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Discontinuation 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 discontinuation of INGREZZA and INGREZZA SPRINKLE.

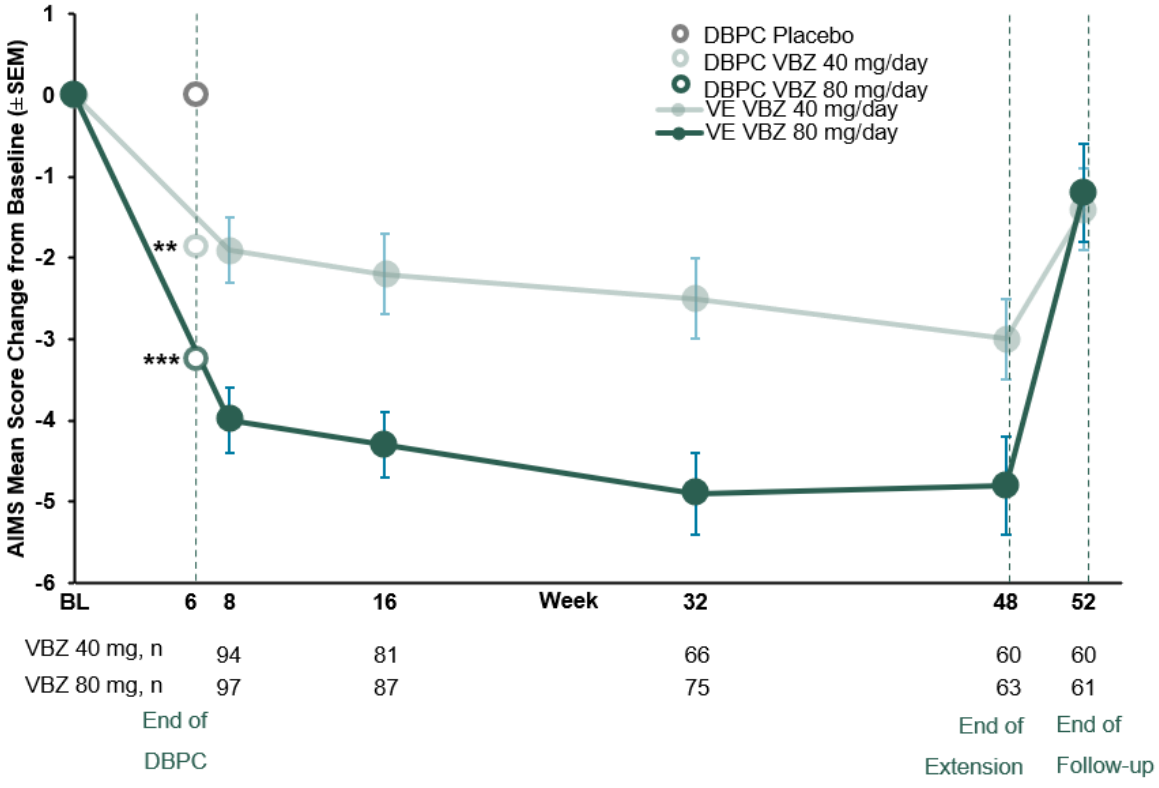
INGREZZA and INGREZZA SPRINKLE are vesicular monoamine transporter 2 (VMAT2) inhibitors indicated for the treatment of adults with tardive dyskinesia.[1]

There are no requirements in the FDA-approved full Prescribing Information for titration when discontinuing INGREZZA and INGREZZA SPRINKLE.

KINECT 3

In the KINECT® 3 study, a Phase 3 randomized, double-blind, placebo-controlled (DBPC) trial of valbenazine for adults with tardive dyskinesia, participants demonstrated sustained reductions in TD severity (as measured by the mean change in abnormal involuntary movement scale [AIMS] total dyskinesia score) through 48 weeks of treatment (**Figure 1**). Following discontinuation of valbenazine treatment (participants were taken off drug from Weeks 48-52), the mean AIMS dyskinesia total scores returned towards baseline levels.[1,2]

Figure 1: AIMS Score Mean Change by Study Visit (ITT Population)



At end of DBPC: **P<0.01; ***P<0.001 vs. placebo (statistical significance met for 80 mg/day based on the predefined fixed-sequence testing procedure); results based on least squares mean change from DBPC baseline using a mixed-effects model for repeated measures. VE and drug-free follow-up periods: results based on arithmetic mean changes, with no imputation for missing values or significance testing between dose groups. AIMS, Abnormal Involuntary Movement Scale; BL, baseline; DBPC, double-blind placebo-controlled; ITT, intent-to-treat; SEM, standard error of the mean; VBZ, valbenazine; VE, valbenazine extension.

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An overview of the adverse events (AEs) as well as rates of most commonly reported AEs are summarized in **Tables 1-3.** Treatment emergent adverse events (TEAEs) leading to study discontinuation in more than 2 participants include somnolence (80 mg, n=3) and suicidal ideation (80 mg, n=1; 40 mg, n=2). Cases of discontinuation due to suicidal ideation, suicidal behavior (n=1), or suicide attempt (n=1) were determined by the study investigator to be unlikely related or unrelated to valbenazine. There were no clinically important changes in clinical laboratory, vital signs, or ECG parameters during the DBPC period, treatment extension or washout periods.[2,3]

Table 1. KINECT 3 Adverse Events (Safety Population)

	6-Week, DBPC Period			Double-Blind, Long-Term Extension Period	
Event, %	**Placebo (n=76)**	**VBZ 40 mg (n=72)**	**VBZ 80 mg (n=79)**	**VBZ 40 mg (n=97)**	**VBZ 80 mg (n=101)**
Any AE	43	40	51	62	76
Any severe AE	3	4	5	7	13
Any AE leading to discontinuation	5	6	6	13	18
Any serious AE	4	6	8	13	16

All serious AEs were assessed as not related or unlikely to be related to study drug and resolved, except one case of hepatitis in the valbenazine 80 mg group considered possibly related. AE, adverse event; DBPC double-blind, placebo-controlled; VBZ, valbenazine.

Table 2. KINECT 3 DBPC Period: AEs Reported in ≥5% of Participants (Safety Population)

Event by preferred term, n (%)	Placebo (n=76)	VBZ 40 mg (n=72)	VBZ 80 mg (n=79)
Somnolence	3 (3.9)	4 (5.6)	4 (5.1)
Dry mouth	1 (1.3)	5 (6.9)	0
Suicidal ideation	4 (5.3)	3 (4.2)	1 (1.3)

AE, adverse event; VBZ, valbenazine.

Table 3. KINECT 3 Extension: AEs Reported in ≥5% of Participants (Safety Population)

Event by preferred term, n (%)	VBZ 40 mg (n=97)	VBZ 80 mg (n=101)
Headache	7 (7.2)	7 (6.9)
Urinary tract infection	6 (6.2)	7 (6.9)
Diarrhea	3 (3.1)	8 (7.9)
Dizziness	4 (4.1)	7 (6.9)
Suicidal ideation	5 (5.2)	5 (5.0)
Depression	6 (6.2)	2 (2.0)

AE, adverse event; VBZ, valbenazine.

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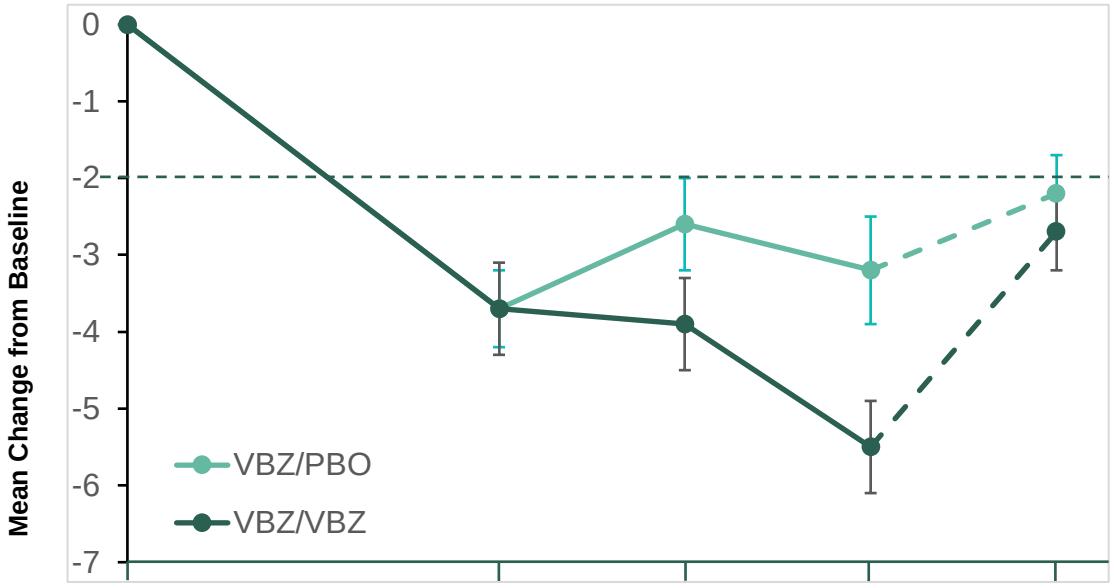
Randomized Withdrawal Study

A Phase 4, double-blind, placebo-controlled, randomized withdrawal study (NCT03891862) was conducted to assess the persistence of valbenazine effects in patients with tardive dyskinesia. Participants in the study started with an initial 8 week open-label treatment period, once-daily valbenazine at 40mg and escalated to 80mg after 1 week (dose reduction was allowed for tolerability). After 8 weeks of open-label valbenazine, participants were randomized (1:1) to receive 8 weeks of placebo (VBZ/PBO group) or continue taking the same valbenazine dose (VBZ/VBZ group). Abnormal Involuntary Movement Scale (AIMS) assessments were conducted at study baseline, Week 8 (end of open-label treatment, randomization baseline), Week 12, and Week 16 (end of randomized withdrawal period). AIMS total score (sum of items 1-7) was based on consensus study by blinded central AIMS video raters.[4]

In the withdrawal study, mean changes in AIMS total scored from study baseline to Week 8 (end of open-label period) indicated improvements with valbenazine treatment. Changes from Week 8 to Week 16 indicated initial loss of valbenazine effect after treatment withdrawal; however, mean changes from study baseline to Week 16 suggested some overall persistence of valbenazine effect. (**Figure 2**).[4]

Figure 2. AIMS Total Score Change from Baseline



VBZ/PBO, n	58	58	56	53	53
VBZ/VBZ, n	59	59	58	56	55

Dashed line indicates minimally clinically important difference (MCID, ≥2 AIMS total score change from study baseline).

AIMS, Abnormal Involuntary Movement Scale; MCID, minimal clinically important difference; PBO, placebo; VBZ, valbenazine.

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Table 3. Randomized Withdrawal: AEs reported in ≥3% of Participants

		DBPC Treatment Period	
	OL VBZ Period (N=132)	VBZ/PBO (N=59)	VBZ/VBZ (N=59)
Summary, n (%)			
Any TEAE	43 (32.6)	19 (32.2)	14 (23.7)
Any Serious TEAE	3 (2.3)	2 (3.4)	1 (1.7)
Any TEAE leading to discontinuation	4 (3.0)	1 (1.7)	0 (0)
Deaths[a]	1 (0.8)	0 (0)	0 (0)
TEAEs by preferred term, n (%)[b]			
Pain in extremity	5 (3.8)	0 (0)	0 (0)
Somnolence	4 (3.0)	0 (0)	0 (0)
UTI	4 (3.0)	6 (10.2)	0 (0)
Weight Increased	2 (1.5)	0 (0)	2 (3.4)
Fall	2 (1.5)	2 (3.4)	0 (0)
Anemia	1 (0.8)	2 (3.4)	1 (1.7)
Suicidal Ideation[c]	1 (0.8)	2 (3.4)	1 (1.7)
Blood CPK Increased	1 (0.8)	0 (0)	2 (3.4)
Blood Glucose Increased	0 (0)	0 (0)	2 (3.4)

[a]One subject had a fatal accidental overdose during OL treatment that was judged not related to study drug; this subject was also included in the count for serious TEAEs.
[b]Reported in ≥3% of participants in any treatment group.
[c]All three participants who experienced suicidal ideation during the study had a lifetime history of suicidality
CPK, creatine phosphokinase; DBPC, double-blind, placebo-controlled; OL, open-label; PBO, placebo; TEAE, treatment-emergent adverse event; UTI, urinary tract infection; VBZ, valbenazine.

Across both studies, there were no new safety signals identified after drug discontinuation.

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. Hauser RA, et al. KINECT 3: a phase 3 randomized, double-blind, placebo-controlled trial of valbenazine for tardive dyskinesia. *Am J Psychiatry.* 2017;174:5,476-484.
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 Clinical Psychiatry. 2017; 78(9):1344-50 (https://www.ncbi.nlm.nih.gov/pubmed/29141124).
4. Jimenez R, et al. Effects of Valbenazine on Tardive Dyskinesia After Treatment Withdrawal. Poster presented virtually at the Professional Society for Health Economics and Outcomes Research Europe Annual Meeting; November 30 – December 3, 2021.

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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
C. Jimenez R, et al. Effects of Valbenazine on Tardive Dyskinesia After Treatment Withdrawal. Poster presented virtually at the Professional Society for Health Economics and Outcomes Research Europe Annual Meeting; November 30 – December 3, 2021.