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# Pharmacologic Characteristics of INGREZZA® (valbenazine) Capsules and INGREZZA® SPRINKLE (valbenazine) Capsules

Thank you for contacting Neurocrine Biosciences with your unsolicited Medical Information request regarding the pharmacologic characteristics of INGREZZA and INGREZZA SPRINKLE.

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]

Valbenazine is a novel, selective inhibitor of the vesicular monoamine transporter 2 (VMAT2), a transporter that regulates monoamine uptake from the cytoplasm to the synaptic vesicle for storage and release. Valbenazine is metabolized to form a single active metabolite, [+]-α-dihydrotetrabenazine ([+]-α-HTBZ, also known as NBI-98782 or R,R,R-HTBZ). Additionally, valbenazine is metabolized to form a mono-oxy metabolite, NBI-136110, and other minor metabolites.[1,2]

Valbenazine inhibits human VMAT2 (Ki ~ 150 nM) with no appreciable binding affinity for VMAT1 (Ki > 10 μM). [+]-α-HTBZ also binds with relatively high affinity to human VMAT2 (Ki ~ 3 nM). Valbenazine and [+]-α-HTBZ have no appreciable binding affinity (Ki > 5000 nM) for dopaminergic (including D2), serotonergic (including 5HT2B), adrenergic, histaminergic or muscarinic receptors.[1]

Using the two valbenazine doses that demonstrated efficacy in the Phase 3 trial of valbenazine in adults with TD (40 and 80 mg), along with the known pharmacokinetic properties of valbenazine and [+]-α-HTBZ, PET methods in nonhuman primates were applied to estimate VMAT2 target occupancy at therapeutic levels of valbenazine for TD treatment. Valbenazine is estimated to maintain a high VMAT2 occupancy throughout each 24-hour period as follows: 40 mg (73% to 82%), 60 mg (82% to 88%), and 80 mg (85% to 91%).[3]

Please refer to the following link to the article by Grigoriadis D, et al. for a more detailed description of the pharmacologic characteristics of valbenazine and its metabolites:
https://www.ncbi.nlm.nih.gov/pubmed/28404690

**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. Grigoriadis D, et al. Pharmacologic characterization of valbenazine (NBI-98854) and its metabolites. J Pharmacol Exp Ther. 2017 Jun;361(3):454-461.Epub 2017 Apr 12. https://www.ncbi.nlm.nih.gov/pubmed/28404690.
3. Terry-Lorenzo R, et al. VMAT2 Target Occupancy at Efficacious Doses of Valbenazine From Nonhuman Primate (NHP) Positron Emission Tomography (PET). Poster presented virtually at ACCP; September 13-17, 2021.

**Enclosures:**

A. INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc.
B. INGREZZA [Important Safety Information]. San Diego, CA: Neurocrine Biosciences, Inc.
C. Terry-Lorenzo R, et al. VMAT2 Target Occupancy at Efficacious Doses of Valbenazine From Nonhuman Primate (NHP) Positron Emission Tomography (PET). Poster presented virtually at ACCP; September 13-17, 2021.