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INGREZZA® (valbenazine) Capsules and INGREZZA® SPRINKLE (valbenazine) Capsules in Adult Patients with Tardive Dyskinesia and Mood Disorder

Thank you for contacting Neurocrine Biosciences with your unsolicited Medical Information request regarding the long-term use of INGREZZA and INGREZZA SPRINKLE in patients with tardive dyskinesia and mood disorder (e.g., major depressive disorder, bipolar disorder).

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

The long-term use of INGREZZA and INGREZZA SPRINKLE in participants with tardive dyskinesia (TD) and mood disorder (MD) was evaluated in multiple studies. Please refer to the brief summaries of the results below.

KINECT® 3: Phase 3 Double-blinded Valbenazine Extension Period

KINECT 3, a randomized, double-blind, placebo-controlled (DBPC) Phase 3 study, was designed to assess the efficacy, safety, and tolerability of valbenazine in the treatment of adults with TD. Participants who completed the DBPC period continued with a 42-week double-blind valbenazine extension (VE) period and a 4-week drug-free follow-up period. Data from the KINECT 3 study were analyzed post-hoc to evaluate the long-term effects of valbenazine in adults with TD and MD.[2]

In participants with MD (n=51), baseline TD severity (as measured by the Abnormal Involuntary Movement Scale [AIMS] mean scores by blinded central raters) was 11.4 and 10.9, respectively, for the valbenazine 40 and 80 mg/day dose groups. At Week 48, AIMS mean score changes from DBPC baseline were -4.2 and -5.8, respectively, for the valbenazine 40 and 80 mg/day dose groups. The mean AIMS scores changes from baseline at Week 52 (during the 4-week period following discontinuation of valbenazine) were -2.7 and -1.6 for the valbenazine 40 and 80 mg/day groups, respectively. At Week 48, the mean Clinical Global Impression of Change-Tardive Dyskinesia (CGI-TD) scores were 2.2 and 2.0, respectively, for the valbenazine 40 and 80 mg/day groups. The mean CGI-TD scores at Week 52 increased to 2.8 and 3.6 for the valbenazine 40 and 80 mg/day groups, respectively.[2,3]

In the pooled long-term safety data, the 3 most commonly reported TEAEs for the MD subgroup (n=121) were headache (12.4%), urinary tract infection (10.7%), and somnolence (9.1%). Mean psychiatric scales scores (Young Mania Rating Scale, YMRS; and Montgomery-Asberg Depression Rating Scale, MADRS) generally remained stable in participants with TD and MD during long-term valbenazine treatment.[4]

KINECT 4: Phase 3, Open-label, Long-term Study

KINECT 4 is an open-label, long-term (48-week open-label treatment period and a 4-week drug-free follow-up period) Phase 3 study to evaluate the safety and tolerability of valbenazine in adults with TD. Participants received a starting dose of once-daily valbenazine 40 mg, which was escalated to 80 mg at the end of Week 4 if both of the following criteria were met: CGI-TD score of ≥3 (minimally improved to very much worse) and acceptable safety/tolerability with the 40 mg dose, based on investigator judgment. From Weeks 4 to 48, a decrease to 40 mg was allowed if the participant was unable to tolerate the dose increase (80→40 mg group). Participants who were unable to tolerate the 40 mg dose were discontinued from the study. Effectiveness was assessed using the AIMS total score (sum of items 1-7), based on consensus scoring by 2 blinded central AIMS video raters (at baseline, Week 8 [first visit after dose escalation] and Week 52 [during the 4-week period following discontinuation of valbenazine]) and by the investigator or site rater (at each study visit).[5]

Data from KINECT 4 were analyzed post-hoc to evaluate the long-term effects of valbenazine in adults with TD and MD (n=44). In the MD group, baseline TD severity (as measured by the AIMS bean scores by site raters) was 13.1 and 15.7, respectively, for the valbenazine 40 and 80 mg/day dose groups. At Week 48, AIMS mean score change from baseline were as follows: valbenazine 40mg (n=6): -10.2; 80 mg (n=22): -11.6. The AIMS mean score change from baseline to Week 52 (end of drug-free period), was -0.7 and -6.6 for the valbenazine 40 and 80 mg/day dose groups, respectively.[5]

Within the MD subgroup, 7% of participants discontinued due to TEAEs. TEAEs reported in ≥10% of participants in the MD subgroup were urinary tract infection (18.2%) and headache (15.9%). Psychiatric

status remained stable from baseline to Week 48: MADRS, -0.3; YMRS, -0.3. Most participants (95%) had no change in the Columbia-Suicide Severity Rating Scale (C-SSRS) score during the study. In participants with no suicidal ideation at baseline (C-SSRS score=0), 93% of the MD subgroup continued to have no suicidal ideation throughout the study (baseline to Week 52). Of the 5 participants who had suicidal ideation at baseline (C-SSRS score=1 to 3), none had any worsening during the study.[5]

1506: Phase 3b, Long-Term, Open-Label, Rollover Study

The open-label, rollover study included participants who completed KINECT 3 or KINECT 4 (48 weeks of treatment and 4-week drug-free follow-up period). Participants in the rollover study received treatment for up to 72 weeks or until valbenazine became commercially available. All rollover study participants received once-daily valbenazine 40 mg for 4 weeks. At Week 4, dosing was escalated to 80 mg based on tolerability and clinical assessment of TD. A dose reduction to 40 mg was allowed after Week 4 if 80 mg was not tolerated, and participants unable to tolerate 40 mg were discontinued from the study.[6]

Data from the rollover study were analyzed post-hoc to further assess the long-term safety and tolerability of once-daily valbenazine in adults with TD and MD (n=56). The percentages of participants in the MD group with a Clinical Global Impression of Severity-TD (CGIS-TD) score $\leq$2 at baseline were 0% (n=0/12) and 24.4% (n=10/41) for the 40 and 80 mg/day groups, respectively. At Week 48, the percentages of MD participants with a CGIS-TD score ≤2 were as follows: valbenazine 40 mg: 50.0% (n=2/4); valbenazine 80 mg: 93.8% (n=15/16).[6]

During treatment initiation (40 mg for 4 weeks), 14.3% of all MD participants had any TEAE. Discontinuation due to a TEAE was reported in 3.6% of all MD participants. Based on available C-SSRS data, 94.6% (n=53/56) of the MD subgroup had no suicidal ideation at baseline (C-SSRS score=0). 96.2% (n=51/53) of the MD subgroup continued to have no emergence of suicidal ideation at any time during the rollover study. Among participants who had some suicidal ideation at baseline (C-SSRS score=1 to 3), none had any worsening in C-SSRS score at any time during treatment. Furthermore, there were no clinically important changes in laboratory parameters, vital signs, or ECG parameters.[6]

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. Correll CU, et al. Long-Term Effects of Valbenazine (NBI-98854) in Subjects with Tardive Dyskinesia and Mood Disorder. Poster presented at the annual meeting of The College of Psychiatric and Neurologic Pharmacists; April 22-26, 2017; Phoenix, AZ.
3. Correll CU, et al. Efficacy of Valbenazine (NBI-98854) in Treating Subjects with Tardive Dyskinesia and Mood Disorders. Poster presented at the annual meeting of the American Psychiatric Association; May 20-24, 2017; San Diego, CA.
4. Josiassen RC, et al. Long-Term Safety and Tolerability of Valbenazine (NBI-98854) in Subjects with Tardive Dyskinesia and a Diagnosis of Schizophrenia or Mood Disorder. Poster presented at the annual meeting of the American Psychiatric Association; May 20-24, 2017; San Diego, CA.
5. Lindenmayer JP, et al. Long-Term Valbenazine Treatment in Patients with Schizophrenia/Schizoaffective Disorder or Mood Disorder and Tardive Dyskinesia. Poster presented at the annual meeting of the American Psychiatric Association; May 5-9, 2018; New York, NY.
6. Grigoriadis D, et al. Long-Term Effects of Valbenazine on Tardive Dyskinesia in Patients with Schizophrenia/Schizoaffective Disorder or Mood Disorder: Results from an Open-Label, Rollover Study. Poster presented at the American College of Neuropsychopharmacology annual meeting; December 9-13, 2018; Hollywood, FL.

Enclosures:

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

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C. Correll CU, et al. Long-Term Effects of Valbenazine (NBI-98854) in Subjects with Tardive Dyskinesia and Mood Disorder. Poster presented at the annual meeting of The College of Psychiatric and Neurologic Pharmacists; April 22-26, 2017; Phoenix, AZ.
D. Correll CU, et al. Efficacy of Valbenazine (NBI-98854) in Treating Subjects with Tardive Dyskinesia and Mood Disorders. Poster presented at the annual meeting of the American Psychiatric Association; May 20-24, 2017; San Diego, CA.
E. Josiassen RC, et al. Long-Term Safety and Tolerability of Valbenazine (NBI-98854) in Subjects with Tardive Dyskinesia and a Diagnosis of Schizophrenia or Mood Disorder. Poster presented at the annual meeting of the American Psychiatric Association; May 20-24, 2017; San Diego, CA.
F. Lindenmayer JP, et al. Long-Term Valbenazine Treatment in Patients with Schizophrenia/Schizoaffective Disorder or Mood Disorder and Tardive Dyskinesia. Poster presented at the annual meeting of the American Psychiatric Association; May 5-9, 2018; New York, NY.
G. Grigoriadis D, et al. Long-Term Effects of Valbenazine on Tardive Dyskinesia in Patients with Schizophrenia/Schizoaffective Disorder or Mood Disorder: Results from an Open-Label, Rollover Study. Poster presented at the American College of Neuropsychopharmacology annual meeting; December 9-13, 2018; Hollywood, FL.