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Cardiovascular Profile of INGREZZA® (valbenazine) Capsules and INGREZZA® SPRINKLE (valbenazine) Capsules in Patients with Tardive Dyskinesia

Thank you for contacting Neurocrine Biosciences with your unsolicited Medical Information request regarding the cardiovascular profile of INGREZZA and INGREZZA SPRINKLE.

INGREZZA and INGREZZA SPRINKLE are vesicular monoamine transporter 2 (VMAT2) inhibitors indicated for the treatment of adults with tardive dyskinesia.[1]

FDA-approved Prescribing Information[1]

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.[1]

CLINICAL PHARMACOLOGY

Cardiac Electrophysiology
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 exposureresponse 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.[1]

Pooled Double-Blind Placebo Controlled (DBPC) Trials:

Data were pooled from three 6-week, randomized, double-blind, placebo-controlled (DBPC) trials of once-daily valbenazine in adults with tardive dyskinesia (2 Phase 2 and 1 Phase 3: KINECT® [NCT01688037], KINECT® 2 [NCT01733121], and KINECT® 3 [NCT02274558], respectively) to evaluate the cardiovascular profile of valbenazine. Outcomes of interest included cardiovascular-related treatment-emergent adverse events (TEAEs), vital sign measurements, and QTcF (Fridericia correction) intervals.[2]

The pooled population included 400 participants (placebo, n=178; 40 mg, n=110; 80 mg, n=112). A history of cardiac disorders was present in 11.8% of participants with 74.3% taking a concomitant

medication with known potential for QT prolongation. Furthermore, the percentages of participants who were taking concomitant medications of interest are presented in **Table 1**.[2]

Table 1. Concomitant medications of interest

Concomitant medication, n (%)	Placebo (n=178)	Valbenazine 40 mg/day (n=110)	Valbenazine 80 mg/day (n=112)
Any concomitant medication	178 (100.0)	109 (99.1)	112 (100.0)
Any antipsychotic[a]	149 (83.7)	98 (89.1)	89 (79.5)
Atypical only	115 (64.6)	73 (66.4)	68 (60.7)
Typical or both	34 (19.1)	24 (21.8)	18 (16.1)
Any antidepressant[a]	111 (62.4)	73 (66.4)	71 (63.4)
Any anxiolytic[a]	49 (27.5)	40 (36.4)	26 (23.2)
Any medication with potential to prolong QT interval[b]	130 (73.0)	87 (79.1)	80 (71.4)

[a]Based on specific WHO Drug ATC Category (i.e., antipsychotics, antidepressants, anxiolytics). [b]Medications with potential to prolong the QT interval.

Mean changes from baseline to Week 6 in supine vital signs were similar across treatment arms (all $p>0.05$ for valbenazine versus placebo). In addition, mean changes from baseline to Week 6 in supine and orthostatic vital signs are presented in **Table 2**.[2]

Table 2. Mean changes from baseline to Week 6 in supine and orthostatic vital sign measurements

	Placebo		Valbenazine 40 mg/day		Valbenazine 80 mg/day	
Vital sign parameter	n	Mean CFB ± SD	n	Mean CFB ± SD	n	Mean CFB ± SD
Supine SBP, mmHg	159	0.2 ± 12.8	96	-2.1 ± 12.7	101	-1.8 ± 15.3
Supine DBP, mmHg	159	-0.1 ± 10.0	96	-1.6 ± 8.5	101	-1.2 ± 9.7
Supine heart rate, bpm	159	-1.7 ± 8.9	96	-2.2 ± 12.1	101	-1.7 ± 11.4
Orthostatic SBP, mmHg	159	-0.8 ± 10.2	96	0.6 ± 10.9	101	0.1 ± 9.2
Orthostatic DBP, mmHg	159	-0.5 ± 8.3	96	1.3 ± 8.4[b]	101	1.1 ± 8.4
Orthostatic heart rate, bpm	159	-0.8 ± 8.3	96	0.0 ± 7.9	101	1.1 ± 7.1

[a]Orthostatic vital sign measurements calculated as standing minus supine values. [b] $P<0.05$ versus placebo.
CFB, change from baseline; DBP, diastolic blood pressure; n, number of participants with available vital assessment at Week 6 (pooled safety population); SBP, systolic blood pressure; SD, standard deviation.

The mean baseline QTcF intervals were 412.0 msec, 414.5 msec and 412.9 msec for the placebo, 40 mg and 80 mg groups, respectively. Mean changes from baseline to Week 6 in QTcF interval were 1.2 msec, 1.1 msec, and 2.1 msec for the placebo, 40 mg and 80 mg groups, respectively. The number of participants with a QTcF interval >450 msec at Week 6 were 5, 11 and 11 for placebo, 40 mg and 80 mg groups, respectively. In addition, the number of participants with >30 msec increase in QTcF interval from baseline to Week 6 were 6, 3 and 11 for the placebo, 40 mg and 80 mg groups, respectively.[2]

Five cardiac-related TEAEs occurred during the 6-week DBPC period, each reported in 1 participant: chest pain (40 mg), bradycardia (40 mg), blood pressure (80 mg), sudden death (80 mg) and myocardial infarction which resulted in death (placebo). Two deaths occurred during the DBPC period and were considered unrelated (placebo) or unlikely related (valbenazine 80 mg) to study drug.[2]

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Double-Blind Extension Study:

The cardiovascular profile of valbenazine was also evaluated in the KINECT 3 double-blind extension study. Participants who completed the DBPC period in the KINECT 3 study were eligible to continue to a 42-week double-blind valbenazine extension period (at the same valbenazine dose) followed by a 4-week drug-free period. Those initially randomized to placebo were re-randomized 1:1 to valbenazine 40 mg or 80 mg. Participants re-randomized to 80 mg of valbenazine dose initially received 40 mg for one week.[2,3]

Of the 205 participants who completed the DBPC period, 198 (96.6%) entered the valbenazine extension period (80 mg, n=101; 40 mg, n=97), 124 (62.6%) participants completed the valbenazine extension period, and 121 (61.1%) completed follow-up.[3]

The mean changes from baseline to Week 48 in supine and orthostatic vital signs were generally similar between valbenazine 40 mg and 80 mg groups (see **Table 3**). Mean changes from baseline to Week 48 in QTcF interval were 5.0 msec and 3.7 msec for the valbenazine 40 mg and 80 mg groups, respectively.[2]

Table 3: Mean changes from baseline to Week 48 in supine and orthostatic vital sign measurements

	Valbenazine 40 mg/day		Valbenazine 80 mg/day	
Vital sign parameter	n	Mean CFB ± SD	n	Mean CFB ± SD
Supine SBP, mmHg	61	0.1 ± 14.8	63	-0.1 ± 15.5
Supine DBP, mmHg	61	0.6 ± 10.0	63	-1.3 ± 10.2
Supine heart rate, bpm	61	-1.9 ± 11.8	63	-0.4 ± 11.3
Orthostatic SBP, mmHg	61	1.1 ± 11.3	63	-0.2 ± 8.7
Orthostatic DBP, mmHg	61	0.0 ± 7.7	63	1.2 ± 10.1
Orthostatic heart rate, bpm	61	0.6 ± 8.8	63	1.5 ± 7.1

[a]Orthostatic vital sign measurements calculated as standing minus supine values.
CFB, change from baseline; DBP, diastolic blood pressure; n, number of participants with available vital assessment at Week 48 (KINECT 3 extension safety population); SBP, systolic blood pressure; SD, standard deviation.

Seventeen cardiac-related TEAEs occurred during the extension period: chest pain (2 in 80 mg and 2 in 40 mg), blood pressure increased (1 in 80 mg), syncope (1 in 80 mg and 3 in 40 mg), cardiac failure (1 in 80 mg), bundle branch block (1 in 80 mg), mitral valve incompetence (1 in 80 mg), tricuspid valve incompetence (1 in 80 mg), arrhythmia supraventricular (1 in 40 mg), coronary artery disease (1 in 40 mg), sinus tachycardia (1 in 40 mg), and supraventricular tachycardia (1 in 40 mg).[2]

For a more complete description of this analysis, please access the manuscript by Thai-Cuarto D, et al.: https://doi.org/10.1007/s40264-017-0623-1.

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. Thai-Cuarto D, et al. Cardiovascular profile of valbenazine: analysis of pooled data from three randomized, double-blind, placebo-controlled trials. *Drug Safety*. 2017. https://doi.org/10.1007/s40264-017-0623-1
3. Factor SA, et al. The effects of valbenazine in participants with tardive dyskinesia: results of the 1-year KINECT 3 extension study. *Journal of Clin Psychiatry*. 2017. http://dx.doi.org/10.4088/JCP.17m11777

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Enclosures:

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