Clinical Policy Title:	valbenazine
Policy Number:	RxA.172
Drug(s) Applied:	Ingrezza®
Original Policy Date:	02/07/2020
Last Review Date:	09/14/2021
Line of Business Policy Applies to:	All lines of business

Background

Valbenazine (Ingrezza®) is a reversible inhibitor of vesicular monoamine transporter 2 (VMAT2), a transporter that regulates monoamine uptake from the cytoplasm to the synaptic vesicle for storage and release. Valbenazine is indicated for the treatment of adults with tardive dyskinesia.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
valbenazine (Ingrezza®)	Tardive dyskinesia	Initial dose is 40 mg orally once daily; after one week, increase to 80 mg orally once daily . For patients with moderate to severe hepatic impairment (Child-Pugh score 7 to 15): 40 mg orally daily For patients who are known CYP2D6 poor metabolizers: 40 mg orally daily	80 mg/day

Dosage Forms

- Capsules: 40 mg, 60 mg, and 80 mg

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

I. Initial Approval Criteria

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

1. Diagnosis of tardive dyskinesia secondary to a centrally acting dopamine receptor blocking agent (DRBA);
   *See Appendix F; if the offending agent is not included in Appendix F, the status of the agent as a centrally acting DRBA as well as its association with tardive dyskinesia should be confirmed

2. Prescribed by or in consultation with a psychiatrist or neurologist;
3. Age 18 ≥ years;
4. At the time of request, tetrabenazine or deutetrabenazine is not prescribed concurrently;
5. Dose does not exceed 80 mg (1 capsule) per day.
6. At the time of request, no documented congenital long QT syndrome or arrythmias associated with a prolonged QT interval. It may cause an increase in QT interval and it is recommended to avoid use. For patients at increased risk of a prolonged QT interval, assess the QT interval before increasing the dose.

Approval Duration
Commercial: 12 months
Medicaid: 6 months

II. Continued Therapy Approval

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

1. Member is currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
2. Member is responding positively to therapy;
3. Tetrabenazine or deutetrabenazine is not prescribed concurrently;
4. If request is for a dose increase, new dose does not exceed 80 mg (1 capsule) per day.
5. No documented congenital QT long syndrome or arrythmias associated with a prolonged QT interval. It may cause an increase in QT interval and it is recommended to avoid use. For patients at increased risk of a prolonged QT interval, assess the QT interval before increasing the dose.

Approval Duration
Commercial: 12 months
Medicaid: 6 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
DRBA: dopamine receptor blocking agent
FDA: Food and Drug Administration
VMAT2: vesicular monoamine transporter 2

APPENDIX B: Therapeutic Alternatives
Not applicable

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Known hypersensitivity to valbenazine or any components of valbenazine.

- Boxed Warning(s):
  - None reported.

APPENDIX D: General Information

- Valbenazine should not be used concurrently with other VMAT2 inhibitors such as tetrabenazine or deutetrabenazine as this is considered duplicate therapy.
- Valbenazine may cause parkinsonism in patients with tardive dyskinesia. In most cases, severe parkinsonism occurred within the first two weeks after starting on increasing the dose. Associated

symptoms have included falls, gait, disturbances, tremors, drooling and hypokinesia. Reduce the dose or discontinue valbenazine in patients with clinically significant parkinson-like sign or symptoms.

- Medication-induced movement disorders, including tardive dyskinesia, are organized in the DSM-5 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 effect of medication.
- Tardive dyskinesia is a type of movement disorder that occurs secondary to therapy with *centrally acting* DRBAs (Appendix E).
- Typical therapeutic drug classes containing DRBAs include first- and second-generation antipsychotics, antiemetics, and tri-cyclic antidepressants (Appendix F).
- 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 depleting agents
  - Dopaminergic agents
  - Glucocorticoids
  - Immunosuppressants
  - Mood stabilizers
  - Muscle relaxants
  - Oral contraceptives

APPENDIX E: DSM-5 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 F: 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*	amoxapine†
Butryophenone	haloperidol	droperidol haloperidol**	
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		

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

APPENDIX G: Dose adjustments due to drug interactions:

Factors	Dose Adjustments for valbenazine
Use of MAOIs with valbenazine	Avoid concomitant use with MAOIs.
Use of strong CYP3A4 inducers with valbenazine	Concomitant use is not recommended.
Use of strong CYP3A4 inhibitors with valbenazine	Recommended dosage is 40 mg once daily.
Use of strong CYP2D6 inhibitors with valbenazine	Recommended dosage is 40 mg once daily.

References

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Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established.	01/2020	02/07/2020
Policy was reviewed: 1. Continued Therapy criteria II.A.1 was rephrased to "Currently receiving medication that has been authorized by RxAdvance..." 2. Reference reviewed and updated. 3. Added Appendix G Dose adjustments due to drug interactions (based on package insert) 4. Approval duration for commercial was updated to	06/18/2020	12/07/2020

12 months from length of benefit.		
Policy was reviewed: 1. Background was updated to include “reversible inhibitor of…” and ”a transporter that regulates monoamine uptake from the cytoplasm…”. 2. Dosing Information doing regimen was updated to include “initial dose is…” and remove “if needed…”. 3. Dosage Forms was updated to include “60mg…” 4. Statement about provider sample ‘‘The provision of provider samples does not guarantee coverage…” was added to Clinical Policy. 5. Initial Approval Criteria I.A.6 was updated to include “At the time of request, no documented congenital long QT syndrome…” 6. Continued Therapy Approval Criteria II.A.1 was rephrased to " Member is currently receiving the medication that has been authorized by..." 7. Continued Therapy Approval criteria II.A.5 was updated to include “No documented congenital QT long syndrome or arrythmias associated…” 8. Appendix D was updated to include “Valbenazine may cause parkinsonism in patients with tardive dyskinesia…” 9. Appendix F antiemetic agents column was updated to remove “thiethylperazine.” 10. References were reviewed and updated.	5/28/2021	9/14/2021