

Effects of INGREZZA® (valbenazine) Capsules and INGREZZA® SPRINKLE (valbenazine) Capsules on the Pharmacokinetic Profile of Concomitant Drugs

Thank you for contacting Neurocrine Biosciences with your unsolicited Medical Information request regarding the effects of INGREZZA and INGREZZA SPRINKLE on the pharmacokinetic (PK) profile of concomitant drugs.

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 unique, highly selective vesicular monoamine transporter 2 (VMAT2) inhibitor that is metabolized to a single, active metabolite, [+] - α -dihydrotetraabenazine ([+] - α -HTBZ; also referred to as (2R,3R,11bR)-dihydrotetraabenazine or O desvalylvalbenazine), through the loss of L-valine by hydrolysis. The potential for valbenazine to affect the PK of concomitant medications was assessed through in vitro and clinical studies (Loewen 2017, enclosed):²

Results from in vitro studies:²

- Valbenazine and [+] - α -HTBZ were weak direct inhibitors of cytochrome P450 2D6 (CYP2D6), but half maximal inhibitory concentration (IC₅₀) values greatly exceeded typical therapeutic exposures; all other CYP IC₅₀ values were greater than 9600 ng/mL
- No time-dependent inhibition of CYP enzymes by valbenazine and [+] - α -HTBZ was observed
- Neither valbenazine nor [+] - α -HTBZ induced CYP enzyme activity
- Valbenazine was a weak inhibitor of P-glycoprotein (P-gp) transport (IC₅₀: 9950 ng/mL); but no other clinically-relevant effects of valbenazine or [+] - α -HTBZ on drug transporter activity were observed

Results from clinical studies:²

- Coadministration of valbenazine with midazolam (sensitive CYP3A4 substrate) did not affect midazolam PK
- Coadministration of valbenazine with digoxin (sensitive P-gp substrate) resulted in increased digoxin maximum concentration (C_{max}) and area under the curve (AUC), without impacting digoxin t_{1/2}

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. Loewen G, et al. Evaluation of Potential for Valbenazine to Elicit Drug Interactions. Poster presented at 57th Annual Meeting of the American Society of Clinical Psychopharmacology; May 29-June 2, 2017; Miami, FL.

Enclosures:

- A. INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc.
- B. INGREZZA [Important Safety Information]. San Diego, CA: Neurocrine Biosciences, Inc.
- C. Loewen G, et al. Evaluation of Potential for Valbenazine to Elicit Drug Interactions. Poster presented at 57th Annual Meeting of the American Society of Clinical Psychopharmacology; May 29-June 2, 2017; Miami, FL.