Xenazine (tetrabenazine)
Policy Number: C3894A

CRITERIA EFFECTIVE DATES:

ORIGINAL EFFECTIVE DATE	LAST REVIEWED DATE	NEXT REVIEW DATE
	02/2019	02/2020
J CODE	**TYPE OF CRITERIA**	**LAST P&T APPROVAL**
J8499	MCP	MCP-075

PRODUCTS AFFECTED:
Oral (tablets)

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

ROUTE OF ADMINISTRATION:
Oral

PLACE OF SERVICE:
Specialty Pharmacy

AVAILABLE DOSAGE FORMS:
Tablets: 12.5 mg, 25 mg

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

COMPENDIAL APPROVED OFF-LABELED USES: Tardive dyskinesia in adults**,** Tourette's syndrome (TS or Gilles de la Tourette's syndrome)

COVERAGE CRITERIA: INITIAL AUTHORIZATION
DIAGNOSIS: Chorea associated with Huntington's Disease; Tardive Dyskinesia; Tourette's syndrome

REQUIRED MEDICAL INFORMATION:
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. Documented trial of at least one alternative treatment (typical neuroleptics, atypical antipsychotics, atypical antipsychotics, benzodiazepines, or amantadine)
   AND
3. STABLE psychiatric status: Member does not have risk for suicidal or violent behavior and does not have untreated or inadequately treated depression
   AND
4. If member has a history of depression and/or suicidal ideation: An evaluation by a neurologist or behavioral health provider prior to starting therapy is required AND member is counseled on receiving treatment and follow-up assessment for psychiatric condition from the Prescriber (neurologist) or behavioral health provider while on therapy. Documentation required.
   AND

5. 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.

B. TARDIVE DYSKINESIA (TD) (Off-Label):
1. Diagnosis of TD with documentation of the following: Involuntary athetoid or choreiform movements; AND History of treatment with a dopamine receptor blocking agent for at least 3 months (or 1 month if older than 60 years) (e.g. antipsychotics; metoclopramide, haloperidol, chlorpromazine, etc); AND Symptoms for at least 3 months
AND
2. 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]
AND
3. Documented trial of at least one other guideline recommended treatment (clonazepam, amantadine)
AND
4. STABLE psychiatric status: Member does not have risk for suicidal or violent behavior, untreated or inadequately treated depression, or unstable psychiatric symptoms
AND
5. If member has a history of depression and/or suicidal ideation: An evaluation by a neurologist or behavioral health provider prior to starting therapy is required AND member is counseled on receiving treatment and follow-up assessment for psychiatric condition from the Prescriber (neurologist) or behavioral health provider while on therapy. Documentation required.
AND
6. If member is on maintenance medication(s) for schizophrenia, schizoaffective disorder, or mood disorders: stable medication doses and therapy required.
AND
7. Baseline evaluation of condition documented by Abnormal Involuntary Movement Scale (AIMS) score OR Extrapyramidal Symptom Rating Scale (ESRI) NOTE: Reauthorization requires positive response or demonstrated efficacy to therapy. Baseline score reviewed at Continuation of Therapy.

C. TOURETTE'S SYNDROME (Off-Label):
1. Diagnosis of Tourette's syndrome. Documentation required
AND
2. Therapy is within recommended dosing for indicaiton: 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) (see background for guidline information for off-label use)

DURATION OF APPROVAL: Initial authorization: 6 months**.** Continuation of Therapy: 6 months

QUANTITY: Maximum dosage: 50mg per day
***Tourette's Syndrome (TS) (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)

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 100mg will not be authorized for any member.

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.
NOTE: Consultation notes must be submitted for initial request and for continuation of treatment requests at least ONCE annually. Submit consultation notes if applicable.

AGE RESTRICTIONS: 18 years of age and older (exception: Tourette's Syndrome-- member must be age 5 to 16)

GENDER:
Male and female

OTHER RESTRICTIONS:
The most cost-effective generic/brand of tetrabenazine will be selected/authorized. For other tetrabenazine brand/generic product requests, a letter of medical necessity with rationale and documentation from member's medical record supporting the following for a case-by-case review:

1) Member's medication history includes use of a generic tetrabenazine
   AND
2) Documented adverse reaction, FDA labeled contraindication, or hypersensitivity to generic tetrabenazine

CONTINUATION OF THERAPY:

A. FOR ALL INDICATIONS:

1. Adherence to therapy at least 85% of the time as verified by Prescriber and member's medication fill history (review Rx history for compliance)
   AND
2. Members continues to be monitored/followed-up by the prescriber/specialist. Chart notes or consultation notes (if applicable) must be submitted at least ONCE annually
   AND
3. Member's condition has stabilized or improved based on Prescriber's assessment while on therapy:
   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

4. STABLE psychiatric status with documentation of the following:
   1) Members on maintenance medication(s) for schizophrenia or schizoaffective disorder, or mood disorders): Stable medication doses and therapy required
   2) Members with a history of depression and/or suicidal thoughts or behaviors, OR members with a current treatment for depression and/or suicidal thoughts or behaviors:
      (a) Regular follow-up and recent evaluation by the Prescriber or behavioral health provider is required, AND
      (b) Member is not experiencing any unstable psychiatric symptoms

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 (c) 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.

Recommended Dose:
<u>Huntington's Chorea: Dose of tetrabenazine is determined individually for each patient</u>
- 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 37.5 mg 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 100 mg

<u>Tardive Dyskinesia in adults</u> (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)

<u>Tourette's Syndrome (TS)</u> (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)

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

APPENDIX:

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	Chlorpromazine 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

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