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Depression and Suicidality in Patients with Tardive Dyskinesia on INGREZZA® (valbenazine) Capsules

Thank you for contacting Neurocrine Biosciences with your unsolicited Medical Information request regarding the potential effects of INGREZZA® (valbenazine) capsules on depression and suicidality in adults with tardive dyskinesia (TD).

INGREZZA is a vesicular monoamine transporter 2 (VMAT2) inhibitor indicated for the treatment of adults with tardive dyskinesia.[1]

Pooled Double-Blind Placebo (PBO)-Controlled Studies

Data were pooled from three 6-week, randomized, double-blind, placebo-controlled trials of once-daily valbenazine in adults with TD (2 Phase 2 and 1 Phase 3): KINECT (NCT01688037), KINECT 2 (NCT01733121), and KINECT 3 (NCT02274558), respectively. Outcomes of interest included treatment-emergent adverse events (TEAEs) related to depression or suicidality. Participants were assessed for depression using the Calgary Depression Scale for Schizophrenia (CDSS) in schizophrenia/ schizoaffective disorders and the Montgomery-Åsberg Depression Rating Scale (MADRS) in mood disorders. The Columbia-Suicide Severity Rating Scale (C-SSRS) was also evaluated to measure suicidal ideation and behavior. All outcomes were analyzed descriptively.[2]

The pooled safety data included 400 participants (80 mg, n=122; 40 mg, n=110; placebo [PBO], n=178). Over one-third of participants in each treatment group had a lifetime history of suicidal ideation or behavior at baseline (80 mg, 39.3%; 40 mg, 44.5%; PBO, 36.5%). The percentages of participants who reported depression (80 mg, 1.8%; 40 mg, 0%; placebo, 1.1%) or suicide ideation (80 mg, 0.9%; 40 mg, 3.6%; placebo, 2.2%) as TEAE were similar across all groups.[2]

Mean CDSS and MADRS total scores generally remained stable throughout treatment across all groups. The mean changes from baseline to Week 6 for CDSS total score were -0.6, -0.5 and -0.3 for the 80 mg, 40 mg and PBO groups, respectively. The mean changes from baseline to Week 6 for MADRS total score were -1.7, -0.2, 0.6 for the 80 mg, 40 mg, and PBO groups, respectively. With regards to C-SSRS scores, greater than 95% of participants with no suicidal ideation at baseline (C-SSRS score=0) had no emergence of suicidal ideation (C-SSRS score=1-5) during the double-blind treatment.[2]

Adverse reactions in the three placebo-controlled studies of 6-week duration reported at incidence rates of >2% and greater than placebo were somnolence (10.9% and 4.2%), anticholinergic effects (5.4% and 4.9%), balance disorders/falls (4.1% and 2.2%), headache (3.4% and 2.7%), akathisia (2.7% and 0.5%), vomiting (2.6% and 0.6%), nausea (2.3% and 2.1%) and arthralgia (2.3% and 0.5% for valbenazine and placebo, respectively).[1]

Long-Term Studies

Three randomized extension studies (KINECT [NCT01688037], KINECT 3 [NCT02274558], and KINECT 4 [NCT02405091]) were pooled to further evaluate the potential long-term effects (up to 48 weeks of treatment followed by a 4-week washout) of once-daily valbenazine on depression and suicidality in adults with TD. Four-hundred and twenty-seven participants (80 mg, n=230; 40 mg, n=197) were included in these analyses.[3]

In this pooled long-term extension analysis, the mean duration of valbenazine exposure in all participants was 204 days (± 119 days); median duration was 225 days (range, 1-356 days). Approximately 40% of participants had a lifetime history of suicidality at baseline (80 mg, 40.4%; 40 mg, 39.1%).[3]

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The percentages of participants who reported depression as a TEAE were 2.2% and 5.0% for the 80 mg and 40 mg groups, respectively. There were 4.8% and 4.5% of the participants who reported suicidal ideation as TEAE in the 80 mg and 40 mg groups, respectively. In addition, the mean CDSS and MADRS total scores generally remained stable during long-term valbenazine treatment. Mean changes from baseline to Week 48 for the CDSS total score were -0.4 in both the 80 mg and 40 mg groups. With regards to the MADRS total scores, the mean changes from baseline to Week 48 were -0.1 and 0.1 in the 80 mg and 40 mg groups, respectively.[3]

After 4 weeks of washout (weeks 48-52) the mean changes from baseline to Week 52 for the CDSS total scores were 0.4 for the 80 mg and -1.1 for the 40 mg. The mean changes from baseline to Week 52 for the MADRS total scores were -0.2 and 2.4 for the 80 mg and 40 mg groups, respectively.[3]

For a more complete description of these analyses, please see attached data presentations from the 2017 Neuroscience Educational Institute Annual Congress by Remington et al. and the 2016 American College of Neuropsychopharmacology Annual Meeting by Remington et al.

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. Remington G, et al. Effects of valbenazine on depression and suicidality in adults with tardive dyskinesia: pooled results of 3 double-blind placebo-controlled trials. Poster presented at the 2017 Neuroscience Education Institute; November 8-12, 2017; Colorado Springs, CO.
3. Remington G, et al. Safety and Tolerability of Valbenazine (NBI-98854) in subjects with Tardive Dyskinesia: Results of Long-Term Exposure Data from Three Studies. Poster presented at the 55th Annual Meeting of the American College of Neuropsychopharmacology; December 4-8, 2016; Hollywood, Florida.

Enclosures:

A. INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc.
B. Remington G, et al. Effects of valbenazine on depression and suicidality in adults with tardive dyskinesia: pooled results of 3 double-blind placebo-controlled trials. Poster presented at the 2017 Neuroscience Education Institute; November 8-12, 2017; Colorado Springs, CO.
C. Remington G, et al. Safety and Tolerability of Valbenazine (NBI-98854) in subjects with Tardive Dyskinesia: Results of Long-Term Exposure Data from Three Studies. Poster presented at the 55th Annual Meeting of the American College of Neuropsychopharmacology; December 4-8, 2016; Hollywood, Florida.