Clinical Policy: Valbenazine (Ingrezza)

Reference Number: ERX.SPA.157
Effective Date: 09.01.17
Last Review Date: 05.21
Line of Business: Commercial, Medicaid

Revision Log

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

Description
Valbenazine (Ingrezza®) is vesicular monoamine transporter 2 inhibitor.

FDA Approved Indication(s)
Ingrezza is indicated for the treatment of adults with tardive dyskinesia (TD).

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.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Ingrezza is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

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

1. Diagnosis of TD secondary to a centrally acting dopamine receptor blocking agent (DRBA) (*see Appendix F*);
2. Prescribed by or in consultation with a psychiatrist or neurologist;
3. Age ≥ 18 years;
4. Evidence of moderate to severe TD is supported by an Abnormal Involuntary Movement Scale (AIMS) score of 3 or 4 on any one of items 1 through 9 (*see Appendix G*);
5. Failure of tetrabenazine (e.g., no improvement on any one of AIMS items 1 through 9) at up to 200 mg per day, unless contraindicated or clinically significant adverse effects are experienced;
6. Ingrezza is not prescribed concurrently with Austedo® or tetrabenazine;
7. Dose does not exceed 80 mg (1 capsule) per day.

Approval duration: 6 months

B. Other diagnoses/indications

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

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

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy as evidenced by a reduction since baseline in any one of AIMS items 1 through 9 (*see Appendix G*);
3. Ingrezza is not prescribed concurrently with Austedo or tetrabenazine;
4. If request is for a dose increase, new dose does not exceed 80 mg (1 capsule) day.

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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 policy – ERX.PA.01 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

AIMS: Abnormal Involuntary Movement Scale
APA: American Psychiatry Association
DRBA: dopamine receptor blocking agent
DSM V: Diagnostic and Statistical Manual, Version 5
FDA: Food and Drug Administration
TD: tardive dyskinesia
VMAT2: vesicular monoamine transporter

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
tetrabenazine (Xenazine®)	**Tardive Dyskinesia** *(off-label)* Typical dosing range (mg/day): 25-75 Comments: Give in divided doses: increase from initial dose of 25-50 mg/day by 12.5 mg/week to maximum of 150-200 mg/day. Retitrate dose for treatment interruptions of more than 5 days. Test for CYP2D6 metabolizer status before giving doses > 50 mg/day. Do not exceed 50 mg/day in poor metabolizers or in patients treated with a strong inhibitor of CYP2D6. *The American Psychiatric Association practice guideline for the treatment of patients with schizophrenia. 2020. Third Ed.*	200 mg/day in divided doses *(off-label)*

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): known hypersensitivity to valbenazine or any components of Ingrezza
- Boxed warning(s): none reported

Appendix D: General Information

- Ingrezza should not be used concurrently with other VMAT2 inhibitors such as tetrabenazine or deutetrabenazine as this is considered duplicate therapy.
- 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.[5]
- Tardive dyskinesia is a type of movement disorder that occurs secondary to therapy with *centrally acting* DRBAs (Appendix E). (DSM V)

- Typical therapeutic drug classes containing DRBAs include first- and second-generation antipsychotics, antiemetics, and tri-cyclic antidepressants (Appendix F). (DSM V)
- Other therapeutic drug classes containing agents that have been variously associated with movement disorders are listed below: (Waln 2013, Meyer 2014, Lerner 2015)
  - 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 E: 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.

(DSM V)

Appendix F: Centrally Acting Dopamine Receptor Blocking Agents (Neuroleptics)[5,6,9,10]

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		

(DSM V, Meyer 2014, Smith 2010, Clinical Pharmacology, Lexicomp)

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

Appendix G: 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 2020 American Psychiatric Association (APA) Practice Guideline for the Treatment of Patients With Schizophrenia recommends that patients who have moderate to severe or disabling TD be treated with a reversible VMAT2 inhibitor (i.e., deutetrabenazine, tetrabenazine, and valbenazine); the guideline notes that the AIMS tool can be instrumental in such decision-making.
- See Munetz 1988 for additional information about the AIMS.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
TD	40 mg PO once daily; after a week, increase to the recommended dose of 80 mg. A dosage of 40 mg or 60 mg once daily may be considered depending on response and tolerability.	80 mg/day

VI. Product Availability

Capsules: 40 mg, 60 mg, 80 mg

VII. References

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Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created.	06.17	08.17
Added new capsule strength: 80 mg. Added statement about duplicate VMAT2 inhibitor therapy in general information appendix.	11.07.17	02.18
2Q 2018 annual review: no significant changes; added requirement for no concomitant use of xenazine or deutetrabenazine for both initial and re-auth requests; references reviewed and updated.	01.31.18	05.18
2Q 2019 annual review: no significant changes; references reviewed and updated.	02.26.19	05.19
2Q 2020 annual review: no significant changes; references reviewed and updated.	02.11.20	05.20
AIMS scoring added to TD criteria; Appendix G added; references reviewed and updated.	07.07.20	08.20
2Q 2021 annual review: tetrabenazine trial added for TD; added tetrabenazine dosing information in Appendix B as a therapeutic alternative; APA guideline clarification added in Appendix H; references reviewed and updated.	02.16.21	05.21
RT4: new dosage form of 60 mg capsule added and dosing regimen updated.	06.04.21	

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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. 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.