Medical Policy

BlueCross BlueShield of Kansas
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Title: VMAT2 Inhibitors

- **Prime Therapeutics will review Prior Authorization requests**
  Prior Authorization Form:
  https://www.bcbsks.com/CustomerService/Forms/pdf/PriorAuth-6508KS-VMAT.pdf

  Link to Drug List (Formulary):
  https://www.bcbsks.com/drugs/

Professional
Original Effective Date: February 1, 2018
Revision Date(s): February 1, 2018; May 1, 2018
Current Effective Date: May 1, 2018

Institutional
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DESCRIPTION

The intent of the VMAT2 Inhibitors Prior Authorization (PA) with Quantity Limit Criteria is to appropriately select patients for therapy according to product labeling and/or clinical guidelines and/or clinical studies and according to dosing recommended in product labeling. The PA criteria will direct its use to the FDA approved and/or clinically supported use. The program will approve doses within the set limit. Doses above the set limit will be approved if the requested quantity is below the FDA limit and cannot be dose

optimized or when the quantity is above the FDA limit and the prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis.

Target Drugs

- **Austedo**® (deutetrabenazine)
- **Ingrezza**® (valbenazine)
- **Xenazine**® (tetrabenazine)[a]

[a] – generic available

FDA Approved Indications and Dosage[1,5]

Brand (generic)	Indication	Dosing
Austedo (deutetrabenazine)	Treatment of chorea associated with Huntington's disease	Not currently treated with tetrabenazine: -6 mg orally once daily -May be increased at weekly intervals in increments of 6 mg per day up to a maximum of 48 mg daily -Total daily doses of 12 mg or above should be divided into two daily doses -In patients receiving strong CYP2D6 inhibitors or who are poor CYP2D6 metabolizers, the total daily dosage should not exceed 36 mg (maximum single dose of 18mg) See package insert for recommended dosing when switching therapy from tetrabenazine to deutetrabenazine
Ingrezza (valbenzaine)	Treatment of adults with tardive dyskinesia	40 mg once daily. After one week, increase to 80 mg once daily. Continuation of 40 mg once daily may be considered for some patients
Xenazine (tetrabenazine)	Treatment of chorea associated with Huntington's disease	Week 1: starting dose is 12.5 mg daily Week 2: 25 mg (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 and up 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

POLICY

Prior Authorization and Quantity Limit Criteria for Approval

VMAT2 Inhibitors will be approved when 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 ALL of the following:
         1. The patient is an adult (≥18 years old)
            AND
         2. 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 the offending agent is not appropriate
            AND
         3. The prescriber has documented the patient's baseline Abnormal Involuntary Movement Scale (AIMS) score
      OR
      ii. The patient has another FDA approved diagnosis or an indication supported by level 1 or 2a evidence
   OR
   B. The requested agent is Austedo/deutetrabenazine and ONE of the following:
      i. The patient has a diagnosis of tardive dyskinesia and ALL of the following:
         1. The patient is an adult (≥18 years old)
            AND
         2. 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 the offending agent is not appropriate
            AND
         3. 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 diagnosis or an indication supported by level 1 or 2a evidence

OR

C. The requested agent is Xenazine (tetrabenazine) and BOTH of the following:
   i. If the request is for brand Xenazine AND then ONE of the following:
      1. The patient's medication history includes use of a generic tetrabenazine agent
      OR
      2. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to generic tetrabenazine
      OR
      3. The prescriber has submitted documentation to support the use of the requested brand over generic

   AND

   ii. ONE of the following:
      1. The patient has a diagnosis of chorea associated with Huntington's disease
      OR
      2. The patient has another FDA approved diagnosis or an indication supported by level 1 or 2a evidence

AND

2. ONE of the following:
   A. The prescriber is a specialist in the area of the patient's diagnosis (e.g., psychiatrist, neurologist)
   OR
   B. The prescriber has consulted with a specialist in the area of the patient's diagnosis

AND

3. The patient does NOT have any FDA labeled contraindications to therapy with the requested agent

AND

4. The patient is receiving only one agent included in this prior authorization program at a time

AND

5. ONE of the following:
   A. The requested quantity (dose) is NOT greater than 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) is less than or equal to the FDA labeled dose
      AND

iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the 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 FDA labeled dose
   AND
   iii. The prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis (must be reviewed by the Clinical Review pharmacist)

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

Renewal Evaluation

This agent will be approved for renewal when the following criteria are met:

1. The patient has been previously approved for therapy with the requested agent through Prime Therapeutics PA process
   AND
2. ONE of the following:
   a. The prescriber is a specialist in the area of the patient's diagnosis (e.g., psychiatrist, neurologist)
      OR
   b. 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 a stabilization or an improvement from baseline in Abnormal Involuntary Movement Scale (AIMS) score
      OR
   b. The diagnosis is another FDA approved diagnosis or an indication supported by level 1 or 2a evidence and the patient has had clinical stabilization or improvement from baseline
   AND
4. The patient does NOT have any FDA labeled contraindications to therapy with the requested agent
   AND

5. ONE of the following:
   a. The requested quantity (dose) is NOT greater than 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) is less than or equal to the FDA labeled dose
         AND
      iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the 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 FDA labeled dose
         AND
      iii. The prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis (must be reviewed by the Clinical Review pharmacist)

Length of Approval: 12 months

Brand (generic)	Quantity Per Day Limit
Austedo (deutetrabenazine)	
6 mg tablet	2 tablets
9 mg tablet	4 tablets
12 mg tablet	4 tablets
Ingrezza (valbenazine)	
40 mg capsule	1 capsule
80 mg capsule	1 capsule
Xenazine (tetrabenazine)[a]	
12.5 mg tablet	8 tablets
25 mg tablet	4 tablets

a – generic available

Agent	Contraindication(s)
Austedo	▪ Patients with Huntington's disease who are suicidal, or have untreated or inadequately treated depression ▪ Patients with hepatic impairment ▪ Patients taking reserpine. At least 20 days should elapse after stopping reserpine before starting ▪ Patients 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 ▪ Patients taking tetrabenazine (Xenazine) or valbenazine
Ingrezza	None
Xenazine	▪ Patients who are actively suicidal, or in patients with untreated or inadequately treated depression ▪ Patients with hepatic impairment ▪ Patients taking monoamine oxidase inhibitors (MAOIs). It should not be used in combination with an MAOI, or within a minimum of 14 days of discontinuing therapy with an MAOI. ▪ Patients taking reserpine. At least 20 days should elapse after stopping reserpine before starting Xenazine. ▪ Patients taking deutetrabenazine or valbenazine

RATIONALE

Tetrabenazine and deutrabenazine act by depleting monoamines (e.g., dopamine, serotonin, and norepinephrine) from nerve terminals.

Tetrabenazine and deutrabenazine are contraindicated in patients who are actively suicidal or with untreated or inadequately treated depression (boxed warning), in patients with impaired hepatic function and in patients taking monoamine oxidase inhibitors (MAOIs) or reserpine; MAOIs should be discontinued at least 14 days prior to starting both agents and reserpine should be discontinued at least 20 days before starting both agents.[1,5] Besides potentially increasing risk for depression and suicidality, tetrabenazine/deutrabenazine may cause neuroleptic-like adverse effects (e.g., neuroleptic malignant syndrome, akathisia, Parkinsonism, dysphagia, sedation, prolactinemia, tardive dyskinesia, etc.).[1,5] Deutrabenazine also has an FDA labeled contraindication for concomitant use with tetrabenazine.[5] Tetrabenazine has been approved with a required Risk Evaluation and Mitigation Strategy (REMS) to ensure that the drug's benefits outweigh its risks.[1]

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]

Leung JG and Breden EL conducted a literature evaluation on the off label use of tetrabenazine for the treatment of tardive dyskinesia (TD). Literature from 1966 to September 2010 was accessed. Three prospective trials, 8 additional trials, 1 case series, and 8 case reports for the

use of tetrabenazine in the treatment of tardive dyskinesia were identified and evaluated. The authors concluded that small trials indicate tetrabenazine may be effective for the treatment of tardive dyskinesia, however, larger, well-conducted trials are needed. The authors concluded that from the available literature, tetrabenazine exhibits some promise as a potentially effective agent for the treatment of TD, however, there is currently a paucity of efficacy data to recommend tetrabenazine as a useful agent in the management of TD. The authors recommend all other options (e.g. decreasing dose of offending agent, discontinue offending agent, benzodiazepines or tricyclic antidepressants) be exhausted and the risk versus benefit be weighed before using tetrabenazine in this setting.[3]

REVISIONS

02-01-2018	Policy added to the bcbsks.com web site 01-01-2018. Policy effective 02-01-2018.
05-01-2018	Description section updated adding Ingrezza (valbenzaine) to the policy.
	In Policy section: ▪ In Item 1 added: "A. The requested agent is Ingrezza/valbenazine and ONE of the following: i. The patient has a diagnosis of tardive dyskinesia and ALL of the following: 1. The patient is an adult (≥18 years old) AND 2. 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 the offending agent is not appropriate AND 3. The prescriber has documented the patient's baseline Abnormal Involuntary Movement Scale (AIMS) score OR ii. The patient has another FDA approved diagnosis or an indication supported by level 1 or 2a evidence OR B. The requested agent is Austedo/deutetrabenazine and ONE of the following: i. The patient has a diagnosis of tardive dyskinesia and ALL of the following: 1. The patient is an adult (≥18 years old) AND 2. 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 the offending agent is not appropriate AND 3. The prescriber has documented the patient's baseline Abnormal Involuntary Movement Scale (AIMS) score" ▪ In Item 1 B iii removed "for the requested agent" and added "diagnosis or an" and "supported by level 1 or 2a evidence" to read "The patient has another FDA approved diagnosis or an indication supported by level 1 or 2a evidence" ▪ Removed "1. C. The prescriber has submitted documentation supporting the requested agent for the intended diagnosis which has been reviewed and approved by the Clinical Review pharmacist AND 2. If the patient has a diagnosis of depression, the patient is being adequately treated for depression AND 3. If the patient has a diagnosis of suicidal ideation and/or behavior, the patient must not be actively suicidal AND 4. The patient is not receiving a monoamine oxidase inhibitor (MAOI) or the patient's MAOI will be discontinued at least 14 days before starting therapy with the requested agent AND

	5. The patient is not receiving reserpine or the patient's reserpine will be discontinued at least 20 days before starting therapy with the requested agent AND 6. The patient does not have impaired hepatic function AND 7. ONE of the following: A. The patient is requesting a generic tetrabenazine or brand Austedo agent" ▪ Added 2 C "The requested agent is Xenazine (tetrabenazine) and BOTH of the following:" ▪ Added "2. C. ii. ONE of the following: 1. The patient has a diagnosis of chorea associated with Huntington's disease OR 2. The patient has another FDA approved diagnosis or an indication supported by level 1 or 2a evidence AND 2. ONE of the following: A. The prescriber is a specialist in the area of the patient's diagnosis (e.g., psychiatrist, neurologist) OR B. The prescriber has consulted with a specialist in the area of the patient's diagnosis AND 3. The patient does NOT have any FDA labeled contraindications to therapy with the requested agent" ▪ Updated Length of Approval from "12 months" to "Tardive dyskinesia: 3 months; Chorea associated with Huntington's Disease, all other FDA labeled indications, or level 1 or 2a supported indications: 12 months" ▪ Added Renewal Evaluation criteria of: "This agent will be approved for renewal when the following criteria are met: 1. The patient has been previously approved for therapy with the requested agent through Prime Therapeutics PA process AND 2. ONE of the following: a. The prescriber is a specialist in the area of the patient's diagnosis (e.g., psychiatrist, neurologist) OR b. 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 a stabilization or an improvement from baseline in Abnormal Involuntary Movement Scale (AIMS) score OR b. The diagnosis is another FDA approved diagnosis or an indication supported by level 1 or 2a evidence and the patient has had clinical stabilization or improvement from baseline AND 4. The patient does NOT have any FDA labeled contraindications to therapy with the requested agent AND 5. ONE of the following: a. The requested quantity (dose) is NOT greater than 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) is less than or equal to the FDA labeled dose AND iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the 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 FDA labeled dose AND iii. The prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis (must be reviewed by the Clinical Review pharmacist) Length of Approval: 12 months" ▪ Quantity Limits Chart updated to add Ingrezza

	▪ Contraindications Chart added
	Rationale section updated
	References updated

REFERENCES

1. Xenazine Prescribing Information. Lundbeck/Valeant. September 2017
2. Huntington Study Group. Tetrabenazine as anti-chorea therapy in Huntington disease. *Neurology*. 2006;66:366-372.
3. Leung JG, Breden EL. Tetrabenazine for the Treatment of Tardive Dyskinesia. *The Annals of Pharmacotherapy*. 2011;45:525-31.
4. Armstrong MJ, Miyasaki MJ. Evidence-based guideline: Pharmacologic treatment of Chorea in Huntington disease. *Neurology* 2012;79:597-603.
5. Austedo prescribing information. Teva. August 2017.
6. UpToDate. Tardive dyskinesia. Literature review current through: March 2017. Accessed April 2017.
7. Vijayakumar D, Jankovic J. Drug-induced dyskinesia, part 2: Treatment of Tardive Dyskinesia. Drugs 2016;76:779–787.
8. Institute for Clinical and Economic Review (ICER). Vesicular Monoamine Transporter 2 Inhibitors for Tardive Dyskinesia: Effectiveness and Value. Draft Background and Scope. May 8, 2017.
9. Ingrezza prescribing information. Neurocrine Biosciences, Inc. 10/2017.
10. Hauser R, Factor S, Marder S, et al. KINECT 3: A Phase 3 randomized, double-blind, placebo-controlled trial of valbenazine for tardive dyskinesia. Am J Psychiatry 2017;174:476–484.