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Schizophrenia or Schizoaffective Disorder and 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 long-term use of INGREZZA and INGREZZA SPRINKLE in adult patients with tardive dyskinesia and schizophrenia or schizoaffective 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 valbenazine (VBZ) in participants with tardive dyskinesia and schizophrenia/schizoaffective disorder (SZD) was evaluated in multiple studies. Please refer to the brief summaries of the results below.

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

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

In participants with SZD (n=100), baseline TD severity (as measured by the Abnormal Involuntary Movement Scale [AIMS] mean scores by blinded central raters) were 8.8 and 10.1, respectively, for the VBZ 40 and 80 mg/day dose groups. At Week 48, AIMS mean score changes from the DBPC baseline were -2.5 and -4.2, respectively, for the VBZ 40 and 80 mg/day dose groups. The mean AIMS score changes from baseline at Week 52 (during the 4-week period following discontinuation of VBZ) were -0.8 and -1.0 for the 40 and 80 mg/day dose groups, respectively. At Week 48, the mean Clinical Global Impression of Change-Tardive Dyskinesia (CGI-TD) scores were 2.4 and 2.2, respectively, for the VBZ 40 and 80 mg/day groups. The mean CGI-TD scores at Week 52 increased to 3.3 and 3.4 for the VBZ 40 and 80 mg/day groups, respectively.[2,3]

In the pooled long-term safety data, the three most commonly reported TEAEs for the SZD subgroup (n=309) were urinary tract infections (6.1%), headache (5.8%) and somnolence (5.2%). Mean psychiatric scales scores (Positive and Negative Syndrome Scale, PANSS; and Calgary Depression Scale for Schizophrenia, CDSS) generally remained stable in participants with TD and SZD during long-term VBZ 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 VBZ in adults with TD. Participants received a starting dose of once-daily VBZ 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 VBZ]) and by the investigator or site rater (at each study visit).[5]

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Data from KINECT 4 were analyzed post-hoc to evaluate the long-term effects of VBZ in adults with TD and SZD. In the SZD group (n=119), baseline TD severity (as measured by the AIMS mean scores by site raters) were 14.4 and 14.7, respectively, for the VBZ 40 and 80 mg/day dose groups. At Week 48, AIMS mean score changes from baseline were -10.1 and -10.7, respectively, for the VBZ 40 and 80 mg/day dose groups. The AIMS mean score change from baseline to Week 52 (end of drug-free period), were -5.1 and -3.8 for the VBZ 40 and 80 mg/day dose groups, respectively.[5]

Within the SZD subgroup, 18% of participants discontinued due to TEAEs. No TEAEs were reported in ≥10% of participants in the SZD subgroup. Psychiatric status remained stable from baseline to Week 48: PANSS positive, -0.7; PANSS negative, -0.6; CDSS, -0.7. 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), 95.7% of the SZD 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 VBZ became commercially available. All rollover study participants received once-daily VBZ 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 VBZ in adults with TD and SZD (n=104). The percentage of participants in the SZD group with a Clinical Global Impression of Severity-TD (CGIS-TD) score ≤2 ("normal, not at all ill" or "borderline ill"; assessed by site raters) at baseline were 8.7% (n=2/23) and 14.7% (n=11/75) for the VBZ 40 mg and 80mg/day groups, respectively. At Week 48, the percentage of participants with a CGIS-TD score ≤2 was as follows: VBZ 40mg: 37.5% (n=3/8); VBZ 80 mg: 60.9%(n=14/23).[6]

During treatment initiation (40 mg for 4 weeks), 6.7% of all SZD participants had any TEAE. No SZD participants discontinued due to a TEAE. Based on available C-SSRS data, 99.0% (n=102/103) of the SZD subgroup continued to have no emergence of suicidal ideation at any time during the rollover study (C-SSRS score=0). 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:

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1. INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc.
2. Kane JM, et al. Long-Term Effects of Valbenazine (NBI-98854) in Subjects with Tardive Dyskinesia and Schizophrenia or Schizoaffective Disorder. Poster presented at the annual meeting of The College of Psychiatric and Neurologic Pharmacists; April 22-26, 2017; Phoenix, AZ.
3. Kane JM, et al. Efficacy of Valbenazine (NBI-98854) in Treating Subjects with Tardive Dyskinesia and Schizophrenia or Schizoaffective Disorder. 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.
C. Kane JM, et al. Long-Term Effects of Valbenazine (NBI-98854) in Subjects with Tardive Dyskinesia and Schizophrenia or Schizoaffective Disorder. Poster presented at the annual meeting of The College of Psychiatric and Neurologic Pharmacists; April 22-26, 2017; Phoenix, AZ.
D. Kane JM, et al. Efficacy of Valbenazine (NBI-98854) in Treating Subjects with Tardive Dyskinesia and Schizophrenia or Schizoaffective Disorder. 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.