

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209241Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	209241
PDUFA Goal Date	April 11, 2017
OSE RCM #	2016-2014
Reviewer Name(s)	Mona Patel, Pharm.D.
Team Leader	Leah Hart, Pharm.D.
Deputy Division Director	Jamie Wilkins Parker, Pharm.D.
Review Completion Date	March 22, 2017
Subject	Evaluation of Need for a REMS
Established Name	Valbenazine
Trade Name	Ingrezza
Name of Applicant	Neurocrine Biosciences, Inc.
Therapeutic Class	Vesicular Monoamine Transporter 2 (VMAT 2)
Formulation(s)	capsule
Dosing Regimen	80 mg once daily

Table of Contents

EXECUTIVE SUMMARY3

1 Introduction.....3

2 Background3

 2.1 Product Information.....3

 2.2 Regulatory History4

3 Therapeutic Context and Treatment Options4

 3.1 Description of the Medical Condition4-5

 3.2 Description of Current Treatment Options5

4 Benefit Assessment5-6

5 Risk Assessment & Safe-Use Conditions6-7

6 Expected Postmarket Use7

7 Risk Management Activities Proposed by the Applicant.....7

8 Discussion of Need for a REMS.....7-8

9 Conclusion & Recommendations8

11 Materials Reviewed8

12 Appendices8

 12.1 References8-9

EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Ingrezza (valbenazine) is necessary to ensure the benefits of this product outweigh its risks. Neurocrine Biosciences, Inc. submitted a New Drug Application (NDA) 209241 for valbenazine with the proposed indication for the treatment of tardive dyskinesia (TD). The risks associated with the use of valbenazine include somnolence and QTc prolongation. The applicant proposed a REMS to include a Medication Guide (MG).

In this reviewer's opinion, a REMS is not needed to ensure the benefits of valbenazine outweigh its risks of somnolence and QT_c prolongation; these risks can be communicated through labeling.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Ingrezza (valbenazine) is necessary to ensure the benefits of this product outweigh its risks. Neurocrine Biosciences, Inc. submitted a New Drug Application (NDA) 209241 for valbenazine with the proposed indication for the treatment of tardive dyskinesia (TD). This application is under review in the Division of Psychiatry Products (DPP). The applicant's proposed REMS consists of a Medication Guide (MG).

2 Background

2.1 PRODUCT INFORMATION

Ingrezza (valbenazine), an NME, is a vesicular monoamine transporter 2 (VMAT 2) inhibitor that causes reversible reduction of dopamine release at the presynaptic nerve terminal by inhibiting presynaptic VMAT 2.^a FDA revised indication for valbenazine is for the treatment of *adult* patients with TD. Another drug in this class, Xenazine (tetrabenazine) was approved in 2008 in the U.S. for the treatment of chorea associated with Huntington's disease. Tetrabenazine was approved with a REMS for the risk of depression and suicidality to include a MG and Communication Plan, but it was determined in 2012 that the MG was no longer necessary to ensure the benefits of tetrabenazine outweighed the risks and was subsequently removed from the REMS. In 2015, the REMS for tetrabenazine was eliminated. Tetrabenazine's labeling contains a boxed warning for depression and suicidality and a MG.

Valbenazine will be available as a capsule for oral route in 40 milligrams for both inpatient and outpatient use and is likely to be prescribed by general practitioners and specialists. The recommended starting dose is 40 mg administered once daily. After week one, the recommended (b) (4) dose is 80 mg, taken as two 40 mg capsules once daily based on therapeutic response and tolerability.^b Valbenazine was granted Fast Track Designation on January 24, 2012, and Breakthrough Therapy Designation on October 28, 2014. The drug is not currently approved in any jurisdiction.

^a Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

^b Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 209241 relevant to this review:

- 01/24/2012: Fast Track Designation Request granted
- 10/28/2014: Breakthrough Therapy Designation granted
- 02/04/2016: Applicant informed at pre-NDA meeting to include data to support company's proposed risk management strategy for proposing a MG under a REMS.
- 03/29/2016: Rolling review granted
- 08/11/2016: NDA 209241 submission for TD received
- 11/29/2016: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that required a REMS for valbenazine
- 02/07/2017: A Late Cycle Meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, that no issues related to risk management had been identified to date.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Tardive dyskinesia (TD) is a neurological condition characterized by involuntary movements of the orofacial region (i.e., tongue, lips, jaw, and face) and choreoathetoid movements in the extremities and trunk.^c TD is persistent and progressive in nature emerging mainly after long-term neuroleptic treatment (e.g., dopamine receptor D₂ antagonists such as haloperidol or fluphenazine) over months to years and can often persist even after discontinuation of such medications. In addition to duration and amount of neuroleptic exposure, other risk factors for TD include older age, schizophrenia, and cognitive impairment. The prevalence of TD in psychiatric patients persists in the setting of increasing use of atypical antipsychotic medications with estimates in the 20 to 30% range for those receiving chronic treatment.¹ The incidence of TD is between 3 and 8%.^{d,2} The incidence of TD in the elderly patients during a continuous exposure to a variety of potent antipsychotic drugs is approximately 10 to 20%.²

Tardive dyskinesia can be disabling and impact day-to-day functioning and quality of life. The involuntary movements can interfere with speech, walking, and cause swallowing and breathing difficulties. With severe cases of TD, these involuntary movements can cause bodily harm such as lip or tongue lacerations, bruises, joint inflammation, and falls. In addition to the debilitating nature of these

^c Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

^d Section 505-1 (a) of the FD&C Act: FDAAA factor (A): *The estimated size of the population likely to use the drug involved.*

involuntary movements, patients must contend with public and societal perception of their symptoms, which can result in shame, anger, and depression.

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

There is currently no approved drug for the treatment of TD. The standard of care in patients exhibiting signs of TD is to stop or reduce the dose of the dopamine antagonist drug suspected of causing the condition or switching from a first to second generation antipsychotic drug such as clozapine and quetiapine. Two pharmacologic interventions that are not FDA-approved for TD but have produced more than slight to moderate benefit in clinical practice include the use of a benzodiazepine such as clonazepam, or a VMAT 2 inhibitor such as tetrabenazine, to control symptoms of TD.^{3,4} Clonazepam is a benzodiazepine approved in 1975 in the U.S. for the treatment of seizure disorder and panic disorder.⁵ Concomitant use with opioids, interference with cognitive and motor performance, and suicidal behavior and ideation are listed as warnings for this drug. For tetrabenazine, depression and suicidality, laboratory tests, neuroleptic malignant syndrome (NMS), akathisia, restlessness, agitation, parkinsonism, dysphagia, sedation and somnolence, QTc prolongation, hypotension and orthostatic hypotension, hyperprolactinemia, TD, and binding to melanin-containing tissues are risks listed in the label under Warnings & Precautions.⁶ Tetrabenazine also carries a boxed warning for depression and suicidality. Clonazepam and tetrabenazine are both available as a tablet to be administered orally with individualized doses.

Two additional non-FDA approved approaches with possibility of reducing dyskinesia is off-label botulinum toxin injections or deep brain stimulation following the surgical implantation of electrodes.⁴ Evidence for the effectiveness of botulinum toxin for TD is limited to retrospective case series and case reports. Adverse effects of botulinum toxin injections are excessive weakness of injected or neighboring muscles. There is a clear unmet medical need with the lack of FDA-approved treatment options to treat TD.

4 Benefit Assessment

The Applicant considered the efficacy of valbenazine to be supported by two pivotal studies, a phase 2 study (1202) and a phase 3 study (1304) for the treatment of patients with TD.

The phase 3 study, 1304, was a double-blind, parallel-group, fixed-dose study to investigate the efficacy, safety, tolerability, and pharmacokinetics (PK) of valbenazine compared with placebo in subjects with schizophrenia or schizoaffective disorder, or mood disorder with TD. Valbenazine was administered at 40 mg orally, once daily or 40 mg, once daily for 1 week and then 80 mg once daily for 5 weeks. After 6 weeks, subjects could continue to receive valbenazine for an additional 42 weeks. The primary endpoint was the mean change from baseline at the end of week 6 in the Abnormal Involuntary Movement Scale (AIMS) dyskinesia total score, defined as the sum of the scores of the first 7 items of the AIMS, as scored by blinded, Central AIMS Video Raters.¹ The secondary objectives were to evaluate the efficacy using the Clinical Global Impression of Change-Tardive Dyskinesia (CGI-TD) and to evaluate the safety and tolerability of two doses of valbenazine administered for up to 48 weeks.

From sites within Puerto Rico, Canada, and the United States, 225 subjects were treated in the initial 6-week double-blind period and 122 subjects remained at the end of the 48-week treatment. The negative change (indicating improvement) in the AIMS dyskinesia total score for valbenazine-treated subjects was statistically significant for the 40 mg (-1.9)(p value=0.0021) and 80 mg (-3.2)(p value <0.0001) doses at the end of the 6-week period.⁷ Among the subjects remaining in the study at the end of the 48-week treatment, the mean AIMS dyskinesia total score worsened following discontinuation of valbenazine.

Study 1202 was a phase 2 randomized, double-blind, dose-titration, placebo-controlled study to investigate the efficacy, safety, tolerability, and PK of valbenazine in subjects with schizophrenia or schizoaffective disorder, or mood disorder with neuroleptic-induced TD, or subjects with GI-disorder with metoclopramide-induced TD. Valbenazine was administered in the range of 25 to 75 mg, once daily for 6 weeks. The primary endpoint was the change from baseline at the end of week 6 in the AIMS dyskinesia total score. The secondary objectives were to evaluate the safety and tolerability of valbenazine and evaluate plasma exposure measures of valbenazine, its active metabolite α -dihydrotrabenazine, and other metabolites.

From sites within Puerto Rico and the United States, 89 subjects were treated. At the end of Week 6, the number of patients per dose group were N=5 at 25 mg, N=9 at 50 mg, and N=31 at 75 mg. The negative change in the AIMS dyskinesia total score for valbenazine treated subjects (-2.6) was statistically superior to placebo (-.2) with an overall p value of 0.0005.⁷

In both phase 3 studies, the exclusion criteria were limited to evaluate patients who are likely to receive the drug in clinical practice. Overall, the results of both trials had statistically significant and clinically meaningful effects on TD.^e

5 Risk Assessment & Safe-Use Conditions

The safety of valbenazine is based on analysis of safety and efficacy clinical trial data from 846 patients with TD. The most frequently reported adverse reactions (incidence $\geq 2\%$ and $>$ placebo) were headache, akathisia, fatigue, dry mouth, vomiting, and arthralgia. The most commonly reported adverse reaction (incidence $> 5\%$ and at least twice the rate of placebo) was somnolence. Somnolence was reported in 11% of patients taking valbenazine versus 4.2% for those on placebo.⁸ The incidence was slightly higher in the 40 mg once daily treatment groups (4/72) than the 80 mg once daily treatment groups (4/79).⁹

Another adverse event of concern seen in valbenazine-treated patients was QT_c prolongation. Patients taking the 80 mg dose of valbenazine with increased exposure (e.g. taking a concomitant strong CYP3A4 or CYP2D6 inhibitor) may have a mean QT_c prolongation of 11.7 msec (14.7 msec upper bound of double-sided $\frac{(b)}{(4)}\%$ CI) as compared to otherwise healthy volunteers, who had a mean QT_c prolongation of 6.7 msec (8.4 msec).^{8,10} The increase in QT_c prolongation in patients taking concomitant medications

^e Section 505-1 (a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

was significant (11.7msec); however, the risk was not consistent across all populations tested in clinical trials and did not show up consistently in EKG data and AEs thus it was determined that this risk would be placed in Warnings & Precautions versus a Boxed Warning. In comparison with tetrabenazine, this drug caused an approximately 8 msec mean increase in QTc (90% CI: 5.0, 10.4 msec) and data suggest that inhibition of CYP2D6 in healthy subjects given a single 50 mg dose of tetrabenazine did not further increase the effect on the QTc interval. Valbenazine should be avoided in patients with congenital long QT_c syndrome and in patients with a history of cardiac arrhythmias. Somnolence and QT_c prolongation are expected adverse events due to the class effect of VMAT 2 inhibitors. The risks of somnolence and QT_c prolongation with valbenazine will be communicated via labeling in the Warnings & Precautions section of the label. At the time of this review, the label was still under review with the DPP.

6 Expected Postmarket Use

Valbenazine will be administered in the inpatient and outpatient setting and the likely prescribers will be general practitioners and psychiatrists who should be familiar with the risks and management of somnolence and signs and symptoms with QT_c prolongation due to the class effect of VMAT2 inhibitors. At the time of this review, no additional postmarketing studies will be required from the applicant.

7 Risk Management Activities Proposed by the Applicant

A REMS was submitted by Neurocrine Biosciences which includes a MG with a goal to inform patients about the proposed serious risks of somnolence, QT_c prolongation, and a warning against concomitant use of valbenazine and alcohol, VMAT 2 inhibitors, and monoamine oxidase inhibitors associated with valbenazine.

Discussion of Need for a REMS

The Clinical Reviewer recommends approval of Ingrezza (valbenazine) on the basis of the efficacy and safety information currently available.

The efficacy data for valbenazine supports approval for the treatment of patients with TD. In study 1304, the negative change (indicating improvement) in the AIMS dyskinesia total score for valbenazine-treated subjects was statistically significant for the 40 mg (-1.9) and 80 mg (-3.2) doses, and in study 1202, the negative change in the AIMS dyskinesia total score for valbenazine treated subjects with titrating doses (-2.6) was statistically superior to placebo (-.2).

Tetrabenazine, the other currently approved VMAT 2 inhibitor, was approved in 2008 with a REMS to include a MG, Communication Plan, and timetable for submission of assessments with the goal to inform healthcare providers of the increased risk of drug-associated depression and suicidality, proper titration and dosing, and the risk of drug-drug interactions with strong CYP2D6 inhibitors, the MG was subsequently removed in 2012 from the REMS as FDA determined that the MG was no longer necessary to ensure the benefits of tetrabenazine outweighed the risks. After review of the applicant's 6-year

assessment report and available safety information, DRISK believed that a CP was no longer necessary as an element of the REMS to ensure that the benefits of the drug outweighed the risks and recommended that the tetrabenazine REMS be eliminated. The REMS for tetrabenazine was eliminated in 2015. Tetrabenazine's labeling contains a boxed warning for depression and suicidality and a MG.

The applicant proposed a REMS to include a MG for valbenazine, but it is the opinion of this reviewer that a REMS is not necessary for the identified risks of somnolence and QT_c prolongation, and DPP determined that a MG will not be a required part of labeling. Valbenazine should be avoided in patients with congenital long QT_c syndrome and in patients with a history of cardiac arrhythmias. Somnolence and QT_c prolongation are expected adverse events due to the class effect of VMAT 2 inhibitors such as tetrabenazine. As the prescribing population for both these drugs may overlap, prescribers should be familiar with the risks due to the class of drugs.

8 Conclusion & Recommendations

Based on the available data, this reviewer believes a REMS is not necessary to ensure the benefits outweigh the risks. The safety concerns associated with this drug are class effects of the VMAT 2 inhibitors and healthcare providers who treat tardive dyskinesia should be familiar with the risk and the importance of patient monitoring. Should DPP have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.

9 Materials Reviewed

The following is a list of materials informing this review:

1. (b) (4) (valbenazine) Clinical Overview (Module 2.5) August 25, 2016
2. Miller, Brian. Clinical Review for Ingrezza (valbenazine), NDA 209241, February 9, 2017 (draft)
3. Davis, Michael. Clinical Review for Ingrezza (valbenazine), NDA 209241, February 9, 2017 (draft)
4. Guerrieri, Gioia M. Clinical Midcycle Meeting Slides for Ingrezza (valbenazine), NDA 209241, November 18, 2016
5. Johannesen, Lars. QTIRT Review for Ingrezza (valbenazine), NDA 209241, December 29, 2016

10 Appendices

a. REFERENCES

¹ (b) (4) (valbenazine) Clinical Overview (Module 2.5) August 25, 2016

² Tarsy D, Baldessarini RJ. Epidemiology of tardive dyskinesia: is risk declining with modern antipsychotics? *Mov Disord* 2006; 21:589.

³ Miller, Brian. Clinical Review for Ingrezza (valbenazine), NDA 209241, February 9, 2017 (draft)

⁴ Bhidayasiri R, Fahn S, Weiner WJ, Gronseth GS, Sullivan KL, Zesiewicz TA. Evidence-based guideline: treatment of tardive syndromes: report of the Guideline Development Subcommittee of the American Academy of Neurology. *American Academy of Neurology*. 2013 Jul;81(5):463-9.

⁵ Klonopin (clonazepam) US Prescribing Information (December 2016)

⁶ Xenazine (tetrabenazine) US Prescribing Information (June 2015)

⁷ Davis, Michael. Clinical Review for Ingrezza (valbenazine), NDA 209241, February 9, 2017 (draft)

⁸ Ingrezza (valbenazine) US Prescribing Information (February 22, 2017) (draft)

⁹ Guerrieri, Gioia M. Clinical Midcycle Meeting Slides for Ingrezza (valbenazine), NDA 209241, November 18, 2016

¹⁰ Johannesen, Lars. QTIRT Review for Ingrezza (valbenazine), NDA 209241, December 29, 2016

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/s/

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