(p) 877-641-3461
(f) 913-451-6409
12780 El Camino Real San Diego, CA 92130
http://www.neurocrinemedical.com/

Dosing of INGREZZA® (valbenazine) Capsules in Known CYP2D6 Poor Metabolizers

Thank you for contacting Neurocrine Biosciences with your unsolicited Medical Information request regarding dosing of valbenazine in known CYP2D6 poor metabolizers.

INGREZZA® (valbenazine) capsules is indicated in adults for the treatment of tardive dyskinesia and for the treatment of chorea associated with Huntington's disease.[1]

The INGREZZA Full Prescribing Information states the following[1]:

DOSAGE AND ADMINISTRATION

2.3 Dosage Recommendations for Known CYP2D6 Poor Metabolizers

The recommended dosage for known CYP2D6 poor metabolizers is INGREZZA 40 mg once daily.

WARNINGS AND PRECAUTIONS

5.4 QT Prolongation

INGREZZA may prolong the QT interval, although the degree of QT prolongation is not clinically significant at concentrations expected with recommended dosing. In patients taking a strong CYP2D6 or CYP3A4 inhibitor, or who are CYP2D6 poor metabolizers, INGREZZA concentrations may be higher and QT prolongation clinically significant. For patients who are CYP2D6 poor metabolizers or are taking a strong CYP2D6 inhibitor, dose reduction may be necessary. For patients taking a strong CYP3A4 inhibitor, reduce the dose of INGREZZA to 40 mg once daily. INGREZZA should be avoided in patients with congenital long QT syndrome or with arrhythmias associated with a prolonged QT interval. For patients at increased risk of a prolonged QT interval, assess the QT interval before increasing the dosage.

USE IN SPECIFIC POPULATIONS

8.6 CYP2D6 Poor Metabolizers

Dosage reduction of INGREZZA is recommended for known CYP2D6 poor metabolizers. Increased exposure (C_{max} and AUC) to valbenazine's active metabolite was observed in CYP2D6 poor metabolizers. Increased exposure of active metabolite may increase the risk of exposure-related adverse reactions.

CLINICAL PHARMACOLOGY

12.5 Pharmacogenomics

CYP2D6 metabolizes the active metabolite of valbenazine ([+]-α-HTBZ). The gene encoding CYP2D6 has polymorphisms that impact protein function. CYP2D6 poor metabolizers are individuals with two nonfunctioning alleles, resulting in no enzyme activity.

Pharmacokinetic data from CYP2D6 poor metabolizers (n=25) treated with valbenazine demonstrate an approximate 2-fold higher AUC_{inf} and a 1.8-fold higher C_{max}, of ([+]-α-HTBZ) compared to normal metabolizers. Dosage reduction is recommended in CYP2D6 poor metabolizers.

In a clinical study, AUC of [+]-α-HTBZ was 22% higher and C_{max} was 9% lower in intermediate metabolizers (n=7) as compared to normal metabolizers (n=11), which is not considered clinically relevant. The effects of ultrarapid metabolizer status on the pharmacokinetics of [+]-α-HTBZ have not been studied.

Approximately 7% of White populations, 2% of Asian populations, and 2% of African-American populations are poor metabolizers.

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.

Reference:

1. INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc.

Enclosure:

A. INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc.