse and Mental Health Administration,NIMH Psychopharmacology Research Branch, Division of Extramural Research Programs, 1976: 534–7
14. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA, American Psychiatric Association, 2013.
15. Austedo® and Austedo® XR package insert. Parsippany, NJ: Teva Pharmaceuticals; 2023 Feb.

16. Bachoud-Levi AC, Ferreira J, Massart R et al. International Guidelines for Huntington's Disease. *Front Neurol*. 2019;10:710. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6618900/ (Accessed June 14, 2020)
17. Dean M and Sung VW. Review of deutetrabenazine: a novel treatment for chorea associated with Huntington's disease. *Drug Des Devel Ther*. 2018; 12:313-319. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5818866/ (Accessed June 14, 2020)
18. Ingrezza® package insert. San Diego, CA: Neurocrine Biosciences, Inc. 2021 Apr
19. Keepers GA, Fochtmann LJ, Anzia JM, *e al*; (Systematic Review). The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia. *Am J Psychiatry*. 2020 Sep 1;177(9):868-872.

APPENDIX A.

Brand Name	Generic Name
Austedo/Austedo XR	deutetrabenazine IR/ER tablets
Ingrezza/Ingrezza Sprinkle	valbenazine capsules
Xenazine	tetrabenazine tablet