Clinical Policy: Tetrabenazine (Xenazine)

Reference Number: CP.PHAR.92
Effective Date: 12.01.11
Last Review Date: 05.25
Line of Business: Commercial, HIM, Medicaid Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Tetrabenazine (Xenazine®) is a vesicular monoamine transporter 2 (VMAT) inhibitor.

FDA Approved Indication(s)

Xenazine is indicated for the treatment of chorea associated with Huntington's disease.

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 health plans affiliated with Centene Corporation® that Xenazine is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Chorea Associated with Huntington Disease (must meet all)**:**

1. Diagnosis of chorea associated with Huntington disease;
2. Prescribed by or in consultation with a neurologist;
3. Age ≥ 18 years;
4. Targeted mutation analysis demonstrates a cytosine-adenine-guanine (CAG) trinucleotide expansion of ≥ 36 repeats in the huntingtin (HTT) gene;
5. Evidence of chorea is supported by a Unified Huntington Disease Rating Scale (UHDRS) score ranging from 1 to 4 on any one of chorea items 1 through 7 (*see Appendix D*);
6. If request is for Xenazine, member must use generic tetrabenazine, unless contraindicated or clinically significant adverse effects are experienced;
7. Tetrabenazine is not prescribed concurrently with Austedo®/Austedo® XR or Ingrezza®;
8. Dose does not exceed 50 mg per day (*100 mg per day if genotype testing confirms extensive or intermediate CYP2D6 metabolizer status*).

Approval duration:
Medicaid/HIM – 6 months
Commercial – 12 months or duration of request, whichever is less

B. Tardive Dyskinesia (off-label) (must meet all)**:**

1. Diagnosis of tardive dyskinesia (TD) secondary to treatment with a centrally acting dopamine receptor blocking agent (DRBA) (*see Appendix G*);
2. Prescribed by or in consultation with a psychiatrist or neurologist;

3. Age ≥ 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 H*);
5. If request is for Xenazine, member must use generic tetrabenazine, unless contraindicated or clinically significant adverse effects are experienced;
6. Tetrabenazine is not prescribed concurrently with Austedo/Austedo XR or Ingrezza;
7. Dose does not exceed 200 mg per day.

Approval duration:
Medicaid/HIM – 6 months
Commercial – 12 months or duration of request, whichever is less

C. 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 formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 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.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. All Indications in Section I (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 meets one of the following (a or b):
   a. For Huntington disease: Member is responding positively to therapy as evidenced by a reduction since baseline in any one of UHDRS chorea items 1 through 7 (*see Appendix D*);
   b. For TD: Member is responding positively to therapy as evidenced by a reduction since baseline in any one of AIMS items 1 through 9 (*see Appendix H*);
3. If request is for Xenazine, member must use generic tetrabenazine, unless contraindicated or clinically significant adverse effects are experienced;

4. Tetrabenazine is not prescribed concurrently with Austedo/Austedo XR or Ingrezza;
5. Request meets one of the following (a or b):
   a. For Huntington disease: If request is for a dose increase, new dose does not exceed 50 mg per day (*100 mg per day if genotype testing confirms extensive or intermediate CYP2D6 metabolizer status*);
   b. For TD: If request is for a dose increase, new dose does not exceed 200 mg per day.

Approval duration:
Medicaid/HIM – 12 months
Commercial – 12 months or duration of request, whichever is less

B. 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 formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 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.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and 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.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid, or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

AIMS: Abnormal Involuntary Movement Scale
AAN: American Academy of Neurology
DRBA: dopamine receptor blocking agent
DSM-5-TR: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision
FDA: Food and Drug Administration
APA: American Psychiatric Association
HTT: huntingtin
MAOI: monoamine oxidase inhibitors
TD: tardive dyskinesia
UHDRS: Unified Huntington Disease Rating Scale
VMAT2: vesicular monoamine transporter

Appendix B: Therapeutic Alternatives
Not applicable

Appendix C: Contraindications/Boxed Warnings
- Contraindication(s):
  - Actively suicidal, or who have depression which is untreated or undertreated
  - Hepatic impairment
  - Taking monoamine oxidase inhibitors (MAOIs) or reserpine
  - Taking deutetrabenazine or valbenazine
- 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: General Information
- Medication-induced movement disorders, including tardive dyskinesia, are organized in the DSM-5-TR 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.
- Tardive dyskinesia is a type of movement disorder that occurs secondary to therapy with an antipsychotic medication or other DRBA (*see Appendix F*). (DSM-5-TR)
- Typical therapeutic drug classes containing DRBAs include first- and second-generation antipsychotics, antiemetics, and tri-cyclic antidepressants (*see Appendix G*). (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 F: Tardive Dyskinesia: DSM-5-TR Definition

Tardive Dyskinesia *(ICD-10 G24.01)*
• 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 ≥ 4 weeks and may be choreiform (rapid, jerky, nonrepetitive), athetoid (slow, sinuous, continual), or semirhythmic (e.g., stereotypies) in nature. • 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 ≥ 3 months (or 1 month in individuals age ≥ 60 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 ≥ 4 weeks, a diagnosis of tardive dyskinesia may be warranted.

Appendix G: Tardive Dyskinesia: Centrally Acting Dopamine Receptor Blocking Agents

Pharmacologic Class	**Therapeutic Class**		
	First-generation (typical) antipsychotics	**Antiemetic agents**	**Tri-cyclic antidepressants**
Phenothiazine	Chlorpromazine Fluphenazine Perphenazine Thioridazine Thiothixene Trifluoperazine	Chlorpromazine Perphenazine Prochlorperazine Promethazine* Thiethylperazine	Amoxapine†
Butryophenone	Haloperidol	Droperidol Haloperidol**	
Substituted benzamide		Metoclopramide Trimethobenzamide	
Dibenzazepine	Loxapine		
Diphenylbutylpiperidine	Pimozide		

Pharmacologic Class	**Second-generation (atypical) antipsychotics**
Quinolone	Aripiprazole, brexpiprazole
Dibenzazepine	Asenapine
Piperazine	Cariprazine
Dibenzodiazephine	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 H: Tardive Dyskinesia: The Abnormal Involuntary Movement Scale (AIMS) & APA 2020 Practice Guideline for the Treatment of Patients With Schizophrenia

- 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.
- 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.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Chorea associated with Huntington's disease	12.5 mg PO QD for first week, then 12.5 mg PO BID for second week, then titrate by 12.5 mg weekly thereafter to tolerated dose that reduces chorea; doses of 37.5 mg and up to 50 mg/day should be administered in 3 divided doses per day	50 mg/day (max single dose of 25 mg) Extensive or intermediate CYP2D6 metabolizer: 100 mg/day (max single dose of 37.5 mg)
TD (*off-label*)*	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.	150-200 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 H.*

VI. Product Availability

Tablets: 12.5 mg, 25 mg

VII. References

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Huntington Disease

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Tardive Dyskinesia

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Reviews, Revisions, and Approvals	Date	P&T Approval Date
2Q 2021 annual review: added off-label indication of TD supported by APA 2020 Practice Guideline and relevant appendices E, F, G, and H for supporting information; Commercial line of business added; references for HIM line of business off-label use revised from HIM.PHAR.21 to HIM.PA.154; references reviewed and updated.	02.16.21	05.21
Revised approval duration for Commercial line of business from length of benefit to 12 months or duration of request, whichever is less.	09.27.21	02.22
2Q 2022 annual review: no significant changes; references reviewed and updated.	01.24.22	05.22
Per May SDC and prior clinical guidance, added redirection for both initial and continuation of therapy to require redirection to generic tetrabenazine.	05.20.22	08.22
Template changes applied to other diagnoses/indications and continued therapy section.	10.12.22	
2Q 2023 annual review: no significant changes; references reviewed and updated.	02.05.23	05.23
2Q 2024 annual review: no significant changes; added Austedo XR formulation as additional concurrent treatment exclusion; references reviewed and updated.	01.12.24	05.24
2Q 2025 annual review: no significant changes; updated Appendix definitions per updated DSM-5-TR; references reviewed and updated.	02.21.25	05.25

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.