NEUROCRINE® BIOSCIENCES

(p) 877-641-3461
(f) 913-451-6409

12780 El Camino Real San Diego, CA 92130
http://www.neurocrinemedical.com/

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

Thank you for contacting Neurocrine Biosciences with your unsolicited Medical Information request regarding the potential effects of valbenazine on somnolence in patients with chorea associated with Huntington's disease.

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

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

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

> **WARNING AND PRECAUTIONS**
> **Somnolence and Sedation**
> INGREZZA can cause somnolence and sedation, which was the most common adverse reaction in placebo-controlled trials. 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.

Clinical Study Results:

In KINECT-HD, the 12-week, Phase 3, double-blind placebo-controlled study to evaluate the safety and efficacy of valbenazine (VBZ) for the treatment of chorea associated with HD, somnolence and sedation adverse events (AEs) occurred collectively in 18.8% patients treated with valbenazine (10 patients somnolence, 1 patient lethargy, and 1 patient sedation) and 3.2% of placebo-treated patients (2 patients somnolence). Fatigue occurred in 14.1% of patients on valbenazine and 9.5% of patients on placebo (Table 1)[1,2]

Table 1: KINECT-HD Treatment Emergent Adverse Events Related to Somnolence[1,2]

	Placebo (N=63) n (%)	Valbenazine (N=64) n (%)
Somnolence	2 (3.2%)	10 (15.6)
Fatigue	6 (9.5%)	9 (14.1%)
Lethargy	0	1 (1.6%)
Sedation	0	1 (1.6%)

All somnolence-related AEs in the VBZ group were mild (80%) or moderate (20%). Most events occurred during the dose adjustment period, the first 6 weeks of VBZ treatment. The onset of events occurred at 40 mg for 45% of patients, 60 mg for 15% of patients, and 80 mg for 40% of patients.[3]

No patient in the VBZ group discontinued study treatment due to somnolence. One patient in the VBZ group discontinued study treatment due to AEs of urticaria, sedation, anxiety and akathisia that occurred on the same day as urticaria.[3]

AEs leading to dose reduction occurred in 9 patients (14.1%) in the VBZ group and 3 patients (4.8%) in the placebo group. In the VBZ group, the most common AEs leading to dose reductions were fatigue (4 patients), followed by somnolence (3 patients). All events of fatigue and somnolence were mild or moderate and all patients in the VBZ group with dose reductions completed the study.[3]

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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.

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.

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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-0003. Data on file.

Enclosures:

A. INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc.
B. INGREZZA [Important Safety Information]. San Diego, CA: Neurocrine Biosciences, Inc.