(p) 877-641-3461 6027 Edgewood Bend Ct. San Diego, CA 92130
(f) 913-451-6409 http://www.neurocrinemedical.com/

# Drug-Induced Parkinsonism 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 INGREZZA and INGREZZA SPRINKLE and drug-induced parkinsonism in patients with tardive dyskinesia (TD).

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

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

**WARNING AND PRECAUTIONS**

**5.6 Parkinsonism**

INGREZZA and INGREZZA SPRINKLE may cause parkinsonism. 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.

In a placebo-controlled clinical study in patients with chorea associated with Huntington's disease, the incidence of parkinson-like adverse events was 4.7% in patients treated with INGREZZA and 0% in placebo-treated patients. Because rigidity can develop as part of the underlying disease process in Huntington's disease, it may be difficult to distinguish between potential drug-induced parkinsonism and progression of underlying Huntington's disease. Drug-induced parkinsonism has the potential to cause more functional disability than untreated chorea for some patients with Huntington's disease.

Postmarketing safety reports have described parkinson-like symptoms in patients taking INGREZZA for tardive dyskinesia, 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 or INGREZZA SPRINKLE treatment in patients who develop clinically significant parkinson-like signs or symptoms.

## Clinical Study Results:

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 the changes in the Simpson Angus Scale (SAS)[2] Global scores (range: 0-4) during 6 week treatment. 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 score is 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 (VBZ) 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 VBZ treated participants (n=222) and -0.1 (0.24) for participants receiving placebo (n=159).[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 VBZ groups at baseline. The mean (SD) SAS Global score at baseline was

(p) 877-641-3461 6027 Edgewood Bend Ct. San Diego, CA 92130
(f) 913-451-6409 http://www.neurocrinemedical.com/

0.25 (0.301) for all VBZ 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 VBZ treated participants (n=90).[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 VBZ (<1%). Upon review of all potential preferred terms associated with the parkinson-like events, 7/254 participants (3%) who received VBZ 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 VBZ participants), drooling (2/254 VBZ participants), and musculoskeletal stiffness (1/178 placebo participant). No participant discontinued due to these events in the studies; 1 participant in the VBZ group had a dose reduction due to an AE of tremor. In most cases, severe parkinsonism occurred within the first two weeks after starting or increasing the dose of VBZ.[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.

**Enclosures:**

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