NEUROCRINE® BIOSCIENCES

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Drug-Drug Interactions with INGREZZA® (valbenazine) Capsules

Thank you for contacting Neurocrine Biosciences with your unsolicited Medical Information request regarding potential drug interactions when valbenazine is used concomitantly with other medications.

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]

Effect of Concomitant Medications on Pharmacokinetics (PK) of Valbenazine:

Valbenazine is converted to an 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

Effect of Valbenazine on PK of Concomitant Medications:

The potential for valbenazine to affect the PK of concomitant medications was assessed through *in vitro* and clinical studies (Loewen 2017, enclosed) [3]:

Results from *in vitro* studies[3]:

- 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 (IC_{50}: 9950 ng/mL); but no other clinically-relevant effects of valbenazine or [+]-α-HTBZ on drug transporter activity were observed

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Results from clinical studies[3]:

- 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 $t_{1/2}$

FDA-Approved Full Prescribing Information[1]

DRUG INTERACTIONS

Clinically Significant Drug Interactions with INGREZZA

Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Implication:	Concomitant use of INGREZZA with MAOIs may increase the concentration of monoamine neurotransmitters in synapses, potentially leading to increased risk of adverse reactions such as serotonin syndrome, or attenuated treatment effect of INGREZZA.
Prevention or Management:	Avoid concomitant use of INGREZZA with MAOIs, or within 14 days of discontinuing therapy with an MAOI.
Strong CYP3A4 Inhibitors	
Clinical Implication:	Concomitant use of INGREZZA with strong CYP3A4 inhibitors increased the exposure (C_{max} and AUC) to valbenazine and its active metabolite compared with the use of INGREZZA alone. Increased exposure of valbenazine and its active metabolite may increase the risk of exposure-related adverse reactions.
Prevention or Management:	Reduce INGREZZA dose when INGREZZA is coadministered with a strong CYP3A4 inhibitor.
Strong CYP2D6 Inhibitors	
Clinical Implication:	Concomitant use of INGREZZA with strong CYP2D6 inhibitors may increase the exposure (C_{max} and AUC) to valbenazine's active metabolite compared with the use of INGREZZA alone. Increased exposure of active metabolite may increase the risk of exposure-related adverse reactions.
Prevention or Management:	Reduce INGREZZA dose when INGREZZA is coadministered with a strong CYP2D6 inhibitor.
Strong CYP3A4 Inducers	
Clinical Implication:	Concomitant use of INGREZZA with a strong CYP3A4 inducer decreased the exposure of valbenazine and its active metabolite compared to the use of INGREZZA alone. Reduced exposure of valbenazine and its active metabolite may reduce efficacy.
Prevention or Management:	Concomitant use of strong CYP3A4 inducers with INGREZZA is not recommended.
Digoxin	
Clinical Implication:	Concomitant use of INGREZZA with digoxin increased digoxin levels because of inhibition of intestinal P-glycoprotein (P-gp).
Prevention or Management:	Digoxin concentrations should be monitored when co-administering INGREZZA with digoxin. Increased digoxin exposure may increase the risk of exposure related adverse reactions. Dosage adjustment of digoxin may be necessary.

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CLINICAL PHARMACOLOGY

Pharmacokinetics
In Vitro Drug Interactions
The results of in vitro studies suggest that valbenazine and [+]-α-HTBZ are unlikely to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1 or CYP3A4/5, or induce CYP1A2, CYP2B6 or CYP3A4/5 at clinically relevant concentrations.

The results of in vitro studies suggest that valbenazine and [+]-α-HTBZ are unlikely to inhibit the transporters (BCRP, OAT1, OAT3, OCT2, OATP1B1, or OATP1B3) at clinically relevant concentrations.

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.
3. 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. 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.
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.