Clinical Policy: VMAT2 Inhibitors (Ingrezza, Austedo, Xenazine)

Reference Number: AZ.CP.PHAR.340
Effective Date: 07.18
Last Review Date10.20
Line of Business: Arizona Medicaid (AzCH-CCP and Care1st) Revision Log

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

Description
Valbenazine (Ingrezza™), Deutetrabenazine (Austedo™) and Tetrabenazine (Xenazine®) are vesicular monoamine transporter 2 (VMAT2) inhibitors.

FDA Approved Indication(s)
Ingrezza and Austedo are indicated for the treatment of adults with tardive dyskinesia. Austedo and Xenazine are 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 Arizona Complete Health-Complete Care Plan and Care1st that Austedo, Ingrezza, and Xenazine are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Tardive Dyskinesia (must meet all)**:**

1. Diagnosis of tardive dyskinesia (TD) has been clinically established by and is being prescribed by a neurologist or a psychiatrist;
2. Request is for one of the following: Ingrezza or Austedo;
3. Age ≥ 18 years;
4. The member must have been prescribed and is currently taking a drug that has tardive dyskinesia as a documented adverse reaction;
   **See Appendix E; if the offending agent is not included in Appendix E, the status of the agent as a centrally acting DRBA as well as its association with tardive dyskinesia should be confirmed.*
5. Documentation of symptomatic moderate to severe TD as defined by one of the following (a or b):
   a. Documentation within 90 days of member's baseline score defined with one of the following assessment tools:
      i. Abnormal Involuntary Movement Scale (AIMS) with a score of 3 or 4 on item 8 (severity of abnormal movement overall) www.cqaimh.org/pdf/tool_aims.pdf
      ii. Extrapyramidal Symptom Rating Scale (ESRS) score ≥ 4.
   b. Patient has been clinically diagnosed with TD by meeting ***all*** DSM-V Criteria (i, ii and iii):

i. Involuntary athetoid or choreiform movements;
ii. History of treatment with a neuroleptic agent (i.e. antipsychotic);
iii. Symptoms lasting longer than 8 weeks.

6. Previous trial and failure, intolerance or contraindication to amantadine for at least 2 months;
7. At the time of request, member is not taking any other VMAT2 inhibitor concurrently (VMAT2 inhibitors include valbenazine (Ingrezza), tetrabenazine (Xenazine) or deutrabenazine (Austedo);
8. Dose does not exceed 80 mg/day (1 capsule/day) of Ingrezza or 48mg/day of Austedo.

Approval duration: Medicaid - 3 months

B. Chorea Associated with Huntington's Disease (must meet all):

1. Diagnosis of chorea associated with Huntington's disease;
2. Request is for one of the following: Austedo or Xenazine;
3. Prescribed by or in consultation with a neurologist;
4. Age ≥ 18 years;
5. Targeted mutation analysis demonstrates a cytosine-adenine-guanine (CAG) trinucleotide expansion of ≥ 36 repeats in the huntingtin (HTT) gene;
6. 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);
7. If the request is for Austedo, failure of tetrabenazine (e.g., no improvement on any one of UHDRS chorea items 1 through 7) at up to 100 mg/day unless contraindicated or clinically significant adverse effects are experienced;
8. Member will not be taking any other VMAT2 inhibitor concurrently (VMAT2 inhibitors include valbenazine (Ingrezza), tetrabenazine (Xenazine) or deutrabenazine (Austedo);
9. Dose does not exceed 48 mg/day of Austedo or 50mg/day of Xenazine (100 mg/day if genotype testing confirms extensive or intermediate CYP2D6 metabolizer status).

Approval duration: Medicaid - 6 months

C. Other diagnoses/indications

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): AZ.CP.PMN.53 for Arizona Medicaid.

II. Continued Therapy

A. Tardive Dyskinesia (must meet all)**:**

1. Request is for one of the following: Ingrezza or Austedo
2. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;

3. Member is responding positively to therapy as documented by improvement in the past 90 days by one of the following:
   a. AIMS-decrease by 2 points from baseline or
   b. ESRS-decrease from baseline by 4 points
4. At the time of the request, member is not taking any other VMAT2 inhibitor concurrently (VMAT2 inhibitors include: Valbenazine (Ingrezza), Tetrabenazine (Xenazine) and deutrabenazine (Austedo);
5. If request is for a dose increase, new dose does not exceed 80 mg/day (1 capsule/day) of Ingrezza or 48mg/day of Austedo.

   Approval duration: Medicaid - 6 months

B. Huntington's Disease (must meet all):
1. Request is for one of the following: Austedo or Xenazine
2. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
3. Member is responding positive to therapy
4. At the time of the request, member is not taking any other VMAT2 inhibitor concurrently (VMAT2 inhibitors include Valbenazine (Ingrezza), Tetrabenazine (Xenazine) and Deutrabenazine (Austedo).
5. If request is for a dose increase, new dose does not exceed 48 mg/day of Austedo or 50 mg/day of Xenazine (100mg per day if genotype testing confirms extensive or intermediate CYP2D6 metabolizer status).

   Approval duration: Medicaid - 12 months

C. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.

   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): AZ.CP.PMN.53 for Arizona 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 – AZ.CP.PMN.53 for Arizona Medicaid or evidence of coverage documents.
- **B.** Dual therapy with other VMAT2 inhibitors
- **C.** Use as a preventative agent for the development of tardive dyskinesia.
- **D.** Concurrent use with monoamine oxidase inhibitors (MAOI): selegiline, Nardil, tranylcypromine, or Marplan.

IV. Appendices/General Information *Appendix A: Abbreviation/Acronym Key*

DRBA: dopamine receptor blocking agent
TD: tardive dyskinesia
FDA: Food and Drug Administration
VMAT2: vesicular monoamine transporter 2
AIMS: Abnormal involuntary Movements Scale
ESRS: Extrapyramidal Symptom Rating Scale
DSM-V: Diagnostic and Statistical Manual of Mental disorders 5th Edition

Appendix B: Therapeutic Alternatives
Amantadine 100mg: 100mg BID up to a maximum dose of 400mg per day in divided doses.

Appendix C: General Information

- VMAT2 inhibitors should not be taken concurrently. They include Valbenazine (Ingrezza), tetrabenazine (Xenazine) or deutetrabenazine (Austedo) as this is considered duplicate therapy.
- Dose reduction to Ingrezza 40mg per day is recommended for Child Pugh Class B or C (≥ 7) for moderate to severe hepatic impairment.
- Dose reduction to Austedo in patients who are poor CYP2D6 metabolizers or on strong CYP2D6 inhibitors. Do not exceed 18 mg/dose or 36 mg/day.
- Dose reduction to Xenazine in patients who are poor CYP2D6 metabolizers or on strong CYP2D6 inhibitors. Do not exceed 25 mg/dose or 50 mg/day
- Medication-induced movement disorders, including tardive dyskinesia, are organized in the DSM V as follows: neuroleptic-induced parkinsonism/other 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 *centrally acting* DRBAs (*Appendix E*).
- Amantadine doses 100mg daily up to 400mg per day in 3-4 divided doses.
- Typical therapeutic drug classes containing DRBAs include first- and second-generation antipsychotics, antiemetics, and tri-cyclic antidepressants (*Appendix E*).
- Other therapeutic drug classes containing agents that have been variously associated with movement disorders are listed below:
  - 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 D: DSM-V Definition of Tardive Dyskinesia

Tardive Dyskinesia *(ICD-9 333.85/ICD-10 G24.01)*
• Involuntary athetoid or choreiform movements (lasting at least a few weeks) generally of the tongue, lower face and jaw, and extremities (but sometimes involving the pharyngeal, diaphragmatic, or trunk muscles) developing in association with the use of a neuroleptic medication for at least a few months. • Symptoms may develop after a shorter period of medication use in older persons. In some patients, movements of this type may appear after discontinuation, or after change or reduction in dosage, of neuroleptic medications, in which case the condition is called neuroleptic withdrawal emergent dyskinesia. Because withdrawal emergent dyskinesia is usually time limited, lasting less than 4-8 weeks, dyskinesia that persists beyond this window is considered to be tardive dyskinesia.

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

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		Metoclopromide 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		

**First generation H1 antagonist*
***Off-label use*
†A dibenzoxapine that shares properties with phenothiazines

Appendix F: The Abnormal Involuntary Movement Scale (AIMS)

- 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.
- The American Psychiatric Association (APA) guidelines recommend that patients who have moderate to severe or disabling TD be treated with a reversible VMAT2 inhibitor; the guidelines note that the AIMS tool can be instrumental in such decision-making.
- See Munetz 1988 for additional information about the AIMS.

(APA Guidelines 2020, Munetz 1988)

V. Dosage and Administration

Drug	Indication	Dosing Regimen	Maximum Dose
Ingrezza	Tardive dyskinesia	40 mg once daily; after a week, increase to 80 mg if needed	80 mg/day
Austedo	Huntington's chorea	6 mg/day (6 mg once daily) PO; may be increased weekly by increments of 6 mg/day to a maximum of 48 mg/day	48 mg/day (18 mg/dose and 36 mg/day in poor CYP2D6 metabolizers)
Austedo (cont.)	Tardive dyskinesia	12 mg/day (6 mg twice daily) PO; may be increased weekly by increments of 6 mg/day to a maximum of 48 mg/day	48 mg/day (18 mg/dose and 36 mg/day in poor CYP2D6 metabolizers)

Xenazine	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)

VI. Product Availability

Ingrezza Capsules: 40 mg, 80 mg
Austedo Tablets: 6 mg, 9 mg, 12 mg
Xenazine Tablets: 12.5 mg, 25 mg

VII. References

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Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy modified from corporate policy CP.PHAR.340	03.06.19	03.19
Updated off-label use policy for Arizona Medicaid, Updated references	09.06.19	09.19

2Q 2020 annual review: no significant changes; updated contraindications; references reviewed and updated	02.07.20	05.20
Genetic testing and UHDRS scoring added to chorea criteria; AIMS scoring added to TD criteria; Appendix F added; references reviewed and updated.	10.20	10.20
Added Care1st logo. Added verbiage to specify that criteria also applies to Care1st.	5.10.21	04.21

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.

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.