Original Effective Date:
Current Effective Date: 06/21/2023
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Policy Number: C3894-A

Xenazine (tetrabenazine)

PRODUCTS AFFECTED

Xenazine (tetrabenazine), tetrabenazine

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.
This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Chorea associated with Huntington’s Disease; Tardive Dyskinesia; Tourette's syndrome

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review.

A. CHOREA ASSOCIATED WITH HUNTINGTON’S DISEASE:
1. Diagnosis of Huntington’s disease with chorea symptoms confirmed by documentation of:
   (a) Huntington Disease Mutation Analysis: indicating an expanded CAG repeat (≥ 36) in the Huntington gene (HTT) (also known as HD gene)
   OR

(b) A positive family history of HD, with autosomal dominant inheritance pattern
AND

2. Prescriber attests that member does not have serious untreated or undertreated psychiatric illness, such as depression, AND is not suicidal
AND
3. Baseline evaluation and documentation of Total Chorea Score ([using the Unified Huntington's Disease Rating Scale (UHDRS)] NOTE: Reauthorization requires positive response or demonstrated efficacy to therapy. Baseline score reviewed at Continuation of Therapy.
AND
4. Prescriber attests to (or the clinical reviewer has found that) the member not having any FDA labeled contraindications that haven't been addressed by the prescriber within the documentation submitted for review [Contraindications to Xenazine (tetrabenazine) include: Actively suicidal or who have depression, which is untreated or undertreated, Hepatic impairment, taking MAOIs, reserpine, deutetrabenazine or valbenazine]

B. TARDIVE DYSKINESIA (TD) (Off-Label):
1. Documented diagnosis of moderate to severe tardive dyskinesia (TD)
AND
2. Documentation member has had an inadequate response to at least ONE of the following alternative approaches to treat tardive dyskinesia: (a) Adjustments to possible offending medication(s) known to cause TD (dose reduction or discontinuation) were attempted but ineffective in resolving TD symptoms, OR (b) Switched from a first-generation to a second-generation antipsychotic, OR (c) Member is not a candidate for a trial of dose reduction, tapering, discontinuation of the offending medication or switching to an alternative antipsychotic therapy [Appendix] [DOCUMENTATION REQUIRED]
AND
3. Prescriber attests that member does not have serious untreated or undertreated psychiatric illness, such as depression, AND is not suicidal
AND
4. Baseline evaluation of condition documented by Abnormal Involuntary Movement Scale (AIMS) score OR Extrapyramidal Symptom Rating Scale (ESRS) [DOCUMENTATION REQUIRED] NOTE: Reauthorization requires positive response or demonstrated efficacy to therapy. Baseline score reviewed at Continuation of Therapy.
AND
5. Prescriber attests to (or the clinical reviewer has found that) the member not having any FDA labeled contraindications that haven't been addressed by the prescriber within the documentation submitted for review [Contraindications to Xenazine (tetrabenazine) include: Actively suicidal or who have depression, which is untreated or undertreated, Hepatic impairment, taking MAOIs, reserpine, deutetrabenazine or valbenazine]

C. TOURETTE'S SYNDROME (Off-Label) - see Appendix for guideline citation:
1. Diagnosis of Tourette's syndrome. [DOCUMENTATION REQUIRED]
AND
2. Documentation that Comprehensive Behavioral Intervention for Tics (CBIT) has not been successful or is not accessible for the member
AND
3. Documentation of trial and failure of 3 months of adherent utilization of OR clinical contraindication to TWO of the following: clonidine, guanfacine, haloperidol, risperidone, aripiprazole, or fluphenazine
AND
4. Prescriber attests that member does not have serious untreated or undertreated psychiatric illness, such as depression, AND is not suicidal
AND
5. Prescriber attests to (or the clinical reviewer has found that) the member not having any

FDA labeled contraindications that haven't been addressed by the prescriber within the documentation submitted for review [Contraindications to Xenazine (tetrabenazine) include: Actively suicidal or who have depression which is untreated or undertreated, Hepatic impairment, taking MAOIs, reserpine, deutetrabenazine or valbenazine]

CONTINUATION OF THERAPY:

A. ALL INDICATIONS:

1. Adherence to therapy at least 85% of the time as verified by the prescriber and member's medication fill history (review Rx history for compliance)
   AND
2. Documentation member's condition has stabilized or improved based on Prescriber's assessment while on therapy [DOCUMENTATION REQUIRED]:
   a. TD: Disease stabilization or improvement in TD symptoms as documented by decrease from baseline in AIMS score of at least 2 points OR ESRI score of at least 4 points
   OR
   b. Chorea Associated with HD: Disease stabilization or improvement from baseline in Total Maximal Chorea Scores OR chorea symptoms
   c. Tourette's Syndrome (TS): Disease stabilization or improvement in signs and symptoms of TS due to Xenazine therapy
   AND
3. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity

DURATION OF APPROVAL:

Initial authorization: 12 months; Continuation of Therapy: 12 months

PRESCRIBER REQUIREMENTS:

Tardive Dyskinesia and Tourette's syndrome: Prescribed by, or in consultation with, a board-certified psychiatrist or neurologist.
Chorea associated with Huntington's disease: Prescribed by, or in consultation with, a board-certified neurologist with expertise in HD.
[If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:

Tourette's Syndrome: Ages 5 and older
Chorea and tardive dyskinesia: Age 18 or older

QUANTITY:

Maximum dosage: 50mg per day
[Daily doses above 50 mg should not be administered without CYP2D6 genotyping]
Tardive dyskinesia (off-label use): Initial: 50 mg/day in divided doses; if needed, may increase daily dose by 50 mg every two weeks up to maximum of 150 mg/day in divided doses.

***Tourette's Syndrome (TS) adults (off-label): Initial Dose: 12.5-25 mg once daily at bedtime or twice daily in adults, with titration up to a target dosage of 25 mg 3 times daily, Recommended Dose: 25 to 150 mg daily, Maximum Dose: 150 mg/day in divided doses (50 mg 3 times daily)-children and adolescents: Initial: 6.25 mg 2 to 3 times daily; may be increased by 6.25 mg daily at weekly intervals; should be titrated slowly to maximal tolerated and effective dose (dose is individualized).

Chorea - Huntington's disease: 37.5 mg to 50 mg/day orally in divided doses 3 times a day; MAX single dose, 25 mg; MAX daily dose, 100 mg

EXCEPTIONS For doses greater than 50 mg/day* of Xenazine (tetrabenazine):

1. CYP2D6 genotyping: Documentation of CYP 2D6 genotyping results required and indicates member is a CYP 2D6 intermediate or extensive metabolizer
   ** Daily doses above 50 mg should not be administered without CYP2D6 genotyping to determine whether the patient is a poor, intermediate, or extensive metabolizer.*
   AND
2. An adequate trial of 50 mg per day dosing with an inadequate response. Documentation of trial and inadequate response required.
   AND
3. Maximum Dose: 150 mg daily
   NOTE: Requests for doses greater than the maximum recommended dose of 150mg will not be authorized for any member.

PLACE OF ADMINISTRATION:
The recommendation is that oral medications in this policy will be for pharmacy benefit coverage and patient self-administered.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Oral

DRUG CLASS:
Central Monoamine-Depleting Agent; Vesicular Monoamine Transporter 2 (VMAT2) Inhibitor

FDA-APPROVED USES:
Chorea associated with Huntington's disease

COMPENDIAL APPROVED OFF-LABELED USES:
Tardive dyskinesia, Tourette syndrome

APPENDIX

APPENDIX:
Reserved for State specific information. *Information includes, but is not limited to, State contract language, Medicaid criteria and other mandated criteria.*

State Specific Information
State Marketplace
Nevada (Source: Nevada Legislature)
"Chapter 689A of Nevada Revised Statutes (NRS) is hereby amended by adding thereto a new section to read as follows:

1. A policy of health insurance which provides coverage for prescription drugs must not require an insured to submit to a step therapy protocol before covering a drug approved by the Food and Drug Administration that is prescribed to treat a psychiatric condition of the insured, if:
   a. The drug has been approved by the Food and Drug Administration with indications for the psychiatric condition of the insured or the use of the drug to treat that psychiatric condition is otherwise supported by medical or scientific evidence;
   b. The drug is prescribed by:
      i. A psychiatrist
      ii. A physician assistant under the supervision of a psychiatrist;
      iii. An advanced practice registered nurse who has the psychiatric training and experience

prescribed by the State Board of Nursing pursuant to NRS 632.120; or

iv. A primary care provider that is providing care to an insured in consultation with a practitioner listed in subparagraph (1), (2) or (3), if the closest practitioner listed in subparagraph (1), (2) or (3) who participates in the network plan of the insurer is located 60 miles or more from the residence of the insured; and

c. The practitioner listed in paragraph (b) who prescribed the drug knows, based on the medical history of the insured, or reasonably expects each alternative drug that is required to be used earlier in the step therapy protocol to be ineffective at treating the psychiatric condition…

3. As used in this section:

c. *'Step therapy protocol' means a procedure that requires an insured to use a prescription drug or sequence of prescription drugs other than a drug that a practitioner recommends for treatment of a psychiatric condition of the insured before his or her policy of health insurance provides coverage for the recommended drug*."

Molina Reviewer Note: Medical necessity review for a psychiatric condition cannot require trial of other medications first. This is applicable to formulary medications that require prior authorization and non-formulary medications and is not limited to only medications designated 'ST'. If the requested drug is a brand name and the generic is on formulary, request can be reviewed for specific medical reason generic cannot be used.

Appendix 1: Centrally Acting Dopamine Receptor Blocking Agents (Neuroleptics)

Drugs that most commonly cause TD are older antipsychotic agents such as haloperidol, chlorpromazine, and thioridazine; other drugs that may be associated with TD include antidepressants
(amitriptyline, fluoxetine, phenelzine, sertraline, and trazodone), anti-Parkinson's drugs (levodopa), epilepsy drugs (phenobarbital and phenytoin), and metoclopramide.

NOTE: Table below is a reference only and may not all-inclusive of every causative agent. If the suspected/causative agent is not listed below, confirm the status of the agent as a centrally acting DRBA and its association with tardive dyskinesia.

PHARMACOLOGIC CLASS	THERAPEUTIC CLASS		
	First-Generation (Typical) Antipsychotics	**Antiemetic Agents**	**Tricyclic Antidepressants**
Phenothiazine	Chlorpromazin e Fluphenazine Perphenazine Thioridazine Thiothixene Trifluoperazine	Chlorpromazine Perphenazine Prochlorperazine Promethazine (*First generation H1 antagonist)* Thiethylperazine	Amoxapine (*a dibenzoxapine that shares properties with phenothiazines)*
Butryophenone	Haloperidol	Droperidol Haloperidol *(Off-label use)*	
Substituted benzamide		Metoclopromide Trimethobenzamide	
Dibenzazepine	Loxapine		
Diphenylbutylpiperidine	Pimozide		
	Second-Generation (atypical) Antipsychotics		
Quinolone	Aripiprazole, brexpiprazole		

Dibenzazepine	Asenapine
Piperazine	Cariprazine
Dibenzodiazephine	Clozapine, quetiapine
Benzisoxazole	Iloperidone
Benzisothiazole	Lurasidone, ziprasidone
Thienobenzodiazepine	Olanzapine
Pyrimidinone	Paliperidone, risperidone

Practice guideline recommendations summary: Treatment of tics in people with Tourette syndrome and chronic tic disorders
Neurology | Volume 92, Number 19 | May 7, 2019 Neurology.org/N

The dopamine depletes, tetrabenazine, deutetrabenazine, and valbenazine, act by blocking vesicular monoamine transporter type 2 (VMAT2). Although no randomized controlled trials have been published with theVMAT2 increasingly used off-label. When appropriately dosed, these drugs are generally well- tolerated but maybe associated with drowsiness, depression, and parkinsonism. Although an initial phase II trial of valbenazine did not reach the primary endpoint in adults and children with TS, this was thought to be due to underdosing.
Further and better-designed trials are currently underway with valbenazine and deutetrabenazine for the treatment of tics.

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
A summary of the American Academy of Neurology (AAN) guideline regarding management of tardive syndromes (TDS), including tardive dyskinesias (TDD)
https://www.aan.com/Guidelines/Home/GetGuidelineContent/613
Evidence-based guideline: Treatment of tardive syndromes
Report of the Guideline Development Subcommittee of the American Academy of Neurology
http://n.neurology.org/content/81/5/463.long

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Xenazine (tetrabenazine) are considered experimental/investigational and therefore, will follow Molina's Off-Label policy. History of hypersensitivity to tetrabenazine or any of its components.
Hepatic impairment* *Appropriate labs and/or additional documentation may be requested at the discretion of the Pharmacy/Medical Director. Arrhythmias associated with a prolonged QT interval
NOTE: Members with congenital long QT syndrome or arrhythmias associated with prolonged QT interval, or members at risk of prolonged QT interval: An EKG may be required prior to therapy and before increasing the dosage. Actively suicidal or patients with untreated or inadequately treated depression.
Concomitant therapy with ANY of the following: (a) Other VMAT2 inhibitors: Ingrezza (valbenazine) or Austedo (deutetrabenazine) (b)MAOIs [e.g., selegiline (Emsam), isocarboxazid (Marplan), phenelzine (Nardil), tranylcypromine (Parnate)]--coadministration with or within 14 days of discontinuing MAOIs
(a) Reserpine-- coadministration with or within 20 days of discontinuing reserpine (d) QTc-prolonging agents [e.g., antipsychotic agents (e.g., chlorpromazine, haloperidol), antibiotics (e.g., moxifloxacin), class IA and III antiarrhythmic agents]
NOTE: Peer-to-Peer and/or additional documentation may be requested at the discretion of the Pharmacy/Medical Director.

OTHER SPECIAL CONSIDERATIONS:
Black Box Warnings: Depression and suicidality
Tetrabenazine can increase the risk of depression and suicidal thoughts and behavior (suicidality) in patients with Huntington disease. The risks of depression and suicidality with the clinical need for control

of chorea must be considered. Close observation of patients for the emergence or worsening of depression, suicidality, or unusual changes in behavior should accompany therapy. Caution in treating individuals with a history of depression or prior suicide attempts or ideation, which are increased in frequency in Huntington disease.

Tetrabenazine is contraindicated in patients who are actively suicidal, and in patients with untreated or inadequately treated depression.

Huntington's Chorea: Dose of tetrabenazine is determined individually for each patient

- Initial Dose: 12.5 mg orally once daily in the morning
- Recommended Dose: After 1 week, the dose may be increased to 12.5 mg twice daily. Tetrabenazine should be titrated slowly at weekly intervals by 12.5 mg. If a dose of 37.5mg to 50 mg per day is required, it should be given in divided doses 3 times a day.
- Maximum Dose: Max recommended single dose is 25 mg; maximum daily dose is 100mg Tardive Dyskinesia in adults (off-label)
- Initial Dose: 50 mg/day in divided doses. May increase daily dose by 50 mg every 2 weeks
- Recommended Dose: Dose is individualized based on efficacy and tolerance
- Maximum Dose: 150 mg/day in divided doses (50 mg 3 times daily)

Tourette's Syndrome (TS) (off-label)

Clinical experience with tetrabenazine in the treatment of TS is limited

- Initial Dose: 12.5-25 mg once daily at bedtime or twice daily in adults, with titration up to a target dosage of 25 mg 3 times daily
- Recommended Dose: 25 to 150 mg daily
- Maximum Dose: 150 mg/day in divided doses (50 mg 3 times daily)

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
NA	

AVAILABLE DOSAGE FORMS:

Tetrabenazine TABS 12.5MG, Tetrabenazine TABS 25MG, Xenazine TABS 12.5MG, Xenazine TABS 25MG

REFERENCES

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Tardive Dyskinesia
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SUMMARY OF REVIEW/REVISIONS	DATE
REVISION-Notable Revisions: Required Medical Information Continuation of Therapy Quantity Compendial Approved Off-Labeled Uses Available Dosage Forms References	Q2 2023
REVISION-Notable Revisions: Prescriber Requirements	Q2 2022
Q2 2022 Established tracking in new format	Historical changes on file