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INGREZZA® (valbenazine) capsules and Acute Dopamine Receptor Blocking Agent (DRBA)-Induced Movement Disorders

Thank you for contacting Neurocrine Biosciences with your unsolicited Medical Information request regarding INGREZZA and potential other DRBA-induced movement disorders.

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

The INGREZZA FDA-approved Full Prescribing Information states the following regarding parkinsonism:[1]

> **WARNING AND PRECAUTIONS**
>
> **Parkinsonism**
>
> INGREZZA may cause parkinsonism in patients with tardive dyskinesia. Parkinsonism has also been observed with other VMAT2 inhibitors. In the 3 placebo-controlled clinical studies in patients with tardive dyskinesia, the incidence of parkinson-like adverse events was 3% of patients treated with INGREZZA and <1% of placebo-treated patients. Postmarketing safety reports have described parkinson-like symptoms, some of which were severe and required hospitalization. In most cases, severe parkinsonism occurred within the first two weeks after starting or increasing the dose of INGREZZA. Associated symptoms have included falls, gait disturbances, tremor, drooling and hypokinesia. In cases in which follow-up clinical information was available, parkinson-like symptoms were reported to resolve following discontinuation of INGREZZA therapy. Reduce the dose or discontinue INGREZZA treatment in patients who develop clinically significant parkinson-like signs or symptoms.

Clinical Study Results – Parkinsonism

Data were pooled from 3 placebo controlled clinical trials (two Phase 2 studies – KINECT and KINECT 2; one Phase 3 study – KINECT 3) to assess changes in the Simpson-Angus Scale (SAS2) Global scores. The SAS is a 10-item scale used to assess drug-induced parkinsonism. Each item is rated on a 0-4 scale of increasing severity with definitions given for each item (e.g., gait, rigidity, tremor). The SAS Global scores were calculated as the mean of the scores of the 10 individual items comprising the scale. The SAS Global score mean values were assessed at each visit and summarized for the Phase 2/3 study pools.[3]
SAS Global scores were similar for participants in all treatment groups at baseline. Mean (SD) baseline scores were 0.3 (0.31) for valbenazine-treated participants (n=254) and 0.3 (0.31) for placebo participants (n=178). The mean (SD) change from baseline to Week 6 for SAS Global scores were -0.1 (0.19) for valbenazine treated participants and -0.1 (0.24) for participants receiving placebo.[3]

In addition, long-term data were pooled from 3 clinical trials (KINECT, KINECT 3 blinded Extension, and KINECT 4 open label study) to further evaluate the changes in the SAS Global scores. SAS scores were similar for participants in all valbenazine groups at baseline. The mean (SD) SAS Global score at baseline was 0.25 (0.301) for all valbenazine-treated participants (n=427). The mean (SD) change from baseline to Week 48 in the SAS Global score was -0.12 (0.292) for all valbenazine-treated participants.[3]

In the 3-placebo-controlled clinical studies (KINECT, KINECT 2 and KINECT 3), the preferred term of tremor was reported 2/254 of all participants who received valbenazine (<1%). Upon review of all potential preferred terms associated with the parkinson-like events, 7/254 participants (3%) who received valbenazine and 1/178 participant who received placebo (<1%) experienced an adverse event of special interest (AESI) of parkinsonism. Additional preferred terms associated with the parkinsonism AESI upon review of the Medical Dictionary for Regulatory Activities (MedDRA) standardized medical query (SMQ) were gait disturbance (3/254 valbenazine participants), drooling (2/254 valbenazine participants), and musculoskeletal stiffness (1/178 placebo participant). No participant discontinued due to these events in the studies; 1 participant in the valbenazine group had a dose reduction due to an AE of tremor. In most

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cases, severe parkinsonism occurred within the first two weeks after starting or increasing the dose of valbenazine.[3]

Clinical Study Results - Akathisia

Data were pooled from 3 placebo controlled clinical trials (two Phase 2 studies – KINECT and KINECT 2; one Phase 3 study – KINECT 3) to assess changes in the Barnes Akathisia Rating (BARS[4]) Total and Global scores during 6 week treatment. The BARS scale is administered by healthcare providers to assess the severity of drug-induced akathisia. The BARS total score is calculated as the sum of Items 1 through 3 of the BARS scale (1 objective and two subjective questions regarding akathisia; range: 0-3, with higher scores indicating a more severe rating). The BARS Global score (Item 4 of the BARS Scale; range 0-5, with higher scores indicating more severe akathisia) is a global clinical assessment of akathisia. The BARS Total score (sum ranging from 0-9) and Global score mean values were assessed at each visit and summarized for the Phase 2/3 study pools.[3]
At baseline, BARS Total scores were similar for participants in all treatment groups, with mean (SD) baseline values of 1.5 (1.88) for valbenazine-treated participants (n=254) and 1.6 (2.01) for participants receiving placebo (n=178). The BARS Global scores at baseline were also similar for participants in all treatment groups, with mean (SD) baseline values of 0.8 (0.96) for valbenazine-treated participants (n=254) and 0.7 (0.95) for participants receiving placebo (n=178). The mean (SD) change from baseline to Week 6 for BARS Total scores were -0.3 (1.72) for valbenazine-treated participants and -0.5 (1.63) for participants receiving placebo. Additionally, the mean (SD) change from baseline to Week 6 for BARS Global scores were -0.1 (0.87) for valbenazine-treated participants and -0.1 (0.76) for participants receiving placebo.[3]

In addition, long-term data were pooled from 3 clinical trials (KINECT, KINECT 3 blinded Extension, and KINECT 4 open label study) to further evaluate the changes in the BARS Total and Global scores with long-term (up to 48 weeks) valbenazine treatment in adults with TD. At baseline, the mean (SD) BARS Total score was 1.4 (1.79) for all valbenazine treated participants (n=427). The mean (SD) BARS Global score at baseline was 0.6 (0.86) for all valbenazine treated participants (n=427). The mean (SD) changes from baseline to Week 48 in BARS Total score (all valbenazine, -0.5 [1.71]) and Global score (all valbenazine, -0.2 [0.85]) generally appeared similar between treatment groups.[3]

Additionally, in the 3-placebo-controlled clinical studies (KINECT, KINECT 2 and KINECT 3), the preferred term of akathisia was reported in 6/254 (2.4%) of all participants taking valbenazine, and 1/178 (<1%) of participants who received placebo. Upon review of all potential preferred terms associated with the akathisia AESI using the MedDRA SMQ for akathisia, the incidence of the AESI in the pooled placebo-controlled clinical studies was 7/254 (3%) of all participants who received valbenazine (due to the inclusion of an event of restlessness in a participant who received valbenazine) and 1/178 (<1%) of participants who received placebo. The akathisia AESI category was associated with discontinuation in 1 participant and dose reduction in 1 participant in these studies, both treated with valbenazine.[3]

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. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl. 1970;212:11-19.
3. Data on file (VBZ-TD-0004). Neurocrine Biosciences, Inc.
4. Barnes TR. A rating scale for drug-induced akathisia. Br J Psychiatry. 1989;154:672-676.

Enclosures:

A. INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc.