

## Clinical Policy: Vesicular Monoamine Transporter 2 (VMAT2) Inhibitors

Reference Number: OR.CP.PHAR.1004

Effective Date: 07.01.22

Last Review Date: 06.25

Line of Business: Medicaid – Oregon Health Plan

[Revision Log](#)

See [Important Reminder](#) at the end of this policy for important regulatory and legal information.

### Description

The following agents contain a vesicular monoamine transporter 2 (VMAT2) inhibitor and require prior authorization: deutetrabenazine (Austedo, Austedo XR), tetrabenazine (Xenazine), valbenazine (Ingrezza).

### Goal(s):

- Promote safe use of VMAT2 inhibitors in adult patients.
- Promote use that is consistent with medical evidence and product labeling.

### Length of Authorization:

- Initial: Up to 3 months
- Renewal: Up to 12 months

### Requires PA:

- All VMAT2 inhibitors

### Covered Alternatives:

- Current Trillium Preferred Drug List listed at:
  - <https://www.trilliumohp.com/providers/pharmacy.html>

### Policy/Criteria

*Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.*

It is the policy of Trillium Community Health Plan that deutetrabenazine, tetrabenazine or valbenazine are **medically necessary** when the following criteria are met:

#### I. Initial Approval Criteria

##### A. Chorea Associated with Huntington's Disease (must meet all):

1. Diagnosis of chorea associated with Huntington's disease;
2. Prescribed by or in consultation with a psychiatrist or neurologist;
3. Baseline total maximal chorea score of 8 or higher as assessed by the Unified Huntington's disease Rating Scale–Total Chorea Movement subscore (UHDRS-TCS) (*see Appendix D*);
4. Age  $\geq$  18 years;

5. Member is determined to not have uncontrolled depression or be at risk of violent or suicidal behavior;
6. Request is for one of the following (a or b):
  - a. Request is for tetrabenazine;
  - b. Request is for deutetetrabenazine or valbenazine and member has failed treatment with tetrabenazine (e.g., no improvement on any one of UHDRS chorea items 1 through 7) at up to 100 mg per day, unless contraindicated or clinically significant adverse effects are experienced;
7. If request is for Xenazine, member must use generic tetrabenazine, unless contraindicated or clinically significant adverse effects are experienced;
8. Multiple VMAT2 inhibitors (tetrabenazine, deutetetrabenazine, valbenazine) are not prescribed concomitantly;
9. Dose does not exceed the FDA-approved maximum recommended dose.

**Approval duration:** 3 months

**B. Tardive Dyskinesia (must meet all):**

1. Diagnosis of moderate to severe tardive dyskinesia secondary to a centrally acting dopamine receptor blocking agent (DRBA) (*see Appendix F*);
2. Prescribed by or in consultation with a psychiatrist or neurologist;
3. Age  $\geq$  18 years;
4. Evidence of moderate to severe TD is supported by an Abnormal Involuntary Movement Scale (AIMS) score of 3 or 4 on any one of items 1 through 9 (*see Appendix G*);
5. Request is for one of the following (a or b):
  - a. Request is for tetrabenazine;
  - b. Request is for deutetetrabenazine or valbenazine and member has failed treatment with tetrabenazine (e.g., no improvement on any one of AIMS items 1 through 9) at up to 200 mg per day, unless contraindicated or clinically significant adverse effects are experienced;
6. If request is for Xenazine, member must use generic tetrabenazine, unless contraindicated or clinically significant adverse effects are experienced;
7. Multiple VMAT2 inhibitors (tetrabenazine, deutetetrabenazine, valbenazine) are not prescribed concomitantly;
8. Dose does not exceed the maximum recommended dose.

**Approval duration:** 3 months

**C. Tourette Syndrome (must meet all):**

1. Diagnosis of tics associated with Tourette syndrome;
2. Prescribed by or in consultation with a psychiatrist or neurologist;
3. Failure of at least two guideline directed medications each from different therapeutic classes, unless clinically significant adverse effects are experienced or all are contraindicated (a, b, or c):
  - a. Alpha-2 Adrenergic Agonist (clonidine or guanfacine);
  - b. Anticonvulsant (topiramate);
  - c. Antipsychotic (pimozide, aripiprazole or risperidone);
4. Request is for tetrabenazine;

5. Dose does not exceed the maximum recommended dose.

**Approval duration:** 3 months

**D. Other diagnoses/indications (must meet 1 or 2):**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
  - a. For drugs on the PDL the no coverage criteria policy for the relevant line of business: CP.PMN.255 for Medicaid; or
  - b. For drugs NOT on the PDL the non-formulary policy for the relevant line of business: OR.CP.PMN.1001 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.PMN.53 for Medicaid.

**II. Continued Therapy**

**A. Huntington's Disease (must meet all):**

1. Member meets one of the following (a or b):
  - a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
  - b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);
2. Patient is responding positively to therapy as documented by evidence of improvement in total maximal chorea score of at least 2 points from baseline;
3. Mental status of the patient is stable and there is no risk of uncontrolled depression or risk of violent or suicidal behavior;
4. If request is for a dose increase, new dose does not exceed the FDA-approved maximum recommended dose.

**Approval duration:** up to 12 months

**B. Tardive Dyskinesia (must meet all):**

1. Member meets one of the following (a or b):
  - a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
  - b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);
2. Patient is responding positively to therapy as documented by evidence of improvement by a reduction in AIMS dyskinesia score (Items 1-7) by at least 50%;
3. Mental status of the patient is stable and there is no risk of uncontrolled depression or risk of violent or suicidal behavior;
4. If request is for a dose increase, new dose does not exceed the FDA-approved maximum recommended dose.

**Approval duration:** up to 12 months

**C. Tourette Syndrome (must meet all):**

1. Member meets one of the following (a or b):
  - a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
  - b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);
2. Member been taking tetrabenazine for >2 months (if ≤2 months then use Initial Approval Criteria to determine medical necessity of request);
3. Member is responding positively to therapy as documented by reduced tic severity from baseline as assessed by the Yale Global Tic Severity Score (YGTSS) Total Tic Score (range 0-50);
4. If request is for a dose increase, new dose does not exceed the maximum recommended dose.

**Approval duration:** up to 12 months

**D. Other diagnoses/indications (must meet 1 or 2):**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
  - a. For drugs on the PDL the no coverage criteria policy for the relevant line of business: CP.PMN.255 for Medicaid; or
  - b. For drugs NOT on the PDL the non-formulary policy for the relevant line of business: OR.CP.PMN.1001 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.PMN.53 for Medicaid.

**III. Diagnoses/Indications for which coverage is NOT authorized:**

- A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.PMN.53 for Medicaid or evidence of coverage documents.

**IV. Appendices/General Information:**

*Appendix A: Abbreviation/Acronym Key*

AAN: American Academy of Neurology  
AIMS: Abnormal Involuntary  
Movement Scale  
APA: American Psychiatric Association  
CAG: cytosine-adenine-guanine  
DRBA: dopamine receptor blocking  
agent

DSM-5-TR: Diagnostic and Statistical  
Manual of Mental Disorders, Fifth  
Edition, Text Revision  
FDA: Food and Drug Administration  
HTT: huntingtin  
MAOI: monoamine oxidase inhibitors  
TD: tardive dyskinesia  
UHDRS: Unified Huntington Disease  
Rating Scale

VMAT2: vesicular monoamine transporter

*Appendix B: General Information*

- The 2020 American Psychiatric Association (APA) Practice guideline for the treatment of patients with schizophrenia recommends that patients who have moderate to severe or disabling TD be treated with a reversible VMAT2 inhibitor (i.e., deutetrabenazine, tetrabenazine, and valbenazine); the guideline notes that the AIMS tool can be instrumental in such decision-making.
- Medication-induced movement disorders, including tardive dyskinesia, are organized in the DSM-5 as follows: medication-induced parkinsonism, neuroleptic malignant syndrome, medication-induced acute dystonia, medication-induced acute akathisia, tardive dyskinesia, tardive dystonia/tardive akathisia, medication-induced postural tremor, other medication-induced movement disorder, antidepressant discontinuation syndrome, and other adverse effects of medication.<sup>5</sup>
- Tardive dyskinesia is a type of movement disorder that occurs secondary to therapy with an antipsychotic medication or other DRBA (*see Appendix E*). (DSM-5-TR)
- Typical therapeutic drug classes containing DRBAs include first- and second-generation antipsychotics, antiemetics, and tri-cyclic antidepressants (*see Appendix F*). (DSM-5-TR)
- Other therapeutic drug classes containing agents that have been variously associated with movement disorders are listed below: (Waln 2013, Meyer 2014, Lerner 2015)
  - Antiarrhythmics
  - Antibiotics
  - Anticholinergics
  - Antidepressants
  - Antiepileptics
  - Antihistamines
  - Antimanics
  - Bronchodilators
  - Calcium channel blockers
  - Central nervous system stimulants
  - Dopamine agonists
  - Dopamine depleting agents
  - Dopaminergics
  - Glucocorticoids
  - Immunosuppressants
  - Mood stabilizers
  - Muscle relaxants
  - Oral contraceptives

*Appendix C: Contraindications/Boxed Warnings*

- Contraindication(s):
  - Known hypersensitivity to the requested drug product
  - Suicidal or untreated/inadequately treated depression (*deutetrabenazine, tetrabenazine*)
  - Hepatic impairment (*deutetrabenazine, tetrabenazine*)
  - Taking reserpine or MAOIs (*deutetrabenazine, tetrabenazine*)
  - Taking another VMAT2 inhibitor
- Boxed warning(s):
  - Depression and suicidality

*Appendix D: The Unified Huntington Disease Rating Scale (UHDRS)*

- The UHDRS encompasses motor, behavioral, cognitive, and functional components for use in evaluating patients with Huntington disease and is commonly used in both research and clinical practice.

- The American Academy of Neurology (AAN) guidelines evaluating pharmacologic therapies for chorea associated with Huntington disease describe the chorea subscore of the UHDRS motor component as a rating of 7 body regions (facial, bucco-oral-lingual, trunk, extremities) on a five-point scale from 0 to 4 with 0 representing no chorea.
- See Huntington Study Group 1996 and Mestre et al. 2018 for additional information about the UHDRS.

(AAN Guidelines 2012, Huntington Study Group 1996, Mestre 2018)

*Appendix E: Tardive Dyskinesia: DSM-5-TR Definition*

| <b>Tardive Dyskinesia (ICD-10 G24.01)</b>   |
|---|
| <ul style="list-style-type: none"> <li>• The essential features of tardive dyskinesia are abnormal, involuntary movements of the tongue, jaw, trunk, or extremities that develop in association with the use of medications that block postsynaptic dopamine receptors, such as first- and second-generation antipsychotic medications and other medications such as metoclopramide for gastrointestinal disorders. The movements are present over a period of <math>\geq 4</math> weeks and may be choreiform (rapid, jerky, nonrepetitive), athetoid (slow, sinuous, continual), or semirhythmic (e.g., stereotypies) in nature.</li> <li>• Signs or symptoms of tardive dyskinesia develop during exposure to the antipsychotic medication or other dopamine blocking agent, or within 4 weeks of withdrawal from an oral agent (or within 8 weeks of withdrawal from a long-acting injectable agent). There must be a history of the use of the offending agent for <math>\geq 3</math> months (or 1 month in individuals age <math>\geq 60</math> years). Dyskinesia that emerges during withdrawal from an antipsychotic medication or other DRBA may remit with continued withdrawal from the medication. If the dyskinesia persists for <math>\geq 4</math> weeks, a diagnosis of tardive dyskinesia may be warranted.</li> </ul> |

*Appendix F: Tardive Dyskinesia: Centrally Acting Dopamine Receptor Blocking Agents*

| <b>Pharmacologic Class</b> | <b>Therapeutic Class</b>   |   |                                   |
|----------------------------|--|---|-----------------------------------|
|                            | <b>First-generation (typical) antipsychotics</b>   | <b>Antiemetic agents</b>  | <b>Tri-cyclic antidepressants</b> |
| Phenothiazine              | Chlorpromazine<br>Fluphenazine<br>Perphenazine<br>Thioridazine<br>Thiothixene<br>Trifluoperazine | Chlorpromazine<br>Perphenazine<br>Prochlorperazine<br>Promethazine*<br>Thiethylperazine | Amoxapine <sup>†</sup>            |
| Butyrophenone              | Haloperidol  | Droperidol<br>Haloperidol**   |                                   |
| Substituted benzamide      |  | Metoclopramide<br>Trimethobenzamide   |                                   |
| Dibenzazepine              | Loxapine   |   |                                   |
| Diphenylbutylpiperidine    | Pimozide   |   |                                   |
| <b>Pharmacologic Class</b> | <b>Second-generation (atypical) antipsychotics</b>   |   |                                   |
| Quinolone                  | Aripiprazole, brexpiprazole  |   |                                   |
| Dibenzazepine              | Asenapine  |   |                                   |

| Pharmacologic Class  | Therapeutic Class                         |                   |                            |
|----------------------|---|-------------------|----------------------------|
|                      | First-generation (typical) antipsychotics | Antiemetic agents | Tri-cyclic antidepressants |
| Piperazine           | Cariprazine                               |                   |                            |
| Dibenzodiazepine     | Clozapine, quetiapine                     |                   |                            |
| Benzisoxazole        | Iloperidone                               |                   |                            |
| Benzisothiazole      | Lurasidone, ziprasidone                   |                   |                            |
| Thienobenzodiazepine | Olanzapine                                |                   |                            |
| Pyrimidinone         | Paliperidone, risperidone                 |                   |                            |

(DSM-5-TR, Meyer 2014, Smith 2010, Clinical Pharmacology, Lexicomp)

\*First generation H1 antagonist

\*\*Off-label use

†A dibenzoxapine that shares properties with phenothiazines

*Appendix G: Tardive Dyskinesia: The Abnormal Involuntary Movement Scale (AIMS)*

- The AIMS is a clinician-rated 12-item assessment tool developed by the National Institute of Mental Health to evaluate severity of involuntary movements in multiple movement disorders including TD. The AIMS is commonly used in both research and clinical practice.
- AIMS items 1-10 are rated on a 5-point scale (0 - none; 1 - minimal; 2 - mild; 3 - moderate; 4 - severe). Items 1-7 assess dyskinesia severity by body region (items 1-4 orofacial; items 5-7 extremity and trunk). Items 8-10 assess overall severity, incapacitation, and patient awareness respectively - item 8 uses the highest score of any one of items 1-7. Items 11 (dental) and 12 (dentures) are yes/no questions which help characterize lip, jaw, and tongue movements.
- See Munetz 1988 for additional information about the AIMS.

*Appendix H: Dosage and Administration*

| Drug Name                              | Dosing Regimen   | Dose Limit/<br>Maximum Dose  |
|--|--|--|
| deutetrabenazine (Austedo, Austedo XR) | <p><b>Huntington's Chorea &amp; TD</b><br/> <u>When not switching from tetrabenazine:</u><br/>                     Recommended starting dose</p> <ul style="list-style-type: none"> <li>• Austedo XR: 12 mg PO QD</li> <li>• Austedo: 6 mg PO BID</li> </ul> <p>Titrate at weekly intervals by 6 mg/day based on reduction of chorea or tardive dyskinesia, and tolerability, up to a maximum recommended daily dosage of 48 mg. When switching between Austedo and Austedo XR, switch to the same total daily dosage.</p> | 48 mg/day (36 mg/day in poor CYP2D6 metabolizers or with strong CYP2D6 metabolizers) |

| Drug Name                   | Dosing Regimen  | Dose Limit/<br>Maximum Dose   |
|-----------------------------|---|---|
|                             | <u>When switching from tetrabenazine</u> : see Prescribing Information dosage chart   |   |
| tetrabenazine<br>(Xenazine) | <b>Huntington's Chorea</b><br>12.5 mg PO QD for 1 week, then 12.5 mg BID, then titrated by 12.5 mg weekly to a tolerated dose up to maximum of 50 mg/day (100 mg/day for CYP2D6 intermediate or extensive metabolizers)   | 50 mg/day (max single dose of 25 mg)<br><br>Extensive or intermediate CYP2D6 metabolizer: 100 mg/day (max single dose of 37.5 mg) |
|                             | <b>Tardive Dyskinesia (off-label)*</b><br>Typical dosing range 25-75 mg/day. Give in divided doses: increase from initial dose of 25-50 mg/day by 12.5 mg/week to maximum of 150-200 mg/day. Retitrate dose for treatment interruptions of more than 5 days. Test for CYP2D6 metabolizer status before giving doses > 50 mg/day. Do not exceed 50 mg/day in poor metabolizers or in patients treated with a strong inhibitor of CYP2D6.<br><i>*Off-label dose supported by the 2020 American Psychiatric Association (APA) Practice Guideline for the Treatment of Patients With Schizophrenia.</i> | 150-200 mg/day  |
|                             | <b>Tourette Syndrome (off-label)</b><br>Increase from initial dose of 25 mg/day, with increases by 25 mg daily until 100 mg daily reached or adverse effects intervene; then subsequently titrate based on response (maximal daily dose, 37.5 to 150 mg daily)  | 150 mg/day  |
| Valbenazine<br>(Ingrezza)   | <b>Huntington's Chorea</b><br>40 mg PO once daily; increase the dose in 20 mg increments every two weeks to the recommended dose of 80 mg once daily. A dosage of 40 mg or 60 mg once daily may be considered depending on response and tolerability.   | 80 mg/day   |
|                             | <b>Tardive Dyskinesia</b><br>40 mg PO once daily; after a week, increase to the recommended dose of 80 mg once daily. A dosage of 40 mg or 60 mg once daily may be considered depending on response and tolerability.   | 80 mg/day   |

*\*Off-label dose supported by the 2020 American Psychiatric Association (APA) Practice Guideline for the Treatment of Patients With Schizophrenia. See additional dosing comments in Appendix B.*

**V. Product Availability**

| <b>Medication</b>                | <b>Formulation and Strength</b>   |
|----------------------------------|---|
| Austedo<br>(deutetrabenazine)    | Immediate release tablets: 6 mg, 9 mg, 12 mg                                    |
| Austedo XR<br>(deutetrabenazine) | Extended-release tablets: 6 mg, 12 mg, 18 mg, 24 mg, 30 mg, 36 mg, 42 mg, 48 mg |
| Ingrezza (valbenazine)           | Capsules: 40 mg, 60 mg, 80 mg   |
| tetrabenazine                    | Tablets: 12.5 mg, 25 mg   |

**VI. References**

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| Reviews, Revisions, and Approvals  | Date     | P&T Approval Date |
|--|----------|-------------------|
| Policy created; adapted from previously approved policy TCHP.PHAR.181 Vesicular Monoamine Transporter 2 (VMAT2) Inhibitors | 03.17.22 | 04.07.22          |

| Reviews, Revisions, and Approvals   | Date     | P&T Approval Date |
|---|----------|-------------------|
| 2Q 2023 annual review: no significant changes; template changes applied to other diagnoses/indications and continued therapy section; references reviewed and updated.  | 03.13.23 | 04.06.23          |
| 2Q 2024 annual review. Updated criteria to match FFS updates: initial approval duration extended to 3 months for all indications; removed QT prolongation contraindication from Chorea initial approval criteria; added tetrabenazine as preferred agent for TD; Tourette syndrome indication added; cleaned up and standardized Appendixes; references reviewed and updated. | 04.17.24 | 05.21.24          |
| 2Q 2025 annual review: no significant changes; updated Appendix definitions per updated DSM-5-TR; references reviewed and updated.  | 04.17.25 | 06.10.25          |

**Important Reminder**

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise

professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

**Note:**

**For Medicaid members,** when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

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