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Vesicular Monoamine Transporter 2 (VMAT2) Inhibitors Prior Authorization with Quantity Limit Program Summary

FDA APPROVED INDICATIONS AND DOSAGE[1-3]

Agent(s)	Indication(s)	Dosage
Austedo® (deutetrabenazine) Tablet	Treatment of chorea associated with Huntington's disease Treatment of tardive dyskinesia in adults	**Chorea associated with Huntington's disease:** Not currently treated with tetrabenazine: 6 mg orally once daily **Tardive dyskinesia:** Not currently treated with tetrabenazine: 12 mg orally (6 mg orally twice daily) - May be increased at weekly intervals in increments of 6 mg per day up to a maximum of 48 mg daily - Administer total daily doses of 12 mg or above in two divided doses See package insert for recommended dosing when switching therapy from tetrabenazine to deutetrabenazine
Ingrezza® (valbenazine) Capsule	Treatment of adults with tardive dyskinesia	40 mg orally once daily. After one week, increase to the recommended dose of 80 mg once daily. A dosage of 40 mg or 60 mg once daily may be considered for some patients

Agent(s)	Indication(s)	Dosage
Xenazine® (tetrabenazine)[a] Tablet	Treatment of chorea associated with Huntington's disease	Week 1: 12.5 mg orally once in the morning Week 2: 25 mg orally (12.5 mg twice daily) After Week 2: slowly titrate at weekly intervals by 12.5 mg to a tolerated dose that reduces chorea - Doses of 37.5 mg to 50 mg per day should be administered in three divided doses per day with a maximum recommended single dose not to exceed 25 mg - Patients requiring doses above 50 mg per day should be genotyped for the drug metabolizing enzyme CYP2D6 to determine if the patient is a poor metabolizer (PM) or an extensive metabolizer (EM) - Maximum daily dose in PMs: 50 mg with a maximum single dose of 25 mg - Maximum daily dose in EMs and intermediate metabolizers (IMs): 100 mg with a maximum single dose of 37.5 mg

a- Generic equivalent available

CLINICAL RATIONALE

Huntington's disease

Huntington's Disease (HD) is an autosomal dominant hereditary neurodegenerative disorder caused by an expansion of a repeating CAG triplet series in the huntingtin gene on chromosome 4, which results in a protein with an abnormally long polyglutamine sequence. The huntingtin gene directs the cell to make huntingtin protein, whose functions within the cell are largely unknown. Huntingtin gene contains a repeating sequence of three base-pairs, called a "triplet repeat" or "trinucleotide repeat." An excess number of CAG repeats in the gene results in a protein containing an excess number of glutamine units. The huntingtin protein appears to be produced in equal quantities, whether it has a normal or excess number of glutamines, but the abnormally elongated protein appears to be processed aberrantly within the neurons, so that its fragments tend to accumulate over time into intranuclear inclusions.[6]

Movement-associated symptoms are a core feature of HD. Chorea is the most recognized motor symptom, but there are a number of additional movement disorders that can occur. More than 90% of people affected by HD have chorea, which is characterized by involuntary movements which are often sudden, irregular and purposeless or semi-purposeful. The movements are often more prominent in the extremities early in the disease, but may eventually include facial grimacing, eyelid elevation, neck, shoulder, trunk, and leg movements as the disease progresses. Chorea typically increases in frequency and amplitude over time and may peak about 10 years after disease onset. In some people chorea plateaus and lessens, while others have inexorable worsening as they enter late stage HD.[6]

Treating chorea is an important part of HD management. The pathophysiology and neurochemical bases of HD are not completely understood. Dopamine and glutamate transmission and interactions are affected. The FDA approved agents target these neurotransmitters and receptors.[4] Tetrabenazine and deutetrabenazine act by depleting monoamines (e.g., dopamine, serotonin, and norepinephrine) from nerve terminals. Tetrabenazine and the major metabolites of deutetrabenazine are centrally-acting dopamine depleting agents that works by reversibly inhibiting vesicular monoamine transporter 2 (VMAT2), resulting in decreased uptake of monoamines into synaptic vesicles and depletion of monoamine stores. The mechanism of action of valbenazine in the treatment of tardive dyskinesia is unknown, but is thought to be mediated through the reversible inhibition of vesicular monoamine transporter 2 (VMAT2).[1,3]

The American Academy of Neurology guidelines for the treatment of chorea in HD recommend tetrabenazine, if the chorea requires treatment. Other agents also shown to be effective in varying degrees for the treatment of chorea include amantadine or riluzole. Adverse events should be discussed and monitored especially the increased risk of depression/suicidality and parkinsonism with the treatment of tetrabenazine.[4]

Tardive dyskinesia
Tardive syndromes are persistent abnormal involuntary movement disorders caused by sustained exposure to antipsychotic medication, the most common of which are tardive dyskinesia, tardive dystonia, and tardive akathisia. They begin later in treatment than acute dystonia, akathisia, or medication-induced parkinsonism and they persist and may even increase, despite reduction in dose or discontinuation of the antipsychotic medication. Tardive dyskinesia has been reported after exposure to any of the available antipsychotic medications. It occurs at a rate of approximately 4-8% per year in adult patients treated with first generation antipsychotics. Evaluation of the risk of tardive dyskinesia is complicated by the fact that dyskinetic movements may be observed with a reduction in antipsychotic medication dose. Fluctuations in symptoms are also common and may be influenced by factors such as psychosocial stressors. Regular assessment of patients for tardive syndromes through clinical examination or through the use of a structured evaluative tool can aid in identification and monitoring, such as the Abnormal Involuntary Movement Scale (AIMS). It should be noted that there is no specific score threshold that suggests a need for intervention, although ranges of scores are noted to correspond with mild, moderate, and severe symptoms. If no other contributing etiology is identified and moderate or severe or disabling tardive dyskinesia persists, treatment is recommended with a VMAT2 inhibitors. A lower dose of antipsychotic medication can be considered. The potential for benefit needs to be weighed against the potential side effects of these medications. A change in antipsychotic therapy to a lower potency medication and particularly to clozapine may also be associated with a reduction in tardive dyskinesia. Again, however, the potential benefits of changing medication should be considered in light of the possibility of symptom recurrence.[7]

Safety[1, 3]
Austedo is contraindicated in patients:
- with Huntington's disease who are suicidal, or have untreated or inadequately treated depression
- with hepatic impairment
- taking reserpine. At least 20 days should elapse after stopping reserpine before starting Austedo

- taking monoamine oxidase inhibitors (MAOIs). Austedo should not be used in combination with an MAOI, or within 14 days of discontinuing therapy with an MAOI
- taking tetrabenazine (Xenazine) or valbenazine (Ingrezza)

Ingrezza is contraindication in patients:

- with a history of hypersensitivity to valbenazine or any components of Ingrezza

Xenazine is contraindicated in patients:

- who are actively suicidal, or in patients with untreated or inadequately treated depression
- with hepatic impairment
- taking monoamine oxidase inhibitors (MAOIs). Tetrabenazine should not be used in combination with an MAOI, or within a minimum of 14 days of discontinuing therapy with an MAOI.
- taking reserpine. At least 20 days should elapse after stopping reserpine before starting Xenazine.
- taking deutetrabenazine or valbenazine

References

1. Austedo prescribing information. Teva. June 2021.
2. Ingrezza prescribing information. Neurocrine Biosciences, Inc. April 2021.
3. Xenazine Prescribing Information. Lundbeck/Valeant. November 2019.
4. Armstrong MJ, Miyasaki MJ. Evidence-based guideline: Pharmacologic treatment of Chorea in Huntington disease. *Neurology* 2012; 79:597-603. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3413759/pdf/znl597.pdf
5. Institute for Clinical and Economic Review (ICER). Vesicular Monoamine Transporter 2 Inhibitors for Tardive Dyskinesia: Effectiveness and Value. Final Evidence Report. December 22, 2017. Available at: http://icerorg.wpengine.com/wp-content/uploads/2020/10/NECEPAC_TD_FINAL_REPORT_122217.pdf
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7. Keepers GA, Fochtmann LJ, Anzia JM et al. The American Psychiatric Associations Practice Guideline for the Treatment of Patients with Schizophrenia (Pre-release edition) Available at: https://www.psychiatry.org/File%20Library/Psychiatrists/Practice/Clinical%20Practice%20Guidelines/APA-Draft-Schizophrenia-Treatment-Guideline-Dec2019.pdf

Vesicular Monoamine Transporter 2 (VMAT2) Inhibitors Prior Authorization with Quantity Limit

TARGET AGENT(S)
Austedo® (deutetrabenazine)
Ingrezza® (valbenazine)
Xenazine® (tetrabenazine)[a]
a – Generic equivalent available

PROGRAM QUANTITY LIMIT

Brand (generic)	GPI	Multisource Code	Quantity Limit (per day or as listed)
Austedo (deutetrabenazine)			
6 mg tablet	62380030000310	M, N, O, or Y	2 tablets
9 mg tablet	62380030000320	M, N, O, or Y	4 tablets
12 mg tablet	62380030000330	M, N, O, or Y	4 tablets
Ingrezza (valbenazine)			
40 mg capsule	62380080200120	M, N, O, or Y	1 capsule
60 mg capsule	62380080200130	M, N, O, or Y	1 capsule
80 mg capsule	62380080200140	M, N, O, or Y	1 capsule
40 mg (7) and 80 mg (21) capsule therapy pack	6238008020B220	M, N, O, or Y	28 capsules/180 days
Xenazine (tetrabenazine)[a]			
12.5 mg tablet	62380070000310	M, N, O, or Y	8 tablets
25 mg tablet	62380070000320	M, N, O, or Y	4 tablets

a- Generic equivalent available

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Initial Evaluation
Target Agent(s) will be approved when ALL of the following are met:

1. ONE of the following:
    A. The requested agent is Ingrezza/valbenazine AND ONE of the following:
        i. The patient has a diagnosis of tardive dyskinesia AND BOTH of the following:
            1. ONE of the following:
                a. The prescriber has reduced the dose or discontinued any medications known to cause tardive dyskinesia (i.e., dopamine receptor blocking agents)
                OR
                b. The prescriber has provided clinical rationale indicating that a reduced dose or discontinuation of any medications known to cause tardive dyskinesia is not appropriate

            AND
            2. The prescriber has documented the patient's baseline Abnormal Involuntary Movement Scale (AIMS) score

        OR
        ii. The patient has another FDA approved indication for the requested agent
        OR

iii. The patient has another indication that is supported in compendia for the requested agent

OR

B. The requested agent is Austedo/deutetrabenazine AND ONE of the following:
   i. The patient has a diagnosis of tardive dyskinesia AND BOTH of the following:
      1. ONE of the following:
         a. The prescriber has reduced the dose or discontinued any medications known to cause tardive dyskinesia (i.e., dopamine receptor blocking agents)
         OR
         b. The prescriber has provided clinical rationale indicating that a reduced dose or discontinuation of any medications known to cause tardive dyskinesia is not appropriate

      AND

      2. The prescriber has documented the patient's baseline Abnormal Involuntary Movement Scale (AIMS) score

   OR

   ii. The patient has a diagnosis of chorea associated with Huntington's disease

   OR

   iii. The patient has another FDA approved indication for the requested agent

   OR

   iv. The patient has another indication that is supported in compendia for the requested agent

OR

C. The requested agent is Xenazine/tetrabenazine and ONE of the following:
   i. The patient has a diagnosis of chorea associated with Huntington's disease

   OR

   ii. The patient has another FDA approved indication for the requested agent

   OR

   iii. The patient has another indication that is supported in compendia for the requested agent

AND

2. If the request is for one of the following brand agents with an available generic equivalent (listed below), then ONE of the following:
   A. The patient has an intolerance or hypersensitivity to the generic equivalent that is not expected to occur with the brand agent

   OR

   B. The patient has an FDA labeled contraindication to the generic equivalent that is not expected to occur with the brand agent

   OR

   C. The prescriber has provided information to support the use of the requested brand agent over the generic equivalent

Brand	Generic Equivalent
Xenazine	tetrabenazine

AND

3. ONE of the following:
    A. The patient's age is within FDA labeling for the requested indication for the requested agent
    OR
    B. The prescriber has provided information in support of using the requested agent for the patient's age for the requested indication

AND

4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., psychiatrist, neurologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis

AND

5. The patient will NOT be using the requested agent in combination with another agent included in this prior authorization program

AND

6. The patient does NOT have any FDA labeled contraindications to the requested agent

AND

7. ONE of the following:
    A. The requested quantity (dose) does NOT exceed the program quantity limit
    OR
    B. ALL of the following
        i. The requested quantity (dose) is greater than the program quantity limit
        AND
        ii. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication
        AND
        iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit

    OR

    C. ALL of the following:
        i. The requested quantity (dose) is greater than the program quantity limit
        AND
        ii. The requested quantity (dose) is greater than the maximum FDA labeled dose for the requested indication
        AND
        iii. The prescriber has provided information in support of therapy with a higher dose for the requested indication

Compendia Allowed: AHFS, or DrugDex 1 or 2a level of evidence

Length of Approval: Tardive dyskinesia: 3 months
Chorea associated with Huntington's Disease, all other FDA labeled indications, AHFS, or DrugDex level 1 or 2a supported indications: 12 months

Renewal Evaluation

Target Agent(s) will be approved when ALL of the following are met:

1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process

AND

2. The prescriber is a specialist in the area of the patient's diagnosis (e.g., psychiatrist, neurologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis
AND
3. ONE of the following:
    A. The diagnosis is tardive dyskinesia AND the patient has had stabilization or improvement from baseline in Abnormal Involuntary Movement Scale (AIMS) score
    OR
    B. The diagnosis is another FDA approved indication or another indication that is supported in compendia AND the patient has had clinical benefit with the requested agent

AND
4. If the request is for one of the following brand agents with an available generic equivalent (listed below), then ONE of the following:
    A. The patient has an intolerance or hypersensitivity to the generic equivalent that is not expected to occur with the brand agent
    OR
    B. The patient has an FDA labeled contraindication to the generic equivalent that is not expected to occur with the brand agent
    OR
    C. The prescriber has provided information to support the use of the requested brand agent over the generic equivalent

Brand	Generic Equivalent
Xenazine	tetrabenazine

AND
5. The patient will NOT be using the requested agent in combination with another agent included in this prior authorization program
AND
6. The patient does NOT have any FDA labeled contraindications to the requested agent
AND
7. ONE of the following:
    A. The requested quantity (dose) does NOT exceed the program quantity limit
    OR
    B. ALL of the following
        i. The requested quantity (dose) is greater than the program quantity limit
        AND
        ii. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication
        AND
        iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit
    OR
    C. ALL of the following:
        i. The requested quantity (dose) is greater than the program quantity limit
        AND
        ii. The requested quantity (dose) is greater than the maximum FDA labeled dose for the requested indication

AND

iii. The prescriber has provided information in support of therapy with a higher dose for the requested indication

Compendia Allowed: AHFS, or DrugDex 1 or 2a level of evidence

Length of Approval: 12 months