

QT Prolongation 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 INGREZZA and INGREZZA SPRINKLE and potential QT prolongation in patients with chorea associated with Huntington's disease.

INGREZZA and INGREZZA SPRINKLE are indicated in adults for the treatment of 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.

FDA-approved Prescribing Information¹

WARNINGS AND PRECAUTIONS

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. In patients taking a strong CYP2D6 or CYP3A4 inhibitor, or who are CYP2D6 poor metabolizers, INGREZZA and INGREZZA SPRINKLE concentrations may be higher and QT prolongation clinically significant. For patients who are CYP2D6 poor metabolizers or are taking a strong CYP2D6 inhibitor, dose reduction may be necessary. For patients taking a strong CYP3A4 inhibitor, reduce the dose of INGREZZA or INGREZZA SPRINKLE to 40 mg once daily. 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.

CLINICAL PHARMACOLOGY

Cardiac Electrophysiology

INGREZZA and INGREZZA SPRINKLE may cause an increase in the corrected QT interval in patients who are CYP2D6 poor metabolizers or who are taking a strong CYP2D6 or CYP3A4 inhibitor. An exposure-response analysis of clinical data from two healthy volunteer studies revealed increased QTc interval with higher plasma concentrations of the active metabolite. Based on this model, patients taking an INGREZZA 60 mg or 80 mg dose with increased exposure to the metabolite (e.g., being a CYP2D6 poor metabolizer) may have a mean (upper bound of double-sided 90% CI) QT prolongation of 9.6 (12.0) msec or 11.7 (14.7) msec, respectively as compared to otherwise healthy volunteers given INGREZZA, who had a respective mean (upper bound of double-sided 90% CI) QT prolongation of 5.3 (6.7) msec or 6.7 (8.4) msec.

Double-Blind Placebo Controlled (DBPC) Trial:

KINECT[®]-HD was the Phase 3, double-blind placebo-controlled study to evaluate the safety and efficacy of valbenazine for the treatment of chorea associated with HD. The study included 127 participants in the safety analysis set (defined as all randomly assigned participants who received at least one dose of study drug and had any available safety data after baseline); valbenazine n=64, placebo n=63. The mean QTcF change from baseline was less than 3 msec at all visits in the valbenazine group and ranged from -2.3 to -0.47 msec in the placebo group.^{2,3}

Twelve participants had QTcF >450 msec: 7 participants (10.9%) in the valbenazine group and 5 participants (8.2%) in the placebo group (Table 1). One participant in the valbenazine group and none in the placebo group had QTcF >480 msec. See Table 1 below for changes from baseline in QTcF.³

Table 1: QTcF Maximum Observed and Change from Baseline Categories (Safety Analysis Set)^{3,a}

	Placebo (N=63) n (%)	Valbenazine (N=64) n (%)
QTcF Interval		
>450 msec	5 (8.2)	7 (10.9)
>480 msec	0	1 (1.6)
>500 msec	0	0
QTcF Interval Change from Baseline		
>30 msec	2 (3.3)	4 (6.3)
>60 msec	0	0

^aIncludes each participant's highest reported postbaseline value, using the averages of the triplicate values.

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.