INGREZZA®
(valbenazine) capsules

The Effects of Valbenazine in Participants with Tardive Dyskinesia: Results of the 1-Year KINECT 3 Extension Study.

Factor SA, Remington G, Comella CL, et al.
J Clin Psychiatry. 2017;78(9):1344-1350.[a]

[a] Supplementary section of article not provided as part of this reprint.

Important Information

INDICATION & USAGE

INGREZZA® (valbenazine) capsules is indicated for the treatment of adults with tardive dyskinesia.

IMPORTANT SAFETY INFORMATION

WARNINGS & PRECAUTIONS

Somnolence

INGREZZA can cause somnolence. 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.

Please see additional Important Safety Information throughout and full Prescribing Information in inside pocket.

BACKGROUND

Tardive dyskinesia (TD) is a chronic and potentially irreversible drug-induced movement disorder.[1] TD is associated with prolonged exposure to dopamine receptor blocking agents (DRBAs), including first-generation (typical) and second-generation (atypical) antipsychotics.[2,3]

- Even with the advent of second-generation antipsychotics, approximately 20% to 30% of patients with prolonged exposure to DRBAs develop TD[4]
- Dose reduction or discontinuation of the offending antipsychotic may not be effective and may exacerbate the psychiatric disorder[5,6]

Valbenazine, a novel selective VMAT2 inhibitor, is an FDA-approved treatment indicated for adults with TD. In a pivotal, phase 3 study (KINECT 3), valbenazine 80 mg showed significant improvements in TD severity at 6 weeks and had a generally well-tolerated safety profile.[7]

VMAT2, vesicular monoamine transporter.

STUDY OBJECTIVE

The KINECT 3 extension period evaluated the long-term safety and tolerability of once-daily valbenazine (40 mg or 80 mg) in adults with TD. In addition, long-term effects on TD severity were assessed.[8]

METHODOLOGY

In the KINECT 3 study, eligible patients received 6 weeks of once-daily valbenazine (40 mg or 80 mg) or placebo.[6,b] Consenting patients who completed the 6-week DBPC study were then entered into the blinded extension period and randomized to receive either valbenazine 40 mg or 80 mg once daily. During the first week of the extension period, all randomized patients received valbenazine 40 mg once daily. After the first week, patients who were randomized to receive valbenazine 80 mg once daily had their dose increased.[8,c]

DBPC, double-blind, placebo-controlled.
[b] In the 6-week study, the primary efficacy endpoint was change in AIMS dyskinesia score (sum of items 1-7) from baseline to week 6 for valbenazine 80 mg once daily vs placebo.[7]
[c] Those already receiving either valbenazine dose continued the same dose, while those receiving placebo were randomized (1:1) to valbenazine 40 mg or 80 mg once daily. Participants were allowed 1 dose reduction during the study with blinding maintained.[8]

Safety Analyses[8,d,e]

- Treatment-emergent adverse events (TEAEs)
- Psychiatric status
- Treatment-emergent akathisia or parkinsonism
- Emergence of suicidal ideation or behavior
- 12-lead electrocardiogram (ECG)
- Vital signs and laboratory assessments

Efficacy Measures Assessed[8,e,f]

- Mean Abnormal Involuntary Movement Score (AIMS) change from baseline
- Clinical Global Impression of Change-Tardive Dyskinesia (CGI-TD)
- Patient Global Impression of Change (PGIC)

[d] Safety population.[7,8]
[e] All safety data were analyzed descriptively.[8]
[f] Analyzed at each postbaseline visit.[8]

STUDY POPULATION

In the extension study, valbenazine was studied in a broad population of patients with various underlying diagnoses and treatment regimens. All participants had stable psychiatric status at baseline.[8,g]

Key Inclusion Criteria[7,8]	Select Study Demographics[8]
• Medically stable adults • 18 to 85 years of age	• 198 (96.6%) completers from the DBPC study entered the extension period – 124 (62.6%) participants completed the extension period[i] – 121 (61.1%) completed washout and week 52 follow-up visit
• Participants had one of these diagnoses – Schizophrenia – Schizoaffective disorder – Mood disorder	• 64.4% had a diagnosis of schizophrenia or schizoaffective disorder • 35.6% had mood disorder
• Diagnosis of DRBA-induced TD[h] – Moderate to severe TD based on qualitative assessment	• 71.2% of participants were taking second-generation (atypical) antipsychotics • 7.9% were taking first-generation (typical) antipsychotics

[g] Based on the following accepted measurement scales: Brief Psychiatric Rating Scale (BPRS), Positive and Negative Syndrome Scale (PANSS), Calgary Depression Scale for Schizophrenia (CDSS), Young Mania Rating Scale (YMRS), Montgomery-Åsberg Depression Rating Scale (MADRS).[7]
[h] According to the DSM IV, ≥3 months prior to screening.[6]
[i] Treatment-emergent adverse events leading to study discontinuation in >2 participants were somnolence (80 mg once daily, n=3) and suicidal ideation (80 mg once daily, n=1; 40 mg once daily, n=2). These cases of suicidal ideation or behavior/attempt all resolved with hospitalization/medical management, and were judged by the site investigators as unlikely related to valbenazine.[7]

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS & PRECAUTIONS (continued)

QT Prolongation

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

Please see additional Important Safety Information throughout and full Prescribing Information in inside pocket.

SAFETY PROFILE

In the extension period, valbenazine was generally well tolerated in a population of patients with diagnosed schizophrenia, schizoaffective disorder, or mood disorder.[8]

Treatment-emergent adverse events ≥5% in either valbenazine treatment group[8,j]

- Headache (7.1%)
- Urinary tract infection (6.6%)
- Diarrhea (5.6%)
- Dizziness (5.6%)
- Suicidal ideation (5.1%)
- Depression (4.0%)

[j] Combined valbenazine 40 mg and 80 mg once daily.[8]

There were no clinically important changes in clinical laboratory assessments, vital signs, or ECG parameters during the extension or washout periods.[8]

Psychiatric status generally remained stable during the extension study.[8]

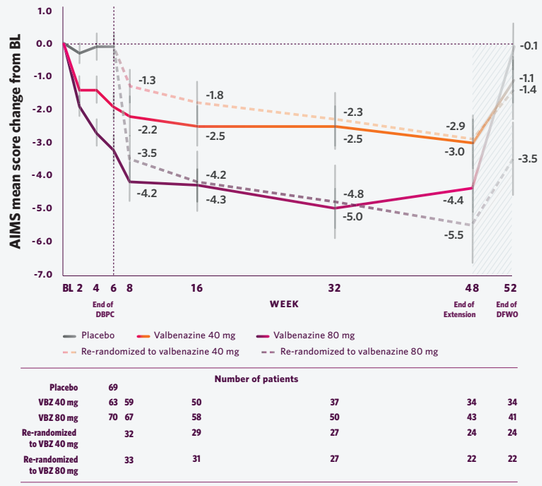
LONG-TERM TREATMENT WITH ONCE-DAILY VALBENAZINE MAY BE AN EFFECTIVE TREATMENT FOR TD IN ADULTS WITH A RANGE OF PRESENTATIONS AND TREATMENT HISTORIES[8]

- Valbenazine was generally well tolerated through 48 weeks, with sustained TD reductions
- TD symptoms tended to return to baseline during the washout period, supporting the maintenance efficacy of ongoing valbenazine treatment

LONG-TERM RESULTS

AIMS mean score showed sustained TD reduction through Week 48[8,9]

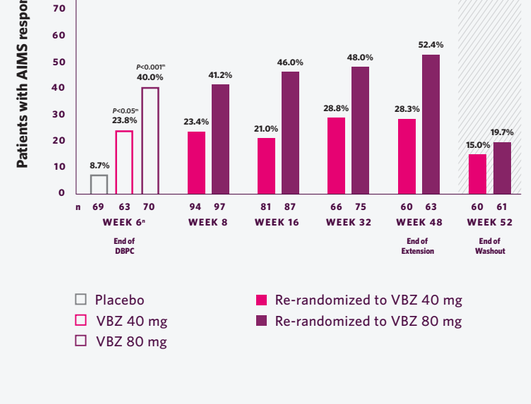
Extension study of valbenazine 40 mg and valbenazine 80 mg (ITT population)[10]



Number of patients						
Placebo	69					
VBZ 40 mg	63	59	50	37	34	34
VBZ 80 mg	70	67	58	50	43	41
Re-randomized to VBZ 40 mg		32	29	27	24	24
Re-randomized to VBZ 80 mg		33	31	27	22	22

AIMS score reduction by ≥50% was generally consistent through Week 48[8]

Percentage of extension study participants with AIMS response[l]



AT 48 WEEKS: **~39% TD reduction** with valbenazine 80 mg[9,k]

[k] In a post hoc analysis that included patients randomized to valbenazine 80 mg at baseline and those who were re-randomized to valbenazine 80 mg at Week 6.[9,10]
AIMS, Abnormal Involuntary Movement Scale; BL, baseline; DFWO, drug-free washout; iTT, intent-to-treat.

[l] AIMS response defined as ≥50% improvement from baseline AIMS dyskinesia score.[8]
[m] Not adjusted for multiplicity. Data presented for ITT analysis set. Treatment group comparison based on Cochran-Mantel-Haenszel test. *P* value vs placebo.[8,9]
[n] Intent-to-treat population.

During the 4-week washout period, mean AIMS scores generally returned toward baseline.[8]

- Based on clinical assessment and need, continued valbenazine treatment may be required to maintain TD reductions

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IMPORTANT SAFETY INFORMATION (continued)

ADVERSE REACTIONS

The most common adverse reaction (≥5% and twice the rate of placebo) is somnolence. Other adverse reactions (≥2% and >placebo) include: anticholinergic effects, balance disorders/falls, headache, akathisia, vomiting, nausea, and arthralgia.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit MedWatch at www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see inside pocket for full Prescribing Information or visit www.INGREZZAHCP.com.

References: 1. Cloud LJ, Zutshi D, Factor SA. Tardive dyskinesia: therapeutic options for an increasingly common disorder. *Neurotherapeutics*. 2014;11(1):166-176. **2.** Stahl SM. *Essential Psychopharmacology Online*. Based on: Stahl SM. *Stahl's Essential Psychopharmacology*. 4th ed. Cambridge, UK: Cambridge University Press; 2013. http://stahlonline.cambridge.org/essential_4th_chapter.jsf?page=chapter5_introduction.htm&name=Chapter%205&title=Conventional%20antipsychotics #c02598-5-1. Accessed February 1, 2017. **3.** Sayers AC, Bürki HR, Ruch W, et al. Neuroleptic-induced hypersensitivity of striatal dopamine receptors in the rat as a model of tardive dyskinesia: effects of clozapine, haloperidol, loxapine and chlorpromazine. *Psychopharmalogia*. 1975;41(2):97-104. **4.** Carbon M, Hsieh CH, Kane JM, Correll CU. Tardive dyskinesia prevalence in the period of second-generation antipsychotic use: a meta-analysis. *J Clin Psychiatry*. 2017;78(3):e264-e278. **5.** Zutshi D, Cloud LJ, Factor SA. Tardive syndromes are rarely reversible after discontinuing dopamine receptor blocking agents: experience from a university-based movement disorder clinic. *Tremor Other Hyperkinet Mov* (NY). 2014;4:266. **6.** Soares KV, McGrath JJ. The treatment of tardive dyskinesia—a systematic review and meta-analysis. *Schizophr Res*. 1999;39(1):1-16. **7.** Hauser RA, Factor SA, Marder SR, 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. **8.** Factor SA, Remington G, Comella CL, et al. The effects of valbenazine in participants with tardive dyskinesia: results of the 1-year KINECT 3 extension study. *J Clin Psychiatry*. 2017;78(9):1344-1350. **9.** Data on file. Neurocrine Biosciences, Inc. **10.** INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc; 2017.

Neurocrine BIOSCIENCES