

Effects of INGREZZA[®] (valbenazine) Capsules and INGREZZA[®] SPRINKLE (valbenazine) Capsules and Neuroleptic Malignant Syndrome

Thank you for contacting Neurocrine Biosciences with your unsolicited Medical Information request regarding the potential effects of INGREZZA and INGREZZA SPRINKLE and neuroleptic malignant syndrome (NMS).

INGREZZA and INGREZZA SPRINKLE are indicated in adults for the treatment of tardive dyskinesia (TD) and for the treatment of chorea associated with Huntington's disease (HD).¹

Please refer to the separately attached FDA-approved full Prescribing Information and the Important Safety Information, including a Boxed Warning.

The FDA-approved full Prescribing Information states the following:¹

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with drugs that reduce dopaminergic transmission. In the post-marketing setting, NMS has been reported in patients taking VMAT2 inhibitors, including INGREZZA. Clinicians should be alerted to the signs and symptoms associated with NMS. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria, rhabdomyolysis, and acute renal failure. The diagnosis of NMS can be complicated; other serious medical illness (e.g., pneumonia, systemic infection) and untreated or inadequately treated extrapyramidal disorders can present with similar signs and symptoms. Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include (1) immediate discontinuation of INGREZZA or INGREZZA SPRINKLE; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

Recurrence of NMS has been reported with resumption of drug therapy. If treatment with INGREZZA or INGREZZA SPRINKLE is needed after recovery from NMS, patients should be monitored for signs of recurrence.

Clinical Study Results:

In the Phase 3, double-blind placebo controlled (DBPC) study evaluating the use of valbenazine for chorea associated with HD (KINECT[®]-HD) and the DBPC study of valbenazine use in tardive dyskinesia (KINECT[®] 3) patients were excluded with a known history of NMS. NMS was not reported as an adverse event in the studies.^{2,3}

NMS Background and Literature Search:

NMS is a life-threatening syndrome associated with the use of dopamine-receptor antagonist medications or with rapid withdrawal of dopaminergic medications. NMS is listed as a warning and potential adverse reaction for neuroleptic medications and VMAT2 inhibitors (including valbenazine).^{1,4-6}

The incidence of NMS has been reported in 0.02% of patients who are treated with antipsychotics. Other medications that affect dopamine neurotransmission have also been implicated, including VMAT2

inhibitors.⁸ The pathophysiology of NMS is not completely understood, but sudden reduction in central dopaminergic activity due to a D2 receptor blockade or abrupt withdrawal of D2 receptor stimulation may account for most of the symptoms including fever, muscle rigidity, altered mental status, irregular pulse/blood pressure, tachycardia, diaphoresis, and irregular heartbeats.⁴

In 2020, a literature review was published which found 13 cases of possible NMS episodes in patients on VMAT2 inhibitors. Ten cases of tetrabenazine, 2 cases of reserpine, and 1 case with valbenazine.⁷ A separate case report in 2022 described a 58 year old woman on valbenazine and fluphenazine who presented with possible atypical NMS.⁸ Please refer to the references for more information.

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. Furr Stimming E, et al. Safety and efficacy of valbenazine for the treatment of chorea associated with Huntington's disease (KINECT-HD): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet Neurol.* 2023;22(6):494-504. doi: 10.1016/S1474-4422(23)00127-8.
3. Hauser R.A, et al. KINECT 3: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial of Valbenazine for Tardive Dyskinesia. *Am J Psychiatry.* 2017;174(5):476-484. doi:10.1176/appi.ajp.2017.16091037
4. Simon LS, et al. Neuroleptic Malignant Syndrome. [Updated 2023 Apr 24]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan
5. AUSTEDO [package Insert]. North Wales, PA: Teva Pharmaceuticals USA, Inc.
6. XENAZINE [package Insert]. Deerfield, IL: Lundbeck Pharmaceuticals, LLC.
7. Caroff SN. Risk of Neuroleptic Malignant Syndrome with Vesicular Monoamine Transporter Inhibitors. *Clin Psychopharmacol Neurosci.* 2020;18(2):322-326. doi: 10.9758/cpn.2020.18.2.322.
8. Vellanki KD, Scott SL, Nguyen DT, Gupta S, Carroll BT. Valbenazine, Fluphenazine, and Possible Neuroleptic Malignant Syndrome in a 58-Year-Old Woman. *J Clin Psychopharmacol.* 2022;42(4):421-422. doi: 10.1097/JCP.0000000000001569.

Enclosures:

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