Drug Monograph

Drug/Drug Class:	**Ingrezza® (valbenazine) capsule/ VMAT2 Inhibitors**
Prepared for:	MO HealthNet
Prepared by:	Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Ingrezza® is available in a capsule that contains 40 mg valbenazine. Manufacturer: Neurocrine Biosciences, Inc., San Diego, CA 92130
Summary of Findings:	The efficacy of valbenazine was demonstrated in the randomized, double-blind, placebo-controlled KINECT 3 clinical trial. Patients with schizophrenia, schizoaffective disorder, or mood disorder were randomized to valbenazine 40 mg, 80 mg, or placebo once daily. The 80 mg group, but no the 40 mg group, had significantly reduced tardive dyskinesia severity scores compared with placebo at 6 weeks. Both doses provided a greater proportion of patients with at least a 50% reduction in scores at week 6.
Status Recommendation:	☒ Prior Authorization (PA) Required ☐ Open Access ☐ Clinical Edit ☐ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Preferred Agent ☒ Appropriate Indications ☐ Under Solicitation

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [3]

Many people with serious and chronic mental illness, such as schizophrenia, require long term treatment with antipsychotic medications. While ongoing antipsychotic treatment can be very helpful or even life-saving for many people, it comes with the risk of developing tardive dyskinesia. The symptoms of tardive dyskinesia are characterized primarily by random movements of different muscles and the tongue, lips or jaw. In some cases people may experience movements of the arms, legs, fingers and toes. In severe cases, symptoms can include swaying movements of the trunk or hips or muscles associated with breathing.

Dosage Form(s) [1]

Ingrezza® is available in a capsule that contains 40 mg valbenazine.

Manufacturer [1]

Neurocrine Biosciences, Inc., San Diego, CA 92130

Indication(s) [1]

Ingrezza® is indicated for the treatment of adults with tardive dyskinesia.

Clinical Efficacy [1,2] (mechanism of action/pharmacology, comparative efficacy)

The precise mechanism of action for valbenazine in tardive dyskinesia is unknown. It is thought to reversibly inhibit the vesicular monoamine transporter 2 (VMAT2), reducing the uptake of monoamines to the synaptic vesicle from the cytoplasm.

Pharmacokinetics:

	Ingrezza®
Protein binding	>99% (active metabolite, 64%)
Half Life	15 to 22 hours
Volume of Distribution	92 L
Metabolism	Liver, via hydrolysis to active metabolite and oxidation via CYP3A4/5 to inactive metabolites; active metabolite via CYP2D6
Excretion	Urine, 60% (active drug, <2%) Feces, 30% (active drug, < 2%)

KINECT 3 STUDY

Valbenazine was associated with improved tardive dyskinesia scores after 6 weeks compared with placebo

STUDY DESIGN	Randomized, double-blind, placebo-controlled, 6-week, phase 3 KINECT 3 clinical trial (N=234)
INCLUSION CRITERIA	Patients with schizophrenia, schizoaffective disorder, or mood disorder for at least 3 months, and a diagnosis of dopamine receptor blocker-induced, moderate to severe tardive dyskinesia.
EXCLUSION CRITERIA	Patients with an unstable psychiatric status, any unstable medical condition, or any other involuntary movement disorder more significant than tardive dyskinesia.
TREATMENT REGIMEN	Patients were randomized to receive Ingrezza® 40 mg orally once daily, 80 mg orally once daily, or placebo for 6 weeks
RESULTS	Ingrezza® 80 mg/day reduced the severity of tardive dyskinesia compared with placebo at 6 weeks, as measured by the least-squares mean change from baseline on the Abnormal Involuntary Movement Scale (AIMS) score (-3.2% vs. -0.1%). Ingrezza® 40 mg/day did not show a difference from placebo (-1.9 vs -0.1). Both valbenazine doses did proved a greater proportion of patients with at least a 50% reduction in AIMS score at week 6 (40 mg/day = 23.8%, 80 mg/day = 40%, and placebo = 8.7%).
SAFETY	The most common adverse events associated with Ingrezza® compared with placebo consisted of somnolence, akathisia, and dry mouth.

Contraindications (1)

- None

Warnings and Precautions (1)

- QT-interval prolongation may occur, particularly in poor CYP2D6 metabolizers or with concomitant strong CYP2D6 or CYP3A4 inhibitors. Monitoring is required.
- Avoid use in patients with congenital long QT syndrome or cardiac arrhythmias associated with prolonged QT interval.
- Avoid use in patients receiving concomitant strong CYP3A4 inducers.
- Approach activities requiring mental alertness with caution until patient knows effects of somnolence.
- Avoid use in patients with severe renal impairment.
- May cause fetal harm; advise pregnant women of risk.

Adverse Effects [1]

Most common, ≥ 2%	Ingrezza (n=262)	Placebo (n=183)
Somnolence	10.9%	4.2%
Anticholinergic effects	5.4%	4.9%
Balance disorders/falls	4.1%	2.2%
Headache	3.4%	2.7%
Akathisia	2.7%	0.5%
Vomiting	2.6%	0.6%
Nausea	2.3%	2.1%
Arthralgia	2.3%	0.5%

Drug Interactions [1]

- CYP2D6 inhibitors, strong: Paroxetine, fluoxetine, quinidine
- CYP3A4 inducers, strong: Rifampin, phenytoin, carbamazepine, St John's wort
- CYP3A4 inhibitors, strong: Clarithromycin, itraconazole, ketoconazole
- Digoxin
- MAOIs: Isocarboxazid, phenelzine, selegiline

Dosage and Administration [1]

The FDA recommended dose for Ingrezza® is 40 mg orally once daily with or without food for 1 week, then increase to 80 mg once daily. Dosage reduction is recommended for moderate to severe hepatic impairment or when used concomitantly with a strong CYP3A4 inhibitor. Dosage reduction should be considered in poor CYP2D6 metabolizers or those receiving a concomitant strong CYP2D6 inhibitor.

Cost

GENERIC NAME	BRAND NAME	MANUFACTURER	DOSE	COST/ MONTH*
Valbenazine	Ingrezza	Neurocrine	40 mg once daily	$5,327.70
			80 mg once daily	$10,655.40

* Maximum Allowable Cost

Conclusion

Ingrezza® is the first FDA approved agent for the treatment of tardive dyskinesia. It is a VMAT2 inhibitor that is administered orally once daily. In the KINECT 3 clinical trial, Ingrezza® 80 mg/day significantly reduced the severity of abnormal involuntary movements compared with placebo at 6 weeks. Ingrezza® was granted breakthrough therapy designation, priority review, and fast track status by the FDA. The cost is approximately $10,655 per month. The most common adverse event is somnolence followed by anticholinergic effects.

Recommendation

The MO HealthNet Division recommends prior authorization status for this product.

References

1) Product Information: Ingrezza™, valbenazine capsules. Neurocrine Biosciences, Inc, San Diego, CA, 04/2017
2) Hauser RA, Factor SA, Marder SR et al: KINECT 3: A phase 3 randomized, double-blind, placebo-controlled trial of valbenazine for tardive dyskinesia. Am J Psychiatry 2017; 174(5): 476-484.
3) Tardive Dyskinesia. Retrieved 11/7/2017 from: https://www.nami.org/Learn-More/Mental-Health-Conditions/Related-Conditions/Tardive-Dyskinesia

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Date: November 7, 2017