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Parkinsonism and INGREZZA® (valbenazine) Capsules and INGREZZA® SPRINKLE (valbenazine) Capsules 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 INGREZZA and INGREZZA SPRINKLE and parkinsonism.

INGREZZA and INGREZZA SPRINKLE are vesicular monoamine transporter 2 (VMAT2) inhibitors indicated for the treatment of adults with chorea associated with Huntington's disease (HD).[1]

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

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

> **WARNING AND PRECAUTIONS**
> **Parkinsonism**
> INGREZZA and INGREZZA SPRINKLE may cause parkinsonism. Parkinsonism has also been observed with other VMAT2 inhibitors. In the 3 placebo-controlled clinical studies in patients with tardive dyskinesia, the incidence of parkinson-like adverse events was 3% of patients treated with INGREZZA and <1% of placebo-treated patients.
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> In a placebo-controlled clinical study in patients with chorea associated with Huntington's disease, the incidence of parkinson-like adverse events was 4.7% in patients treated with INGREZZA and 0% in placebo-treated patients. Because rigidity can develop as part of the underlying disease process in Huntington's disease, it may be difficult to distinguish between potential drug-induced parkinsonism and progression of underlying Huntington's disease. Drug-induced parkinsonism has the potential to cause more functional disability than untreated chorea for some patients with Huntington's disease.
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> Postmarketing safety reports have described parkinson-like symptoms in patients taking INGREZZA for tardive dyskinesia, some of which were severe and required hospitalization. In most cases, severe parkinsonism occurred within the first two weeks after starting or increasing the dose of INGREZZA. Associated symptoms have included falls, gait disturbances, tremor, drooling and hypokinesia. In cases in which follow-up clinical information was available, parkinson-like symptoms were reported to resolve following discontinuation of INGREZZA therapy.
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> Reduce the dose or discontinue INGREZZA or INGREZZA SPRINKLE treatment in patients who develop clinically significant parkinson-like signs or symptoms.

Clinical Study Results:

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, parkinson-like adverse events occurred in 4.7% of patients treated with valbenazine (2 patients tremor, 1 patient drooling) and 0% of placebo-treated patients.[2,3]

Parkinsonism was also evaluated during KINECT-HD using the Unified Huntington's Disease Rating Scale (UHDRS®) motor assessment items for parkinsonsim (retropulsion pull test, finger taps, pronation/supination of hands, arm rigidity, and body bradykinesia). No worsening in the mean parkinsonism score from baseline was noted in either treatment group up to 12 weeks in KINECT-HD (Table 1).[2] A negative change from baseline indicates a favorable effect.

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Table 1: KINECT-HD UHDRS Parkinsonism[2]

Key Safety Measure	Placebo			Valbenazine		
	Baseline*	Maintenance period or week 12*	Change from baseline‡	Baseline*	Maintenance period or week 12*	Change from baseline‡
UHDRS parkinsonism	7.5 (3.7)	6.4 (3.9)	-1.0 (NA)	8.6 (4.4)	8.2 (4.5)	-0.3 (NA)

Data are n (%), mean (SEM), or mean change (95% CI). NA=not applicable, UHDRS=Unified Huntington's Disease Rating Scale.
*Mean (SD) at study baseline (day –1) and week 12.‡Mean changes are presented for UHDRS parkinsonism.

The most common treatment-emergent adverse events (TEAEs) with valbenazine in KINECT-HD were somnolence, fatigue and falls.[2]

IMPORTANT SAFETY INFORMATION
Depression and Suicidality in Patients with Huntington's Disease: VMAT2 inhibitors, including INGREZZA and INGREZZA SPRINKLE, 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 and INGREZZA SPRINKLE are contraindicated in patients with a history of hypersensitivity to valbenazine or any components of INGREZZA or INGREZZA SPRINKLE.

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 or INGREZZA SPRINKLE.

Somnolence and Sedation
INGREZZA and INGREZZA SPRINKLE 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 or INGREZZA SPRINKLE.

QT Prolongation
INGREZZA and INGREZZA SPRINKLE may prolong the QT interval, although the degree of QT prolongation is not clinically significant at concentrations expected with recommended dosing. INGREZZA and INGREZZA SPRINKLE 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

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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 or INGREZZA SPRINKLE, intensive symptomatic treatment and medical monitoring, and treatment of any concomitant serious medical problems. If treatment with INGREZZA or INGREZZA SPRINKLE is needed after recovery from NMS, patients should be monitored for signs of recurrence.

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

ADVERSE REACTIONS
The most common adverse reactions in patients with chorea associated with Huntington's disease (≥5% and twice the rate of placebo) are somnolence/lethargy/sedation, urticaria, rash, and insomnia.

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-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.