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Thank you for contacting Neurocrine Biosciences with your unsolicited Medical Information request regarding the QTc cardiac electrophysiology results from clinical trials of INGREZZA (valbenazine) capsules.

INGREZZA is a vesicular monoamine transporter 2 (VMAT2) inhibitor indicated for the treatment of adults with tardive dyskinesia (TD).

The following is a brief summary of the cardiac electrophysiology data from the Phase 3 valbenazine trial and associated text from the FDA-approved full prescribing information.

KINECT 3

KINECT 3 was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel, fixed-dose study to evaluate the efficacy, safety, and tolerability of 2 doses of valbenazine (40 mg and 80 mg) compared to placebo, administered once daily. The study population included medically stable participants with clinical diagnoses of schizophrenia, schizoaffective disorder, or mood disorder with neuroleptic-induced TD. KINECT 3 included a double-blind, placebo-controlled treatment period for 6 weeks followed by a double-blind valbenazine extension period for 42 weeks. Participants then entered a 4-week posttreatment period with a final study visit at the end of Week 52.[1]

To assess the potential for changes in cardiac electrophysiology in KINECT 3, standard 12-lead electrocardiogram (ECG) was conducted at screening, baseline (Day -1), and at every visit during the double-blind, placebo-controlled period, the valbenazine extension period, and at the follow-up visit (end of Week 52). Mean changes from baseline in corrected QT interval using Fridericia's formula (QTcF) in the placebo, valbenazine 40 mg, and valbenazine 80 mg groups at Week 6 were 1.3 msec, 2.1 msec, and 0.8 msec respectively. Mean changes from baseline in QTcF interval in the valbenazine 40 mg and 80 mg groups at Week 48 were 5.0 msec and 3.7 msec, respectively.[1]

FDA-approved Full Prescribing Information

WARNINGS AND PRECAUTIONS

QT Prolongation

INGREZZA 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 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 to 40 mg once daily. 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.[2]

CLINICAL PHARMACOLOGY
Cardiac Electrophysiology

INGREZZA 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 80 mg dose with increased exposure to the metabolite (e.g., being a CYP2D6 poor metabolizer) may have a mean QT prolongation of 11.7 msec (14.7 msec upper bound of double-sided 90% CI) as compared to otherwise healthy volunteers given INGREZZA, who had a mean QT prolongation of 6.7 msec (8.4 msec).[2]

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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. Data on File, Neurocrine Biosciences, Inc..
2. INGREZZA [package insert]. Neurocrine Biosciences, Inc., San Diego, CA; 2017

Enclosures:

1. INGREZZA [package insert]. Neurocrine Biosciences, Inc., San Diego, CA; 2017
2. Important Safety Information. Neurocrine Biosciences, Inc., San Diego, CA; 2017

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