NEUROCRINE® BIOSCIENCES

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Effects of Concomitant Medications on Pharmacokinetics of INGREZZA® (valbenazine) Capsules

Thank you for contacting Neurocrine Biosciences with your unsolicited Medical Information request regarding the effects of concomitant medications on pharmacokinetics (PK) of valbenazine capsules.

INGREZZA® (valbenazine) capsules is 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-dihydrotetrabenazine ([+]-α-HTBZ; also referred to as (2R,3R,11bR)-dihydrotetrabenazine or O desvalylvalbenazine), through the loss of L-valine by hydrolysis. The potential for concomitant medications to affect valbenazine and [+]-α-HTBZ PK was assessed through in vitro and clinical studies (Loewen 2017, enclosed):[2]

Results from in vitro studies:[2]

- Valbenazine was primarily metabolized to [+]-α-HTBZ by non-cytochrome P450 (CYP)-mediated hydrolysis and to oxidative metabolites by CYP3A4
- [+]-α-HTBZ was primarily metabolized by CYP2D6 and CYP3A4
- Valbenazine and [+]-α-HTBZ were highly membrane permeable
- Valbenazine and [+]-α-HTBZ were not P-gp substrates

Results from clinical studies:[2]

- Coadministration of valbenazine with ketoconazole, a strong CYP3A4 inhibitor, resulted in increased peak (C_{max}) and overall (AUC) exposure to valbenazine and [+]-α-HTBZ
- Coadministration of valbenazine with rifampin, a potent CYP3A4 inducer, resulted in decreased peak and overall exposure to valbenazine and [+]-α-HTBZ
- Mean (±SD) dose-normalized valbenazine concentrations were similar (P=0.249) with (3.375±2.037 ng/mL/mg) or without (3.683±2.360 ng/mL/mg) concomitant CYP2D6 inhibitors
- Mean dose-normalized [+]-α-HTBZ concentrations were also similar (P=0.571) with (0.534±0.321 ng/mL/mg) or without (0.513±0.326 ng/mL/mg) concomitant CYP2D6 inhibitors

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