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Depression and Suicidality in Patients with Chorea Associated with Huntington's Disease on INGREZZA® (valbenazine) Capsules

Thank you for contacting Neurocrine Biosciences with your unsolicited Medical Information request regarding the potential effects of INGREZZA (valbenazine) capsules on depression and suicidality in adults with chorea associated with Huntington's disease (HD).

INGREZZA is a vesicular monoamine transporter 2 (VMAT2) inhibitor indicated for the treatment of adults with chorea associated with Huntington's disease.[1]

Please refer to the separately attached INGREZZA FDA-approved Full Prescribing Information and the Important Safety Information, including a Boxed Warning.

IMPORTANT SAFETY INFORMATION
Depression and Suicidality in Patients with Huntington's Disease: VMAT2 inhibitors, including INGREZZA, can increase the risk of depression and suicidal thoughts and behavior (suicidality) in patients with Huntington's disease. Balance the risks of depression and suicidality with the clinical need for treatment of chorea. Closely monitor patients for the emergence or worsening of depression, suicidal ideation, or unusual changes in behavior. Inform patients, their caregivers, and families of the risk of depression and suicidal ideation and behavior and instruct them to report behaviors of concern promptly to the treating physician. Exercise caution when treating patients with a history of depression or prior suicide attempts or ideation, which are increased in frequency in patients with Huntington's disease.

The INGREZZA FDA-approved Full Prescribing Information states the following:[1]

WARNINGS AND PRECAUTIONS

Depression and Suicidal Ideation and Behavior in Patients with Huntington's Disease

Patients with Huntington's disease are at increased risk for depression, and suicidal ideation or behaviors. VMAT2 inhibitors, including INGREZZA, can increase the risk for suicidal ideation and behaviors in patients with Huntington's disease.

In a 14-week, double-blind, placebo-controlled trial, depression or depressed mood was reported in 4.7% of patients taking INGREZZA compared to 1.6% of patients who received placebo, and no patients taking INGREZZA reported suicidal ideation or behavior compared to 1 patient (1.6%) who received placebo. Patients with significant risk for suicidal behavior or with unstable psychiatric symptoms were excluded from this trial. Suicidal ideation (9 subjects; 7.2%) and suicide attempts (3 subjects; 2.4%) were reported in the longer open-label extension trial (N = 125).

When considering the use of INGREZZA, the risk of suicidal ideation and behaviors must be balanced against the need for treatment of chorea. All patients treated with INGREZZA should be observed for new or worsening depression, suicidal ideation or behaviors. If any of these reactions occur and do not resolve, consider discontinuing treatment with INGREZZA.

Clinical Study Results:

As stated in the Prescribing Information, in KINECT®-HD, the Phase 3, double-blind placebo-controlled study to evaluate the safety and efficacy of valbenazine for the treatment of chorea associated with HD, adverse events of depression or depressed mood was collectively reported in 4.7% of patients taking valbenazine (VBZ), compared to 1.6% in placebo (PBO). In patients taking VBZ, there were no reports of

suicidal ideation or suicide attempts. One patient (1.6%) on PBO reported suicidal ideation (Table 1). During the 12-week study, no participants reported an increase in suicidal ideation on the Columbia-Suicide Severity Rating Scale (C-SSRS).[2]

Additionally, in the interim analysis of KINECT-HD2, the Phase 3, open-label rollover study, suicidal ideation was reported in 9 patients (7.2%) and suicide attempts in 3 patients (2.4%) on VBZ. Depression, depressed mood, and major depression were collectively reported in 15.2% of patients on valbenazine. No new trends in the C-SSRS were identified.[3] Full results and analysis of the KINECT-HD2 study are expected at end of year 2023.

Patients in both KINECT-HD and KINECT-HD2 with significant risk for suicidal behavior or with unstable psychiatric symptoms were excluded from the studies.[2,3]

Table 1: Psychiatric Adverse Events in KINECT-HD

	KINECT-HD[2]	
Depression and suicidality category ‡	**Placebo** (N=63) n (%)	**Valbenazine** (N=64) n (%)
Depression	1 (1.6)	2 (3.1)
Suicidal ideation	1 (1.6)	0
Depressed mood	0	1 (1.6)
Suicide attempt	0	0
Adjustment disorder with depressed mood	0	0
Major depression	0	0

‡By standardized MedDRA query of depression and suicide/self-injury.

Background and Literature Review:

While depression estimates in people with HD can vary greatly in the literature it is generally accepted to affect approximately 40% to 50% of those with HD and suicide is the second most common cause of death following pneumonia.[4-6]

Depression:

The prevalence of medical history of depression in the KINECT-HD and KINECT-HD2 studies were consistent with depression estimates of 40-50% of HD patients worldwide (46.5% in KINECT-HD and 48.4% in the KINECT-HD2 interim analysis).[3] Additionally, the occurrence of depression adverse events (AEs) in the patients who participated in the valbenazine clinical studies was consistent with that described in a 12-month study of 85 patients with genetically confirmed symptomatic HD. In that study, the 12-month incidence of depressive disorders was 17.9%, which is similar to the incidence of all depression and suicidality in the long-term interim analysis of KINECT-HD2 (18.0%).[7] See Table 2 below for more information.

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Suicidality:

The prevalence of medical history of suicidality in patients in KINECT-HD and KINECT-HD2 was consistent with reports in the literature for patients with HD (Table 2).[3] The rates of suicidal ideation and suicide attempt in patients with HD were estimated from a systematic review of articles published from 1993 to 2018. The lifetime rate of suicidal ideation is between 20.0% to 30.0% in patients with HD and the rate of suicide attempt is 7.0% to 10.0% in patients with HD. The incidence of suicidal ideation and suicide attempt in the long-term KINECT-HD2 study interim data is consistent with the increased lifetime rate of suicidality and suicide attempt in patients with HD.[8]

Table 2: Prevalence rates of select psychiatric symptoms and disorders in patients with HD

	Prevalence Estimates in HD Patients	KINECT-HD Population at baseline[3,¶]	Interim KINECT-HD2 Population at baseline[3,¶]
Depression			
	40% to 50%[6,†]	47%	48%
Suicidal ideation			
	20% to 30%[8,‡]	21%	20%
Suicidal behavior			
	7% to 10%[8,§]	5%	5%

†Based on a review of 8 observational and 6 retrospective studies comprising 11,782 and 2,027 patients, respectively. Depression prevalence estimates can vary greatly in the literature.
‡Based on a review of 7 observational studies comprising 14,406 patients.
§Based on a review of 4 observational studies comprising 6,358 patients.
¶Based on medical history. Patients with significant risk of suicidal behavior or unstable/serious medical or psychiatric illness were excluded from the studies.

Given the risk for suicidal ideation and suicide attempts among individuals with Huntington's disease, all patients taking a VMAT2 inhibitor or other medication for chorea should be monitored regularly for suicidal thoughts and behaviors.

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CONTRAINDICATIONS
INGREZZA is contraindicated in patients with a history of hypersensitivity to valbenazine or any components of INGREZZA.

WARNINGS & PRECAUTIONS
Hypersensitivity Reactions
Hypersensitivity reactions, including cases of angioedema involving the larynx, glottis, lips, and eyelids, have been reported in patients after taking the first or subsequent doses

of INGREZZA. Angioedema associated with laryngeal edema can be fatal. If any of these reactions occur, discontinue INGREZZA.

Somnolence and Sedation
INGREZZA can cause somnolence and sedation. Patients should not perform activities requiring mental alertness such as operating a motor vehicle or operating hazardous machinery until they know how they will be affected by INGREZZA.

QT Prolongation
INGREZZA may prolong the QT interval, although the degree of QT prolongation is not clinically significant at concentrations expected with recommended dosing. INGREZZA should be avoided in patients with congenital long QT syndrome or with arrhythmias associated with a prolonged QT interval. For patients at increased risk of a prolonged QT interval, assess the QT interval before increasing the dosage.

Neuroleptic Malignant Syndrome
A potentially fatal symptom complex referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with drugs that reduce dopaminergic transmission, including INGREZZA. The management of NMS should include immediate discontinuation of INGREZZA, intensive symptomatic treatment and medical monitoring, and treatment of any concomitant serious medical problems. If treatment with INGREZZA is needed after recovery from NMS, patients should be monitored for signs of recurrence.

Parkinsonism
INGREZZA may cause parkinsonism. Parkinsonism has also been observed with other VMAT2 inhibitors. Reduce the dose or discontinue INGREZZA treatment in patients who develop clinically significant parkinson-like signs or symptoms.

This letter and the enclosed material are provided in response to your unsolicited medical information inquiry. Please feel free to contact Neurocrine Medical Information at (877) 641-3461 or medinfo@neurocrine.com if you would like to request additional information.

References:

1. INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc.
2. Furr Stimming E, Claassen DO, Kayson E, et al. Safety and efficacy of valbenazine for the treatment of chorea associated with Huntington's disease (KINECT-HD): a phase 3, randomised, double-blind, placebo-controlled controlled trial. *Lancet Neurol.* 2023;22(6):494-504.
3. Neurocrine Biosciences. VBZ-HD-0006. Data on file.
4. Nance M, Paulsen JS, Rosenblatt A, et al. A Physician's Guide to the Management of Huntington's Disease 3rd Edition. Huntington's Disease Society of America. 2011.
5. van Duijn E, et al. European Huntington's Disease Network Behavioural Phenotype Working Group. Neuropsychiatric symptoms in a European Huntington's disease cohort (REGISTRY). J Neurol Neurosurg Psychiatry. 2014 Dec;85(12):1411-8.
6. Paoli RA, et al. Neuropsychiatric Burden in Huntington's Disease. Brain Sci. 2017 Jun 16;7(6):67.
7. van Duijn E, et al. Cross-sectional study on prevalences of psychiatric disorders in mutation carriers of Huntington's disease compared with mutation-negative first-degree relatives. J Clin Psychiatry. 2008 Nov;69(11):1804-10.
8. Kachian ZR, et al. Suicidal ideation and behavior in Huntington's disease: Systematic review and recommendations. J Affect Disord. 2019 May 1;250:319-329.

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Enclosures:

A. INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc.