CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

209241Orig1s016

Trade Name:	INGREZZA
Generic or Proper Name:	(valbenazine)
Sponsor:	Neurocrine Bioscience Inc.
Approval Date:	April 09, 2020
Indication:	INGREZZA is a vesicular monoamine transporter 2 (VMAT2) inhibitor indicated for the treatment of adults with tardive dyskinesia.

CENTER FOR DRUG EVALUATION AND RESEARCH

209241Orig1s016

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APPROVAL LETTER

NDA 209241/S-016

SUPPLEMENT APPROVAL/
FULFILLMENT OF POSTMARKETING REQUIREMENTS

Neurocrine Biosciences, Inc.
Attention: Kristine Kim
Sr. Director, Regulatory Affairs
12780 El Camino Real
San Diego, CA 92130

Dear Ms. Kim:

Please refer to your supplemental new drug application (sNDA) dated and received August 29, 2019, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ingrezza (valbenazine) capsules.

This Prior Approval supplemental new drug application provides for revisions to Highlights, section 2 (Dosage and Administration), section 7 (Drug Interactions), section 8.6 (CYP2D6 Poor Metabolizers), section 8.8 (Renal Impairment), and section 12.3 (Pharmacokinetics) based upon results of your postmarketing requirement studies.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Patient Package Insert) with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

FULFILLMENT OF POSTMARKETING REQUIREMENTS

We have received your submissions dated August 17, 2018, and August 29, 2019, containing the final reports for the following postmarketing requirements listed in the April 11, 2017, approval letter.

3177-1 Conduct an in vitro study to assess the induction potential of NBI-136110 on CYP2B6 enzyme.

3177-2 Conduct a pharmacokinetic trial to quantify the impact of CYP2D6 inhibition on the exposures of the parent compound and major metabolites, either in the presence of a strong CYP2D6 inhibitor or in subjects who are CYP2D6 poor metabolizers (PMs).

3177-3 Conduct a pharmacokinetic trial to assess exposure differences of the parent compound and major metabolites in patients with severe renal impairment and matching subjects with normal renal function receiving the same dose."

We have reviewed your submissions and conclude that the above requirements were fulfilled.

We remind you that there are postmarketing commitments and a postmarketing requirement listed in the April 11, 2017, approval letter that are still open.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, email Simran Parihar, PharmD, at simran.parihar@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Tiffany R. Farchione, MD
Director (Acting)
Division of Psychiatry
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TIFFANY R FARCHIONE
04/09/2020 01:54:49 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209241Orig1s016

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use INGREZZA safely and effectively. See full prescribing information for INGREZZA.

INGREZZA® (valbenazine) capsules, for oral use
Initial U.S. Approval: 2017

----------RECENT MAJOR CHANGES----------

Dosage and Administration (2.3, 2.4)	04/2020
Warnings and Precautions (5.3)	07/2019

----------INDICATIONS AND USAGE----------
INGREZZA is a vesicular monoamine transporter 2 (VMAT2) inhibitor indicated for the treatment of adults with tardive dyskinesia. (1)

----------DOSAGE AND ADMINISTRATION----------
- The initial dosage is 40 mg once daily. After one week, increase the dose to the recommended dosage of 80 mg once daily. (2.1)
- Can be taken with or without food. (2.1)
- The recommended dosage for patients with moderate or severe hepatic impairment is 40 mg once daily. (2.2)
- The recommended dosage for known CYP2D6 poor metabolizers is 40 mg once daily. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
Capsules: 40 mg and 80 mg. (3)

----------CONTRAINDICATIONS----------
Known hypersensitivity to valbenazine or any components of INGREZZA. (4)

----------WARNINGS AND PRECAUTIONS----------
- Somnolence: May impair patient's ability to drive or operate hazardous machinery. (5.1)
- QT Prolongation: May cause an increase in QT interval. Avoid use in patients with congenital long QT syndrome or with arrhythmias associated with a prolonged QT interval. (5.2)
- Parkinsonism: Cases of parkinson-like symptoms, some of which were severe, have been reported in the postmarketing period. Reduce the dose or discontinue INGREZZA treatment in patients who develop clinically significant parkinson-like signs or symptoms. (5.3)

----------ADVERSE REACTIONS----------
Most common adverse reaction (≥5% and twice the rate of placebo): somnolence. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Neurocrine Biosciences, Inc. at 877-641-3461 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
Dose adjustments due to drug interactions (2.4, 7.1):

Factors	Dose Adjustments for INGREZZA
Use of MAOIs with INGREZZA	Avoid concomitant use with MAOIs.
Use of strong CYP3A4 inducers with INGREZZA	Concomitant use is not recommended.
Use of strong CYP3A4 inhibitors with INGREZZA	Recommended dosage is 40 mg once daily.
Use of strong CYP2D6 inhibitors with INGREZZA	Recommended dosage is 40 mg once daily.

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: May cause fetal harm. (8.1)
- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 04/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

INGREZZA is indicated for the treatment of adults with tardive dyskinesia *[see Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing and Administration Information

The initial dosage for INGREZZA is 40 mg once daily. After one week, increase the dose to the recommended dosage of 80 mg once daily. Continuation of 40 mg once daily may be considered for some patients.

Administer INGREZZA orally with or without food *[see Clinical Pharmacology (12.3)]*.

2.2 Dosage Recommendations for Patients with Hepatic Impairment

The recommended dosage for patients with moderate or severe hepatic impairment (Child-Pugh score 7 to 15) is INGREZZA 40 mg once daily *[see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]*.

2.3 Dosage Recommendations for Known CYP2D6 Poor Metabolizers

The recommended dosage for known CYP2D6 poor metabolizers is INGREZZA 40 mg once daily *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.

2.4 Dosage Recommendations for Concomitant Use with Strong CYP3A4 Inducers and Strong CYP3A4 or CYP2D6 Inhibitors

Coadministration with Strong CYP3A4 Inducers

Concomitant use of strong CYP3A4 inducers with INGREZZA is not recommended *[see Drug Interactions (7.1)]*.

Coadministration with Strong CYP3A4 Inhibitors

The recommended dosage for patients receiving strong CYP3A4 inhibitors is INGREZZA 40 mg once daily *[see Drug Interactions (7.1)]*.

Coadministration with Strong CYP2D6 Inhibitors

The recommended dosage for patients receiving strong CYP2D6 inhibitors is INGREZZA 40 mg once daily *[see Drug Interactions (7.1)]*.

3 DOSAGE FORMS AND STRENGTHS

INGREZZA capsules are available in the following strengths:

- 40 mg capsules with a white opaque body and purple cap, printed with ‘VBZ’ and ‘40’ in black ink.
- 80 mg capsules with a purple opaque body and cap, printed with ‘VBZ’ and ‘80’ in black ink.

4 CONTRAINDICATIONS

INGREZZA is contraindicated in patients with a history of hypersensitivity to valbenazine or any components of INGREZZA. Rash, urticaria, and reactions consistent with angioedema (e.g., swelling of the face, lips, and mouth) have been reported *[see Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Somnolence

INGREZZA can cause somnolence. Patients should not perform activities requiring mental alertness such as operating a motor vehicle or operating hazardous machinery until they know how they will be affected by INGREZZA *[see Adverse Reactions (6.1)]*.

5.2 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 *[see Clinical Pharmacology (12.2)]*. 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 *[see Dosage and Administration (2.3, 2.4)]*. 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.

5.3 Parkinsonism

INGREZZA may cause parkinsonism in patients with tardive dyskinesia. Parkinsonism has also been observed with other VMAT2 inhibitors. In the 3 placebo-controlled clinical studies in patients with tardive dyskinesia, the incidence of parkinson-like adverse events was 3% of patients treated with INGREZZA and <1% of placebo-treated patients. Postmarketing safety reports have described parkinson-like symptoms, some of which were severe and required hospitalization. In most cases, severe parkinsonism occurred within the first two weeks after starting or increasing the dose of INGREZZA. Associated symptoms have included falls, gait disturbances, tremor, drooling and hypokinesia. In cases in which follow-up clinical information was available, parkinson-like symptoms were reported to resolve following discontinuation of INGREZZA therapy. Reduce the dose or discontinue INGREZZA treatment in patients who develop clinically significant parkinson-like signs or symptoms.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Hypersensitivity *[see Contraindications (4)]*
- Somnolence *[see Warnings and Precautions (5.1)]*
- QT Prolongation *[see Warnings and Precautions (5.2)]*
- Parkinsonism *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Variable and Fixed Dose Placebo-Controlled Trial Experience

The safety of INGREZZA was evaluated in 3 placebo-controlled studies, each 6 weeks in duration (fixed dose, dose escalation, dose reduction), including 445 patients. Patients were 26 to 84 years of age with moderate to severe tardive dyskinesia and had concurrent diagnoses of mood disorder (27%) or schizophrenia/ schizoaffective disorder (72%). The mean age was 56 years. Patients were 57% Caucasian, 39% African-American, and 4% other. With respect to ethnicity, 28% were Hispanic or Latino. All subjects continued previous stable regimens of antipsychotics; 85% and 27% of subjects, respectively, were taking atypical and typical antipsychotic medications at study entry.

Adverse Reactions Leading to Discontinuation of Treatment

A total of 3% of INGREZZA treated patients and 2% of placebo-treated patients discontinued because of adverse reactions.

Common Adverse Reactions

Adverse reactions that occurred in the 3 placebo-controlled studies at an incidence of ≥2% and greater than placebo are presented in Table 1.

Table 1: Adverse Reactions in 3 Placebo-Controlled Studies of 6-week Treatment Duration Reported at ≥2% and >Placebo

Adverse Reaction[1]	**INGREZZA (n=262) (%)**	**Placebo (n=183) (%)**
General Disorders		
Somnolence (somnolence, fatigue, sedation)	10.9%	4.2%
Nervous System Disorders		
Anticholinergic effects (dry mouth, constipation, disturbance in attention, vision blurred, urinary retention)	5.4%	4.9%
Balance disorders/fall (fall, gait disturbance, dizziness, balance disorder)	4.1%	2.2%
Headache	3.4%	2.7%
Akathisia (akathisia, restlessness)	2.7%	0.5%
Gastrointestinal Disorders		
Vomiting	2.6%	0.6%
Nausea	2.3%	2.1%
Musculoskeletal Disorders		
Arthralgia	2.3%	0.5%

[1] Within each adverse reaction category, the observed adverse reactions are listed in order of decreasing frequency.

Other Adverse Reactions Observed During the Premarketing Evaluation of INGREZZA

Other adverse reactions of ≥1% incidence and greater than placebo are shown below. The following list does not include adverse reactions: 1) already listed in previous tables or elsewhere in the labeling, 2) for which a drug cause was remote, 3) which were so general as to be uninformative, 4) which were not considered to have clinically significant implications, or 5) which occurred at a rate equal to or less than placebo.

Endocrine Disorders: blood glucose increased

General Disorders: weight increased

Infectious Disorders: respiratory infections

Neurologic Disorders: drooling, dyskinesia, extrapyramidal symptoms (non-akathisia)

Psychiatric Disorders: anxiety, insomnia

During controlled trials, there was a dose-related increase in prolactin. Additionally, there was a dose-related increase in alkaline phosphatase and bilirubin, suggesting a potential risk for cholestasis.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of INGREZZA that are not included in other sections of labeling. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders: hypersensitivity reactions (including allergic dermatitis, angioedema, pruritis, and urticaria)

Skin and Subcutaneous Tissue Disorders: rash

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with INGREZZA

Table 2: 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.
Examples:	isocarboxazid, phenelzine, selegiline
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 *[see Clinical Pharmacology (12.3)]*. Increased exposure of valbenazine and its active metabolite may increase the risk of exposure-related adverse reactions *[see Warnings and Precautions (5.2)]*.
Prevention or Management:	Reduce INGREZZA dose when INGREZZA is coadministered with a strong CYP3A4 inhibitor *[see Dosage and Administration (2.4)]*.
Examples:	itraconazole, ketoconazole, clarithromycin

Strong CYP2D6 Inhibitors	
Clinical Implication:	Concomitant use of INGREZZA with strong CYP2D6 inhibitors increased the exposure (C_{max} and AUC) to valbenazine's active metabolite compared with the use of INGREZZA alone *[see Clinical Pharmacology (12.3)]*. Increased exposure of active metabolite may increase the risk of exposure-related adverse reactions *[see Warnings and Precautions (5.2)]*.
Prevention or Management:	Reduce INGREZZA dose when INGREZZA is coadministered with a strong CYP2D6 inhibitor *[see Dosage and Administration (2.4)]*.
Examples:	paroxetine, fluoxetine, quinidine
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 *[see Clinical Pharmacology (12.3)]*.
Prevention or Management:	Concomitant use of strong CYP3A4 inducers with INGREZZA is not recommended *[see Dosage and Administration (2.3)]*.
Examples:	rifampin, carbamazepine, phenytoin, St. John's wort[1]
Digoxin	
Clinical Implication:	Concomitant use of INGREZZA with digoxin increased digoxin levels because of inhibition of intestinal P-glycoprotein (P-gp) *[see Clinical Pharmacology (12.3)]*.
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.

[1] The induction potency of St. John's wort may vary widely based on preparation.

7.2 Drugs Having No Clinically Important Interactions with INGREZZA

Dosage adjustment for INGREZZA is not necessary when used in combination with substrates of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, or CYP3A4/5 based on *in vitro* study results.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited available data on INGREZZA use in pregnant women are insufficient to inform a drug-associated risk. In animal reproductive studies, no malformations were observed when valbenazine was administered orally to rats and rabbits during the period of organogenesis at doses up to 1.8 or 24 times, respectively, the maximum recommended human dose (MRHD) of 80 mg/day based on mg/m^2 body surface area. However, administration of valbenazine to pregnant rats during organogenesis through lactation produced an increase in the number of stillborn pups and postnatal pup mortalities at doses <1 times the MRHD based on mg/m^2 *[see Data]*. Advise a pregnant woman of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage in the U.S. general population is 2 to 4% and 15 to 20% of clinically recognized pregnancies, respectively.

Data

Animal Data

Valbenazine was administered orally to pregnant rats during the period of organogenesis at 1, 5, and 15 mg/kg/day, which are approximately 0.1, 0.6, and 2 times the MRHD of 80 mg/day based on mg/m^2 body surface area. Valbenazine produced a significant decrease in maternal body weight gain at 0.6 and 2 times the MRHD of 80 mg/day based on mg/m^2. No adverse embryo fetal effects were produced when valbenazine was administered at doses up to 2 times the MRHD of 80 mg/day based on mg/m^2.

Valbenazine was administered orally to pregnant rabbits during the period of organogenesis at 20, 50, and 100 mg/kg/day, which are approximately 5, 12, and 24 times the MRHD of 80 mg/day based on mg/m^2. No malformations were observed at doses up to 24 times the MRHD of 80 mg/day based on mg/m^2. However, valbenazine produced a delay in fetal development (decreased fetal weights and delayed ossification) at 24 times the MRHD of 80 mg/day based on mg/m^2, likely secondary to maternal toxicity (decreased food intake and loss in body weight).

Valbenazine was administered orally to pregnant rats during the period of organogenesis through lactation (day 7 of gestation through day 20 postpartum) at 1, 3, and 10 mg/kg/day, which are approximately 0.1, 0.4, and 1.2 times the MRHD of 80 mg/day based on mg/m^2. Valbenazine produced an increase in the incidence of stillbirths and postnatal pup mortality at 0.4 and 1.2 times the MRHD of 80 mg/day based on mg/m^2. Valbenazine did not affect neurobehavioral function including learning and memory and had no effect on sexual maturation at doses <1 times the MRHD of 80 mg/day based on mg/m^2 (because of death in the majority of the high dose group (1.2 times the MRHD), these parameters were not assessed in this group).

8.2 Lactation

Risk Summary

There is no information regarding the presence of valbenazine or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. Valbenazine and its metabolites have been detected in rat milk at concentrations higher than in plasma following oral administration of valbenazine at doses 0.1 to 1.2 times the MRHD based on mg/m^2. Based on animal findings of increased perinatal mortality in exposed fetuses and pups, advise a woman not to breastfeed during treatment with INGREZZA and for 5 days after the final dose.

8.4 Pediatric Use

Safety and effectiveness of INGREZZA have not been established in pediatric patients.

8.5 Geriatric Use

No dose adjustment is required for elderly patients. In 3 randomized, placebo-controlled studies of INGREZZA, 16% were 65 years and older. The safety and effectiveness were similar in patients older than 65 years compared to younger patients.

8.6 CYP2D6 Poor Metabolizers

Dosage reduction of INGREZZA is recommended for known CYP2D6 poor metabolizers *[see Dosage and Administration (2.3)]*. Increased exposure (C_{max} and AUC) to valbenazine's active metabolite is anticipated in CYP2D6 poor metabolizers. Increased exposure of active metabolite may increase the risk of exposure-related adverse reactions *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

Dosage reduction of INGREZZA is recommended for patients with moderate or severe hepatic impairment *[see Dosage and Administration (2.2)]*. Patients with moderate to severe hepatic impairment (Child-Pugh score 7 to 15) had higher exposure of valbenazine and its active metabolite than patients with normal hepatic function *[see Clinical Pharmacology (12.3)]*.

8.8 Renal Impairment

Dosage adjustment is not necessary for patients with mild, moderate, or severe renal impairment. INGREZZA does not undergo primary renal clearance *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

10.1 Human Experience

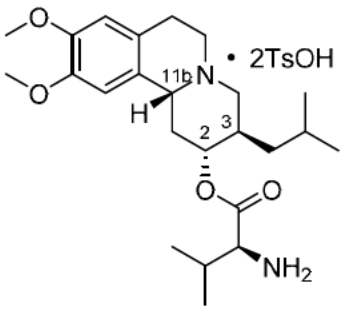
The pre-marketing clinical trials involving INGREZZA in approximately 850 subjects do not provide information regarding symptoms with overdose.

10.2 Management of Overdosage

No specific antidotes for INGREZZA are known. In managing overdose, provide supportive care, including close medical supervision and monitoring, and consider the possibility of multiple drug involvement. If an overdose occurs, consult a Certified Poison Control Center (1-800-222-1222 or www.poison.org).

11 DESCRIPTION

INGREZZA contains valbenazine, a vesicular monoamine transporter 2 (VMAT2) inhibitor, present as valbenazine tosylate salt, with the chemical name, L-Valine, (*2R,3R*,11b*R*)-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-3-(2-methylpropyl)-2*H*-benzo[*a*]quinolizin-2-yl ester, 4-methylbenzenesulfonate (1:2). Valbenazine tosylate is slightly soluble in water. Its molecular formula is $C_{38}H_{54}N_2O_{10}S_2$, and its molecular weight is 762.97 g/mol (ditosylate salt) with the following structure:



The molecular formula of valbenazine free base is $C_{24}H_{38}N_2O_4$ and its molecular weight is 418.57.

INGREZZA capsules are intended for oral administration only. Each capsule contains 73 mg or 146 mg of valbenazine tosylate equivalent to 40 mg or 80 mg of valbenazine free base, respectively. The capsule shells contain candurin silver fine, FD&C Blue#1, FD&C Red#40, and gelatin.

Table 3: Contents of INGREZZA

Presentation	Inactive Ingredients
INGREZZA 40 mg, Size 1 capsule	Colloidal silicon dioxide, magnesium stearate, mannitol, pregelatinized starch
INGREZZA 40 mg, Size 2 capsule INGREZZA 80 mg, Size 1 capsule	Hypromellose, isomalt, magnesium stearate, pregelatinized starch, and silicified microcrystalline cellulose

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of valbenazine in the treatment of tardive dyskinesia is unknown, but is thought to be mediated through the reversible inhibition of vesicular monoamine transporter 2 (VMAT2), a transporter that regulates monoamine uptake from the cytoplasm to the synaptic vesicle for storage and release.

12.2 Pharmacodynamics

Valbenazine inhibits human VMAT2 (Ki ~ 150 nM) with no appreciable binding affinity for VMAT1 (Ki > 10 μM). Valbenazine is converted to the active metabolite [+]-α-dihydrotetrabenazine ([+]-α-HTBZ). [+]-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.

Cardiac Electrophysiology

INGREZZA may cause an increase in the corrected QT interval in patients who are CYP2D6 poor metabolizers or who are taking a strong CYP2D6 or CYP3A4 inhibitor. An exposure-response analysis of clinical data from two healthy volunteer studies revealed increased QTc interval with higher plasma concentrations of the active metabolite. Based on this model, patients taking an INGREZZA 80 mg dose with increased exposure to the metabolite (e.g., being a CYP2D6 poor metabolizer) may have a mean QT prolongation of 11.7 msec (14.7 msec upper bound of double-sided 90% CI) as compared to otherwise healthy volunteers given INGREZZA, who had a mean QT prolongation of 6.7 msec (8.4 msec) *[see Warnings and Precautions (5.2)]*.

12.3 Pharmacokinetics

Valbenazine and its active metabolite ([+]-α-HTBZ) demonstrate approximate proportional increases for the area under the plasma concentration versus time curve (AUC) and maximum plasma concentration (C_{max}) after single oral doses from 40 mg to 300 mg (i.e., 50% to 375% of the recommended treatment dose).

Absorption

Following oral administration, the time to reach maximum valbenazine plasma concentration (t_{max}) ranges from 0.5 to 1.0 hours. Valbenazine reaches steady state plasma concentrations within 1 week. The absolute oral bioavailability of valbenazine is approximately 49%. [+]-α-HTBZ gradually forms and reaches C_{max} 4 to 8 hours after administration of INGREZZA.

Ingestion of a high-fat meal decreases valbenazine C_{max} by approximately 47% and AUC by approximately 13%. [+]-α-HTBZ C_{max} and AUC are unaffected.

Distribution

The plasma protein binding of valbenazine and [+]-α-HTBZ are greater than 99% and approximately 64%, respectively. The mean steady state volume of distribution of valbenazine is 92 L.

Nonclinical data in Long-Evans rats show that valbenazine can bind to melanin-containing structures of the eye such as the uveal tract. The relevance of this observation to clinical use of INGREZZA is unknown.

Elimination

Valbenazine has a mean total plasma systemic clearance value of 7.2 L/hr. Valbenazine and [+]-α-HTBZ have half-lives of 15 to 22 hours.

Metabolism

Valbenazine is extensively metabolized after oral administration by hydrolysis of the valine ester to form the active metabolite ([+]-α-HTBZ) and by oxidative metabolism, primarily by CYP3A4/5, to form mono-oxidized valbenazine and other minor metabolites. [+]-α-HTBZ appears to be further metabolized in part by CYP2D6.

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.

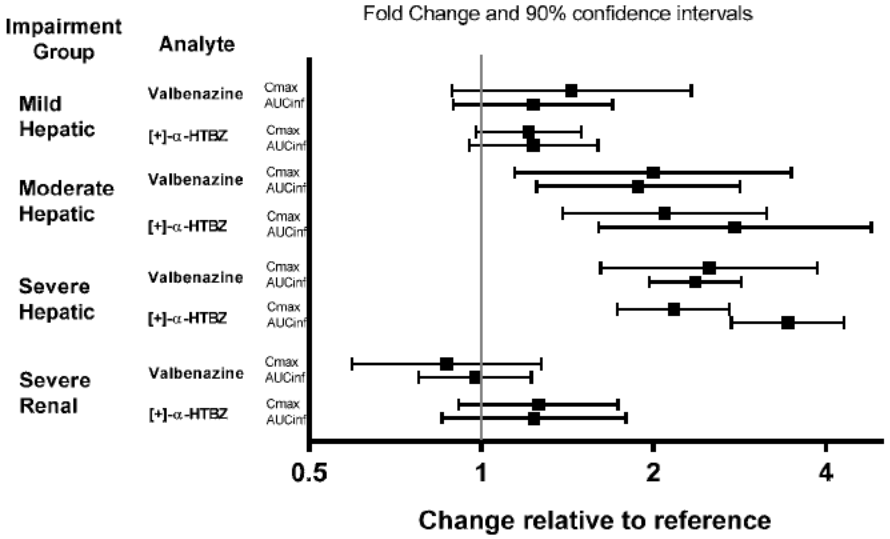
Excretion

Following the administration of a single 50-mg oral dose of radiolabeled C-valbenazine (i.e., ~63% of the recommended treatment dose), approximately 60% and 30% of the administered radioactivity was recovered in the urine and feces, respectively. Less than 2% was excreted as unchanged valbenazine or [+]-α-HTBZ in either urine or feces.

Studies in Specific Populations

Exposures of valbenazine in patients with hepatic and severe renal impairment are summarized in Figure 1.

Figure 1: Effects of Hepatic and Severe Renal Impairment on Valbenazine Pharmacokinetics



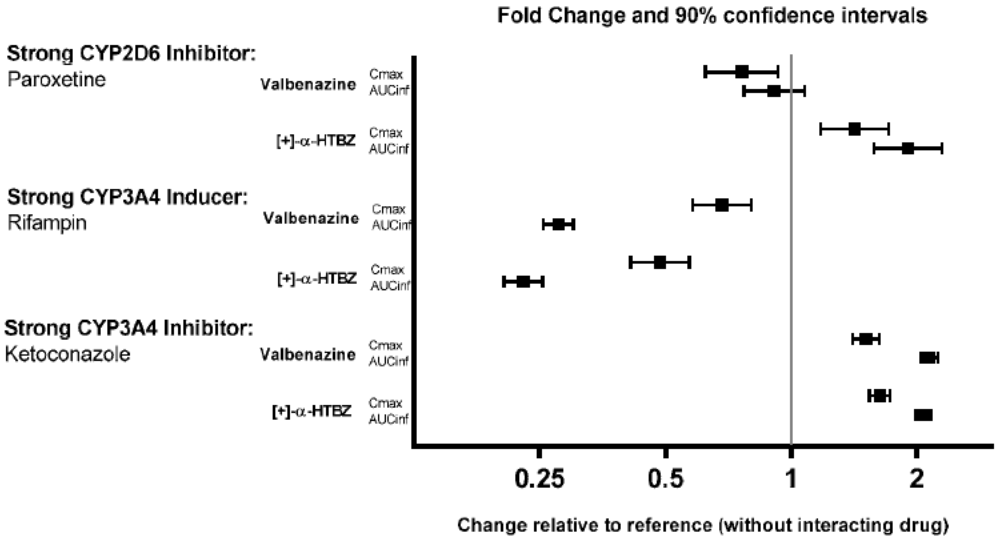
AUC_{inf}=area under the plasma concentration versus time curve from 0 hours extrapolated to infinity

[+]-α-HTBZ=[+]-α-dihydrotetrabenazine (active metabolite)

Drug Interaction Studies

The effects of paroxetine, ketoconazole and rifampin on the exposure of valbenazine are summarized in Figure 2.

Figure 2: Effects of Strong CYP2D6 and CYP3A4 Inhibitors and CYP3A4 Inducers on Valbenazine Pharmacokinetics

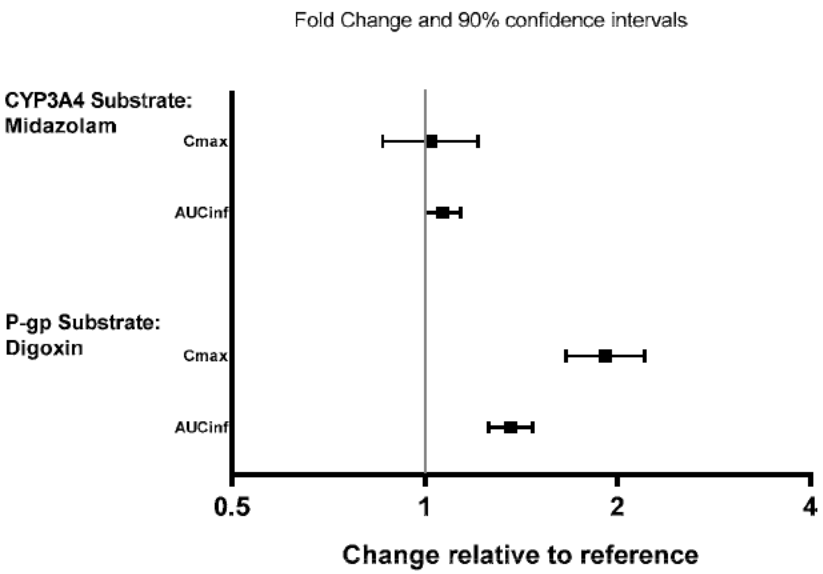


AUC_{inf}=area under the plasma concentration versus time curve from 0 hours extrapolated to infinity

[+]-α-HTBZ=[+]-α-dihydrotetrabenazine (active metabolite)

The effects of valbenazine on the exposure of other coadministered drugs are summarized in Figure 3.

Figure 3: Effects of Valbenazine on Pharmacokinetics of Other Drugs



AUC_{inf}=area under the plasma concentration versus time curve from 0 hours extrapolated to infinity

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Valbenazine did not increase tumors in rats treated orally for 91 weeks at 0.5, 1, and 2 mg/kg/day. These doses are <1 times (0.06, 0.1, and 0.24 times, respectively) the MRHD of 80 mg/day based on mg/m^2.

Valbenazine did not increase tumors in hemizygous Tg.rasH2 mice treated orally for 26 weeks at 10, 30 and 75 mg/kg/day, which are 0.6, 1.9 and 4.6 times the MRHD of 80 mg/day based on mg/m^2.

Mutagenesis

Valbenazine was not mutagenic in the *in vitro* bacterial reverse mutation test (Ames) or clastogenic in the *in vitro* mammalian chromosomal aberrations assay in human peripheral blood lymphocytes or in the *in vivo* rat bone marrow micronucleus assay.

Impairment of Fertility

In a fertility study, rats were treated orally with valbenazine at 1, 3, and 10 mg/kg/day prior to mating and through mating, for a minimum of 10 weeks (males) or through Day 7 of gestation (females). These doses are 0.1, 0.4, and 1.2 times the MRHD of 80 mg/day based on mg/m^2, respectively. Valbenazine delayed mating in both sexes, which led to lower number of pregnancies and disrupted estrous cyclicity at the high dose, 1.2 times the MRHD of 80 mg/day based on mg/m^2. Valbenazine had no effects on sperm parameters (motility, count, density) or on uterine parameters (corpora lutea, number of implants, viable implants, pre-implantation loss, early resorptions and post-implantation loss) at any dose.

14 CLINICAL STUDIES

A randomized, double-blind, placebo-controlled trial of INGREZZA was conducted in patients with moderate to severe tardive dyskinesia as determined by clinical observation. Patients had underlying schizophrenia, schizoaffective disorder, or a mood disorder. Individuals at significant risk for suicidal or violent behavior and individuals with unstable psychiatric symptoms were excluded.

The Abnormal Involuntary Movement Scale (AIMS) was the primary efficacy measure for the assessment of tardive dyskinesia severity. The AIMS is a 12-item scale; items 1 to 7 assess the severity of involuntary movements across body regions and these items were used in this study. Each of the 7 items was scored on a 0 to 4 scale, rated as: 0=no dyskinesia; 1=low amplitude, present during some but not most of the exam; 2=low amplitude and present during most of the exam (or moderate amplitude and present during some of the exam); 3=moderate amplitude and present during most of exam; or 4=maximal amplitude and present during most of exam. The AIMS dyskinesia total score (sum of items 1 to 7) could thus range from 0 to 28, with a decrease in score indicating improvement. The AIMS was scored by central raters who interpreted the videos blinded to subject identification, treatment assignment, and visit number.

The primary efficacy endpoint was the mean change from baseline in the AIMS dyskinesia total score at the end of Week 6. The change from baseline for two fixed doses of INGREZZA (40 mg or 80 mg) was compared to placebo. At the end of Week 6, subjects initially assigned to placebo were re-randomized to receive INGREZZA 40 mg or 80 mg. Subjects originally randomized to INGREZZA continued INGREZZA at their randomized dose. Follow-up was continued through Week 48 on the assigned drug, followed by a 4-week period off-drug (subjects were not blind to withdrawal).

A total of 234 subjects were enrolled, with 29 (12%) discontinuing prior to completion of the placebo-controlled period. Mean age was 56 (range 26 to 84). Patients were 54% male and 46% female. Patients were 57% Caucasian, 38% African-American, and 5% other. Concurrent diagnoses included schizophrenia/schizoaffective disorder (66%) and mood disorder (34%). With respect to concurrent antipsychotic use, 70% of subjects were receiving atypical antipsychotics, 14% were receiving typical or combination antipsychotics, and 16% were not receiving antipsychotics.

Results are presented in Table 4, with the distribution of responses shown in Figure 4. The change from baseline in the AIMS total dyskinesia score in the 80 mg INGREZZA group was statistically significantly different from the change in the placebo group. Subgroup analyses by gender, age, racial subgroup, underlying psychiatric diagnostic category, and concomitant antipsychotic medication did not suggest any clear evidence of differential responsiveness.

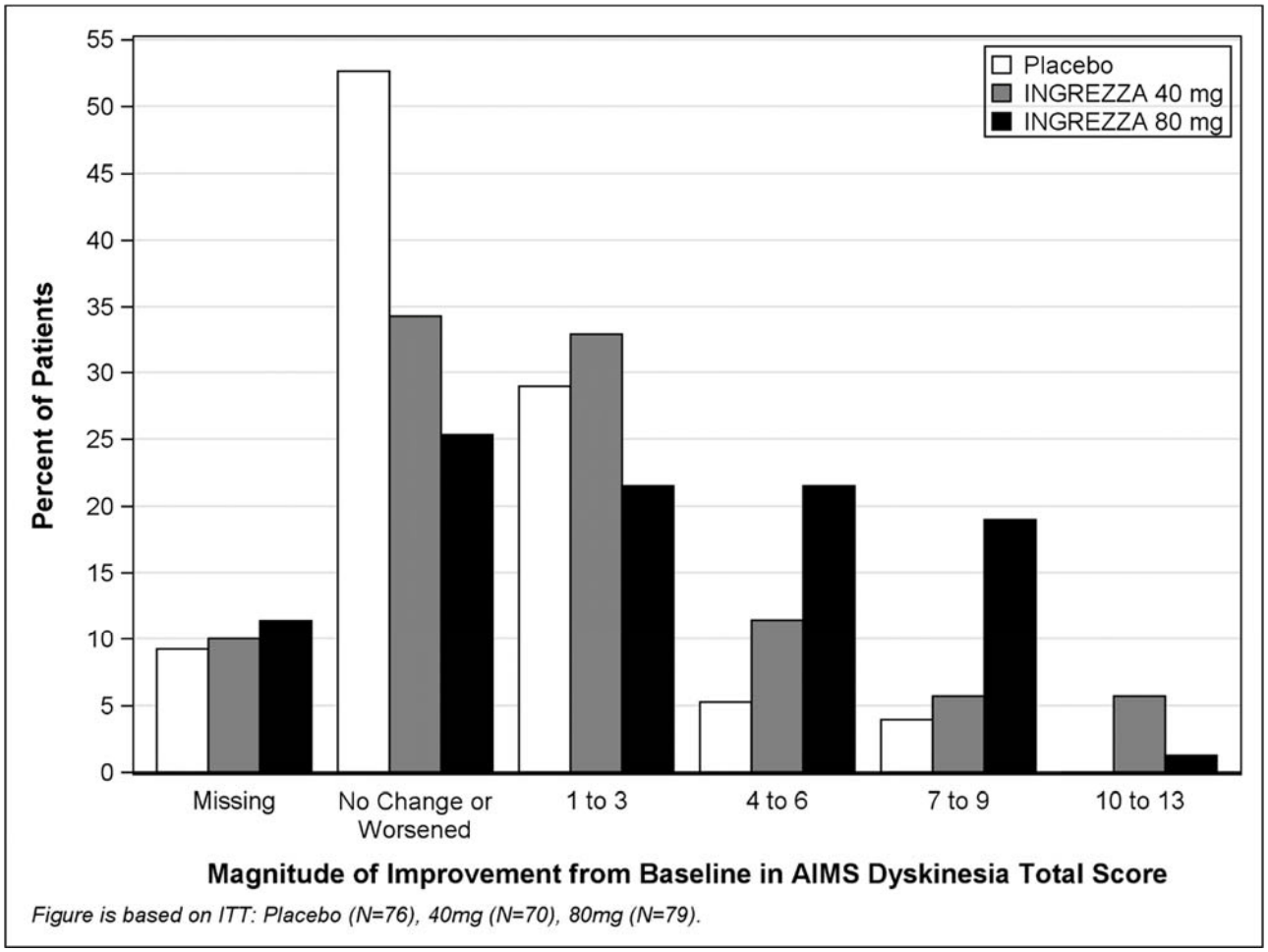
The mean changes in the AIMS dyskinesia total score by visit are shown in Figure 5. Among subjects remaining in the study at the end of the 48-week treatment (N=123 [52.6%]), following discontinuation of INGREZZA, the mean AIMS dyskinesia total score appeared to return toward baseline (there was no formal hypothesis testing for the change following discontinuation).

Table 4: Primary Efficacy Endpoint – Severity of Tardive Dyskinesia at Baseline and the End of Week 6

Endpoint	Treatment Group	Mean Baseline Score (SD)	LS Mean Change from Baseline (SEM)**	Placebo-subtracted Difference (95% CI)
AIMS Dyskinesia Total Score	INGREZZA 40 mg	9.8 (4.1)	-1.9 (0.4)	-1.8 (-3.0, -0.7)
	INGREZZA 80 mg*	10.4 (3.6)	-3.2 (0.4)	-3.1 (-4.2, -2.0)
	Placebo	9.9 (4.3)	-0.1 (0.4)	

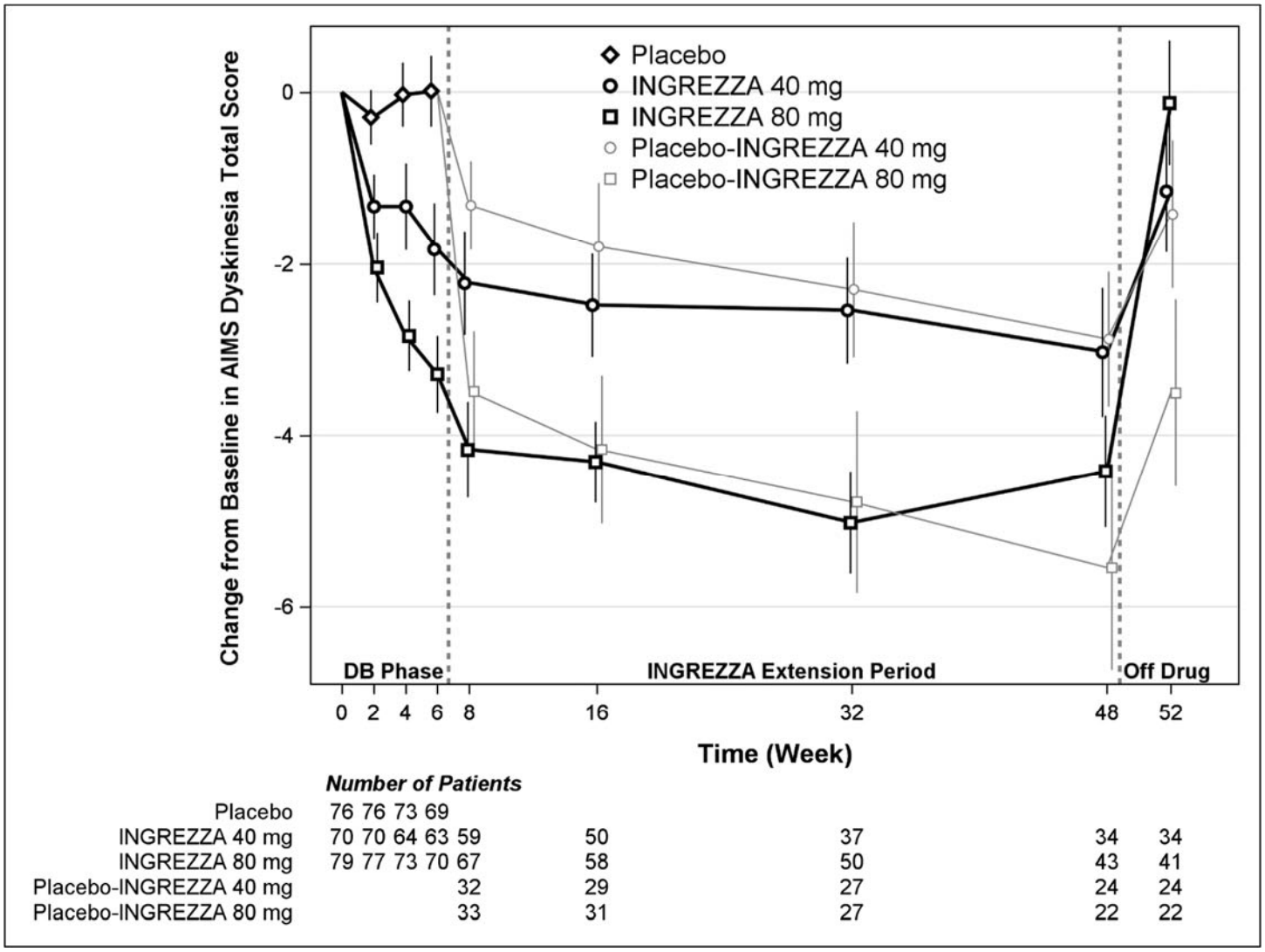
LS Mean=least-squares mean; SD=standard deviation; SEM=standard error of the mean; CI=2-sided 95% confidence interval
*Dose that was statistically significantly different from placebo after adjusting for multiplicity.
**A negative change from baseline indicates improvement.

Figure 4: Percent of Patients with Specified Magnitude of AIMS Total Score Improvement at the End of Week 6



ITT=Intent to Treat; This analysis set includes all randomized patients who had a baseline and at least one post-baseline AIMS dyskinesia total score value reported.

Figure 5: AIMS Dyskinesia Total Score Mean Change from Baseline – Entire Study Duration (Arithmetic Mean)



DB=Double-Blind; After Week 6, subjects initially receiving placebo were re-randomized to receive INGREZZA 40 mg or 80 mg until the end of Week 48. Error bars represent ±1 Standard Error of the Mean (SEM).

16 HOW SUPPLIED/STORAGE AND HANDLING

INGREZZA (valbenazine) capsules are available as:

40 mg Capsule: White opaque body with a purple cap, printed with 'VBZ' and '40' in black ink.

80 mg Capsule: Purple opaque body and cap, printed with 'VBZ' and '80' in black ink.

Package Configuration	Capsule Strength	NDC Number
Bottle of 30	40 mg (Size 1)	NDC 70370-1040-1
Bottle of 30	40 mg (Size 2)	NDC 70370-2040-1
Bottle of 30	80 mg	NDC 70370-1080-1
Bottle of 90	40 mg	NDC 70370-1040-2
4-week Initiation Pack	28-day blister pack containing: 7 x 40 mg (Size 1) and 21 x 80 mg	NDC 70370-1048-6
4-week Initiation Pack	28-day blister pack containing: 7 x 40 mg (Size 2) and 21 x 80 mg	NDC 70370-2048-6

Storage

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). See USP Controlled Room Temperature.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Somnolence
Inform patients that INGREZZA may cause somnolence and may impair the ability to perform tasks that require complex motor and mental skills. Advise patients that until they learn how they respond to INGREZZA, they should be careful or avoid doing activities that require them to be alert, such as driving a car or operating machinery *[see Warnings and Precautions (5.1)]*.

Prolongation of the QT Interval
Inform patients to consult their physician immediately if they feel faint, lose consciousness, or have heart palpitations *[see Warnings and Precautions (5.2)]*. Advise patients to inform physicians that they are taking INGREZZA before any new drug is taken.

Parkinsonism
Inform patients that parkinson-like symptoms may occur while taking INGREZZA. Advise patients to consult their healthcare provider if they experience difficulty moving or loss of ability to move muscles voluntarily, tremor, gait disturbances, or drooling *[see Warnings and Precautions (5.3)]*.

Pregnancy
Advise a pregnant patient of the potential risk to a fetus *[see Use in Specific Populations (8.1)]*.

Lactation
Advise a woman not to breastfeed during treatment with INGREZZA and for 5 days after the final dose *[see Use in Specific Populations (8.2)]*.

For further information on INGREZZA, call 84-INGREZZA (844-647-3992).

Distributed by:
Neurocrine Biosciences, Inc.
San Diego, CA 92130

INGREZZA is a registered trademark of Neurocrine Biosciences, Inc.

PATIENT INFORMATION
INGREZZA® (in greh' zah)
(valbenazine)
capsules

What is INGREZZA?

INGREZZA is a prescription medicine used to treat adults with movements in the face, tongue, or other body parts that cannot be controlled (tardive dyskinesia).

It is not known if INGREZZA is safe and effective in children.

Do not take INGREZZA if you:

- are allergic to valbenazine, or any of the ingredients in INGREZZA. See the end of this Patient Information leaflet for a complete list of ingredients in INGREZZA.

Before taking INGREZZA, tell your healthcare provider about all of your medical conditions including if you:

- have liver problems
- have heart disease that is not stable, have heart failure or recently had a heart attack
- have an irregular heart rhythm or heartbeat (QT prolongation, heart arrhythmia)
- are pregnant or plan to become pregnant. INGREZZA may harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if INGREZZA passes into your breast milk. Do not breastfeed during treatment with INGREZZA and for 5 days after the final dose. Talk to your healthcare provider about the best way to feed your baby during treatment with INGREZZA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements.

Taking INGREZZA with certain other medicines may cause serious side effects. **Do not start any new medicines while taking INGREZZA without talking to your healthcare provider first.**

How should I take INGREZZA?

- Take INGREZZA exactly as your healthcare provider tells you to. Your healthcare provider will tell you how much INGREZZA to take and when to take it.
- Do not stop taking INGREZZA without talking to your healthcare provider first.
- INGREZZA can be taken with or without food.
- If you take too much INGREZZA, call your poison control center at 1-800-222-1222.

What are the possible side effects of INGREZZA?

INGREZZA may cause serious side effects, including:

- **Sleepiness (somnolence).** Do not drive, operate heavy machinery, or do other dangerous activities until you know how INGREZZA affects you.
- **Heart rhythm problems (QT prolongation).** INGREZZA may cause a heart problem known as QT prolongation.
  Symptoms of QT prolongation may include:
  - fast, slow, or irregular heartbeat
  - dizziness or fainting
  - shortness of breath
- **Parkinsonism.** Symptoms include: shaking, body stiffness, trouble moving or walking, or keeping your balance

Tell your healthcare provider right away if you have a change in your heartbeat (a fast or irregular heartbeat), or if you faint.

The most common side effect of INGREZZA is sleepiness (somnolence).

Other common side effects include:

- changes in balance (balance problems, dizziness) or an increased risk of falls
- dry mouth
- headache
- constipation
- feelings of restlessness
- blurred vision

These are not all of the possible side effects of INGREZZA. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store INGREZZA?

- Store INGREZZA at room temperature between 68°F to 77°F (20°C to 25°C).

Keep INGREZZA and all medicines out of the reach of children.

General information about the safe and effective use of INGREZZA

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use INGREZZA for a condition for which it was not prescribed. Do not give INGREZZA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about INGREZZA that is written for healthcare professionals.

What are the ingredients in INGREZZA?

Active ingredient: valbenazine
Inactive ingredients: 40 mg capsule: colloidal silicon dioxide, magnesium stearate, mannitol, and pregelatinized starch; 80 mg capsule: hypromellose, isomalt, magnesium stearate, pregelatinized starch, and silicified microcrystalline cellulose. The capsule shells contain candurin silver fine, FD&C Blue#1, FD&C Red#40, and gelatin.
Distributed by: Neurocrine Biosciences, Inc., San Diego, CA 92130, U.S.A
For more information, go to www.INGREZZA.com or call 84-INGREZZA (844-647-3992).

This Patient Information has been approved by the U.S. Food and Drug Administration Revised 7/2019

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209241Orig1s016

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA	209241 S016
Link to EDR	\\CDSESUB1\evsprod\nda209241\0383\m5
Submission Date	8/29/2019, 8/17/2018
Submission Type	Prior Approval Labeling Supplement, PMR and PMC reports
Brand Name	Ingrezza®
Dosage Form and Strength	40 mg and 80 mg Capsules
Route of Administration	Oral
Indication	Treatment of Tardive Dyskinesia
Applicant	Neurocrine Biosciences
OCP Review Team	Kofi A. Kumi, Ph.D., Luning (Ada) Zhuang, Ph.D.
OCP Final Signatory	Luning (Ada) Zhuang, Ph.D.

Executive Summary

Ingrezza (Valbenazine) is a vesicular monoamine transporter 2 (VMAT2) inhibitor that is approved for the treatment of tardive dyskinesia. A Post Marketing Commitment (PMC) 3177-1 and Post Marketing Requirements (PMR) 3177-2 and 3177-3 were included in the approval letter. PMC-3177-1 committed the sponsor to "Conduct an in vitro study to assess the induction potential of NBI-136110 on CYP2B6". PMR-3177-2 required the sponsor to "Conduct a pharmacokinetic trial to quantify the impact of CYP2D6 inhibition on the exposures of the parent compound and major metabolites, either in the presence of a strong CYP2D6 inhibitor or in subjects who are CYP2D6 poor metabolizers (PMs)." PMR-3177-3 required the sponsor to "Conduct a pharmacokinetic trial to assess exposure differences of the parent compound and major metabolites in patients with severe renal impairment and matching subjects with normal renal function receiving the same dose.". The sponsor has submitted the results of the studies to fulfill the PMC and PMRs and requests the label be updated to reflect the findings in the studies. This is the clinical pharmacology review and findings of the PMRs and PMC.

The clinical Pharmacology findings are summarized below

PMC 3177-1

In vitro studies indicated that treatment with NBI-136110, a metabolite, caused little or no increases in CYP2B6 activity. NBI-136110 caused little or no increase in CYP2B6 mRNA expression that has the potential to be clinically significant. Therefore, this suggests that NBI-136110 does not have the potential to cause clinically relevant induction of CYP2B6.

PMR 3177-2

Valbenazine

The AUC and Cmax of Valbenazine was about 10% and 24% lower, respectively after administration of Valbenazine with Paroxetine compared to Valbenazine alone. This decrease in exposure is not expected to be clinically meaningful.

Median (range) Tmax after administration of Valbenazine with paroxetine compared to Valbenazine alone were 0.5 (0.5, 2) hours and 0.64 (0.5, 1) hours, respectively.

Mean (± SD) T ½ after administration of Valbenazine with paroxetine compared to Valbenazine alone were 19 (4.3) and 18 (3.1) hours, respectively.

NBI-98782 (Active metabolite)

The AUC and Cmax of the major active metabolite (NBI-98782) increased by about 90% and 42%, respectively when Valbenazine is given with paroxetine compared to when Valbenazine is administered alone. Dose reduction is recommended since NBI-98782 is an active metabolite that contributes substantially to the pharmacological activity of Valbenazine.

Median (range) Tmax for NBI-98782 was about 8 (4, 18) and 4 (3, 12) hours, respectively when Valbenazine is given with paroxetine or when Valbenazine is given alone.

Mean (±SD) T ½ for NBI-98782 were 24 (4.1) and 21 (4.6), respectively after administration Valbenazine with paroxetine or Valbenazine alone.

NBI-136100 (Metabolite)
There was no significant effect on the metabolite NB1-136100 when valbenazine was administered with paroxetine or alone.

PMR 3177-3

Valbenazine

Exposure (AUC) of Valbenazine were similar when Valbenazine was administered to patients with normal and severe renal function. Cmax was about 13% lower but is not expected to be clinically meaningful.

Median (range) Tmax for valbenazine were 0.5 (0.5, 1.0) and 0.75 (0.50, 1.0) hours for normal and severe renal impairment, respectively. This is not expected to be clinically meaningful.

Mean (±SD) T ½ for valbenazine were 21 (4.5) and 22 (5.5) hours for normal and severe renal impairment, respectively.

NBI-98782

Exposures (AUC and Cmax) of NBI-9872 increased by about 23-25%. This increase is not expected to be clinically significant.

Median (range) Tmax of NBI-9872 were 6 (4,8) and 6 (4,12) hours for normal and severe renal impaired patients, respectively.

Mean (SD) T ½ of NBI-9872 were 25 (6) and 28 (7.1) hours for normal and severe renal impaired patients, respectively.

Recommendation

The office of Clinical Pharmacology (OCP) has reviewed the studies submitted in fulfilment of PMC-3177-1, PMR-3177-2 and PMR-3177-3 and concludes that the sponsor has met its obligations for the Clinical Pharmacology PMC and PMRs. It is recommended the labeling for Valbenazine be updated to include the following recommendations.

Summary of Labeling Recommendations

Section 2.3

CYP2D6 Poor Metabolizers

The recommended dosage of Ingrezza for known CYP2D6 poor metabolizers is 40 mg once daily

Section 2.4

Coadministration with Strong CYP2D6 Inhibitors

The recommended dosage of Ingrezza for patients receiving strong CYP2D6 inhibitors is 40 mg once daily

Section 7

Strong CYP2D6 Inhibitors	
Clinical Implication:	Concomitant use of INGREZZA with strong CYP2D6 inhibitors increased the exposure (C_{max} and AUC) to valbenazine's active metabolite compared with the use of INGREZZA alone *[see Clinical Pharmacology (12.3)]*. Increased exposure of active metabolite may increase the risk of exposure-related adverse reactions *[see Warnings and Precautions (5.2)]*.
Prevention or Management:	(b) (4) Reduce INGREZZA dose (b) (4) (b) (4) when INGREZZA is coadministered with a strong CYP2D6 inhibitor *[see Dosage and Administration (2.(b) (4))]*.
Examples:	paroxetine, fluoxetine, quinidine

Section 8.6

CYP2D6 Poor Metabolizers

Reduce Ingrezza dose based on tolerability for known CYP2D6 poor metabolizers [see Dosage and Administration (2.3)].

Section 8.8

Dosage adjustment is not necessary for patients with mild, moderate, or severe renal impairment. INGREZZA does not undergo primary renal clearance.

Summary of Clinical Pharmacology Assessment

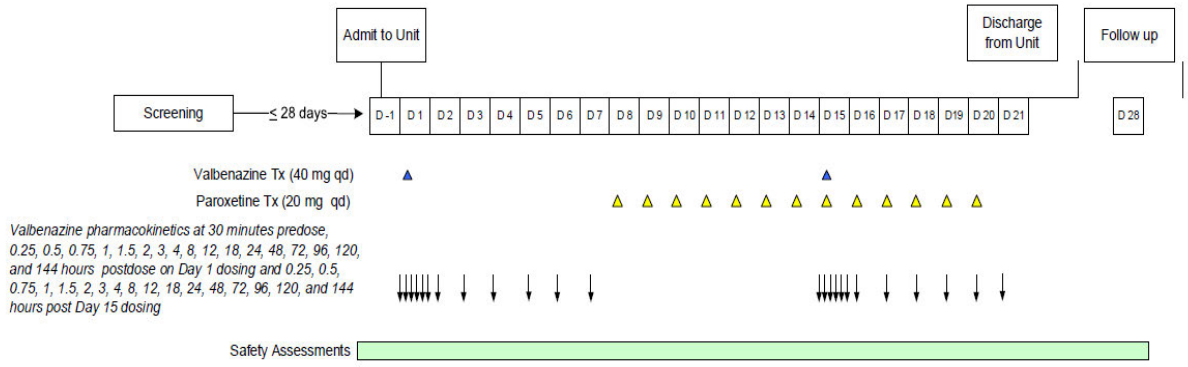
PMR-3177-2

Title (Protocol NBI-98854-1703): A Phase 1, Open-Label, One-Sequence Crossover Study to Assess the Effect of Paroxetine, a Strong CYP2D6 Inhibitor, on the Pharmacokinetics of Valbenazine in Healthy Subjects

Objectives: 1) To evaluate and compare the pharmacokinetics (PK) of valbenazine and its metabolites when valbenazine was administered alone and concomitantly with paroxetine, a strong cytochrome P450 (CYP) 2D6 inhibitor. 2) To evaluate the safety and tolerability of valbenazine when administered alone and concomitantly with paroxetine.

Study Design: This was a Phase 1, open-label, one-sequence crossover drug interaction study of valbenazine in 24 healthy male and female subjects. Subjects were required to fast overnight prior to dose administration. Subjects who had a CYP2D6 poor metabolizer genotype were not eligible for study participation. The study schematic of the study design is provided in following figure

Study Design Schematic



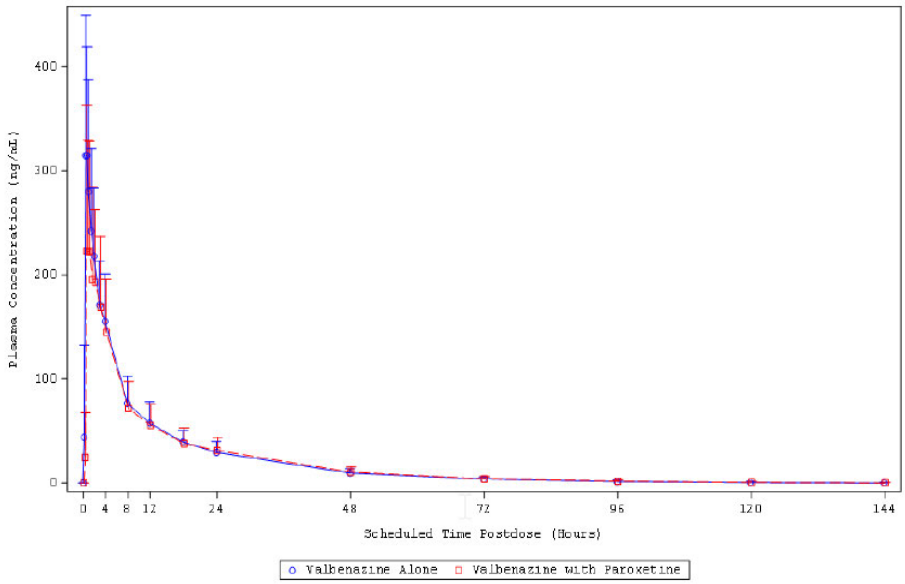
qd=once daily; Tx=treatment.

Bioanalytical Methods
Plasma samples were analyzed for valbenazine, and for metabolites NBI-98782 and NBI-136110. The concentrations of valbenazine, NBI-98782, and NBI-136110 were quantified in plasma samples according to validated methods using liquid chromatography mass spectrometry coupled to tandem mass spectrometry (LC-MS/MS). The mean precision (%CV) and accuracy (% bias) for quality control samples assayed with study samples ranged from 3.8% to 6.4% and 2.0% to 5.2%, respectively, for valbenazine, 4.3% to 7.6% and 3.7% to 5.2%, respectively, for NBI-98782, and 4.8% to 6.5% and 1.1% to 5.2%, respectively, for NBI-136110. Incurred sample reanalysis (ISR) was successfully conducted in this study for all 3 analytes. All analytical results were within acceptable limits and acceptable.

Results

Valbenazine

Figure 1 Mean (+SD) Valbenazine Plasma Concentration Versus Time – Treatment with Valbenazine Alone or in Combination with Paroxetine



Source: Applicant's report for study NBI-98854-1703, Page 34, Figure 2

Table 1 Summary of Valbenazine Pharmacokinetic Parameters

Parameter (unit)	**Statistic**	**Valbenazine Alone (N=24)**	**Valbenazine with Paroxetine (N=23)**
$AUC_{0\text{-}tlast}$ (ng×hr/mL)	Mean (SD) Geom CV(%)	2730 (829) 30.8	2590 (941) 55.7
$AUC_{0\text{-}\infty}$ (ng×hr/mL)	Mean (SD) Geom CV(%)	2770 (832) 30.5	2630 (943) 53.1
C_{max} (ng/mL)	Mean (SD) Geom CV(%)	357 (123) 37.8	280 (110) 62.4
t_{max} (hr)	Median (min, max)	0.64 (0.50, 1.0)	0.50 (0.50, 2.0)
T_{lag} (hr)	Mean (SD)	0.08 (0.12)	0.08 (0.14)
$t_{½}$ (hr)	Mean (SD) Geom CV(%)	18 (3.1) 19	19 (4.3) 24

Source: Applicant's report for study NBI-98854-1703, Page 35, Table 3

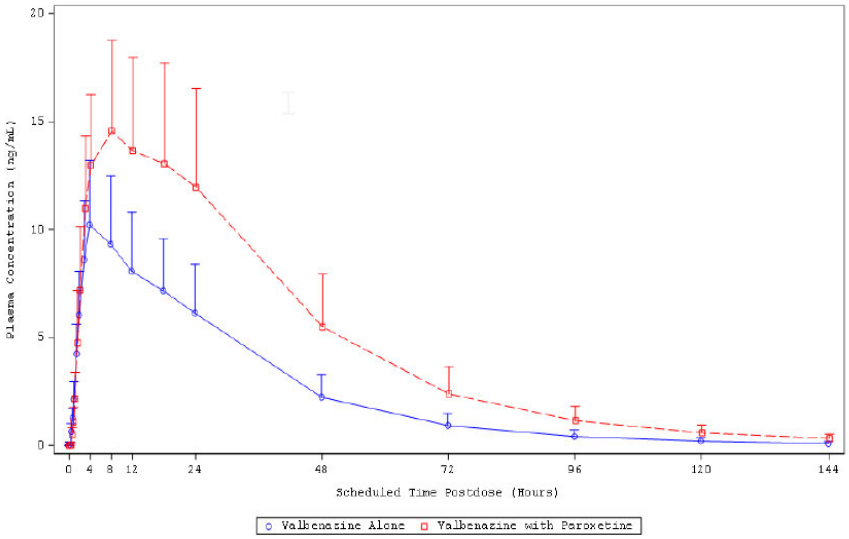
Table 2 Valbenazine Geometric Mean Ratios for Pharmacokinetic Exposure Parameters

Parameter (unit)	Ratio[a] (Valbenazine with paroxetine vs valbenazine alone)	90% CI[b]
$AUC_{0\text{-tlast}}$ (ng×hr/mL)	90.7%	(76.1%, 108.1%)
$AUC_{0\text{-}\infty}$ (ng×hr/mL)	91.1%	(77.1%, 107.8%)
C_{max} (ng/mL)	76.0%	(62.2%, 92.8%)

Source: Applicant's report for study NBI-98854-1703, Page 36, Table 4

NBI-98782 (active metabolite)

Figure 2 Mean (+SD) NBI-98782 Plasma Concentration Versus Time – Treatment with Valbenazine Alone or in Combination with Paroxetine



Source: Applicant's report for study NBI-98854-1703, Page 37, Figure 3

Table 3 Summary of NBI-98782 Pharmacokinetic Parameters

Parameter (unit)	Statistic	Valbenazine Alone (N=24)	Valbenazine with Paroxetine (N=23)
$AUC_{0\text{-tlast}}$ (ng×hr/mL)	Mean (SD) Geom CV(%)	345 (126) 33.4	670 (248) 46.4
$AUC_{0\text{-}\infty}$ (ng×hr/mL)	Mean (SD) Geom CV(%)	350 (128) 33.2	682 (253) 46.0
C_{max} (ng/mL)	Mean (SD) Geom CV(%)	10.5 (3.11) 28.5	15.2 (4.40) 44.5
t_{max} (hr)	Median (min, max)	4.0 (3.0, 12.0)	8.0 (4.0, 18.0)
T_{lag} (hr)	Mean (SD)	0.22 (0.08)	0.27 (0.15)
$t_{½}$ (hr)	Mean (SD) Geom CV(%)	21 (4.6) 23	24 (4.1) 18

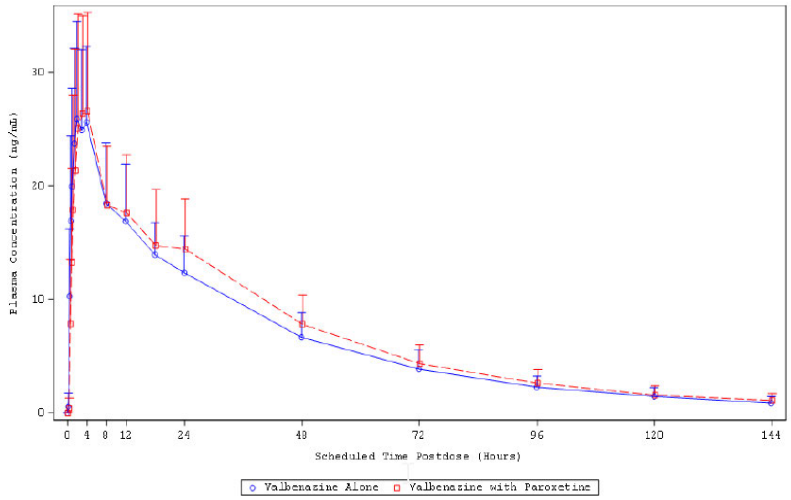
Source: Applicant's report for study NBI-98854-1703, Page 38, Table 5

Table 4 NBI-98782 Geometric Mean Ratios for Pharmacokinetic Exposure Parameters

Parameter (unit)	Ratio[a] (Valbenazine with paroxetine vs valbenazine alone)	90% CI[b]
$AUC_{0\text{-tlast}}$ (ng×hr/mL)	189.6%	(156.8%, 229.2%)
$AUC_{0\text{-}\infty}$ (ng×hr/mL)	190.2%	(157.6%, 229.5%)
C_{max} (ng/mL)	141.8%	(117.7%, 170.8%)

Source: Applicant's report for study NBI-98854-1703, Page 39, Table 6
NBI-136100 (metabolite)

Figure 3 Mean (+SD) NBI-136110 Plasma Concentration Versus Time – Treatment with Valbenazine Alone or in Combination with Paroxetine



Source: Applicant's report for study NBI-98854-1703, Page 10, Figure 4

Table 5 Summary of NBI-136110 Pharmacokinetic Parameters

Parameter (unit)	Statistic	Valbenazine Alone (N=24)	Valbenazine with Paroxetine (N=23)
$AUC_{0\text{-tlast}}$ (ng×hr/mL)	Mean (SD) Geom CV(%)	915 (247) 24.8	1000 (286) 43.3
$AUC_{0\text{-}\infty}$ (ng×hr/mL)	Mean (SD) Geom CV(%)	959 (278) 26.2	1060 (313) 43.0
C_{max} (ng/mL)	Mean (SD) Geom CV(%)	28.5 (7.98) 28.1	28.6 (9.33) 46.0
t_{max} (hr)	Median (min, max)	2.5 (1.5, 4.0)	3.0 (1.5, 4.0)
T_{lag} (hr)	Mean (SD)	0.17 (0.12)	0.16 (0.15)
$t_{½}$ (hr)	Mean (SD) Geom CV(%)	32 (6.1) 19	34 (6.9) 21

Source: Applicant's report for study NBI-98854-1703, Page 41, Table 7

Table 6 NBI-136110 Geometric Mean Ratios for Pharmacokinetic Exposure Parameters

Parameter (unit)	Ratio[a] (Valbenazine with paroxetine vs valbenazine alone)	90% CI[b]
$AUC_{0\text{-tlast}}$ (ng×hr/mL)	106.5%	(91.3%, 124.2%)
$AUC_{0\text{-}\infty}$ (ng×hr/mL)	107.5%	(92.6%, 124.9%)
C_{max} (ng/mL)	97.7%	(82.4%, 115.7%)

Source: Applicant's report for study NBI-98854-1703, Page 42, Table 8 Summary of Results

Compared with administration of valbenazine alone, concomitant administration of valbenazine and paroxetine had minimal effect on valbenazine clearance. Concomitant administration of valbenazine and paroxetine led to about 90% increase in AUC0-∞ and AUC0-tlast of the active metabolite NBI-98782 compared with administration of valbenazine alone. Treatment with valbenazine plus paroxetine had no effect on NBI-136110 (inactive metabolite) PK.
The sponsor reported that overall Valbenazine was well tolerated in healthy subjects when administered alone or concomitantly with paroxetine. There were no deaths or serious AEs reported during the study. Overall, 14 (58.3%) subjects experienced at least 1 TEAE. The most common TEAEs overall were nausea (25%) and somnolence (16.7%). TEAEs were more commonly observed during treatment period 2 (on or after the first dose of paroxetine but prior to the Day 17 dose of valbenazine) than during either treatment period 1 (on or after the first dose of valbenazine but prior to the first dose of paroxetine) or treatment period 3 (on or after the Day 17 dose of valbenazine).

Reviewer comment: No clinically significant effect on exposures of valbenazine and NBI-136110 by coadministration of Valbenazine with Paroxetine compared to Valbenazine alone. However, clinically significant increase in exposure to the active metabolite, NBI-98782, was observed, therefore, dose reduction to ½ the recommended dose is recommended.

PMR 3177-3

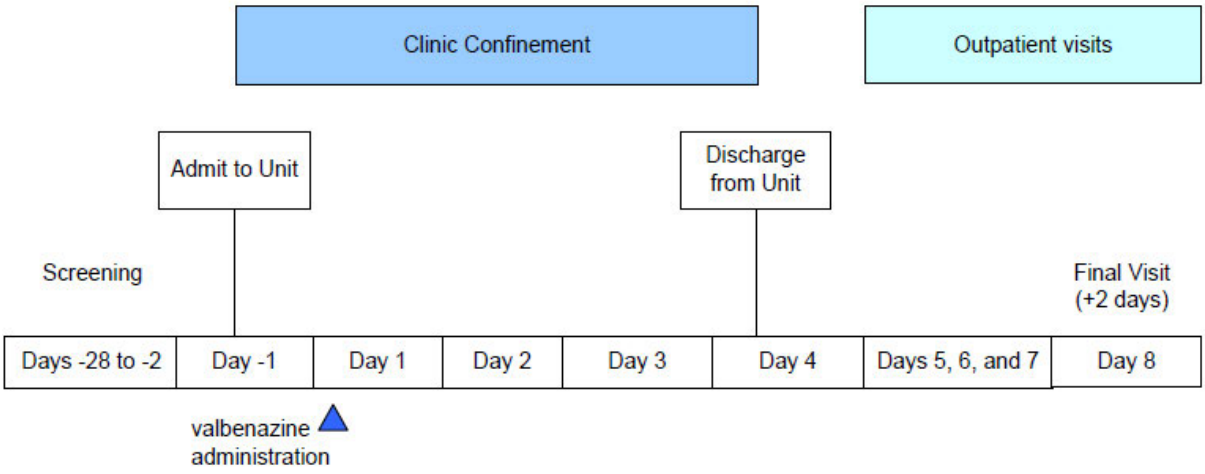
Title (NBI-98854-1701): A Phase 1 Study to Evaluate the Safety and Pharmacokinetics of a Single Dose of Valbenazine (NBI-98854) in Subjects with Normal Renal Function and Severe Renal Impairment.

Objectives: 1) To assess the pharmacokinetics (PK) of valbenazine and its metabolites following oral administration of a single 40 mg dose in subjects with severe renal impairment compared to subjects with normal renal function. 2) To evaluate the safety and tolerability of valbenazine following oral administration of a single 40 mg dose in subjects with severe renal impairment and in subjects with normal renal function.

Study Design: This was a Phase 1, single-dose, open-label study. Approximately 16 male and female subjects aged 18 to 80 years who met the eligibility criteria were enrolled. The estimated glomerular filtration rate (eGFR) was used to categorize the degree of renal function/impairment for assignment of subjects to the normal renal function group and the severe renal impairment group. Subjects were genotyped at screening to determine their cytochrome P450 (CYP) 2D6 status. Subjects who had a CYP2D6 poor metabolizer genotype were not eligible for study

participation. Subjects received a single dose of valbenazine 40 mg after having fasted for at least 10 hours.

Study Design Schematic



Bioanalytical Methods

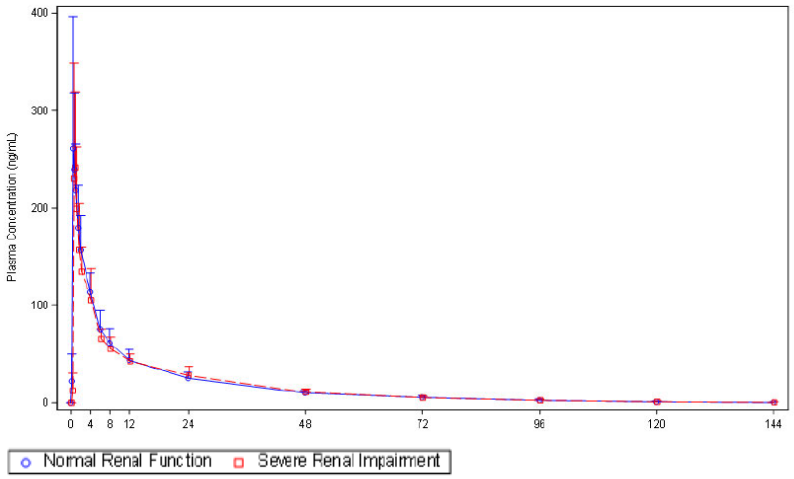
Concentrations of valbenazine and the metabolites, NBI-98782 and NBI-136110, were quantified in plasma samples according to a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method. The method has a validated range of 1.00 to 500 ng/mL with a lower limit of quantification (LLOQ) of 1.00 ng/mL for valbenazine, a range of 0.100 to 50.0 ng/mL with an LLOQ of 0.100 ng/mL for NBI-98782, and a range of 0.200 to 100 ng/mL with an LLOQ of 0.200 ng/mL for NBI-136110 in human plasma. The mean precision (%CV) and accuracy (% bias) for quality control samples assayed with study samples ranged from 5.8% to 6.7% and 0.5% to 7.5%, respectively, for valbenazine, 5.3% to 8.5% and 0.9% to 3.1%, respectively, for NBI-98782, and 4.5% to 6.8% and -1.0% to 6.6%, respectively, for NBI-136110.
Concentrations of valbenazine and the metabolites, NBI-98782 and NBI-136110, were quantified in urine samples according to a validated LC-MS/MS method. The bioanalytical method has a validated range of 100 to 50000 ng/mL with an LLOQ of 100 ng/mL for valbenazine. The mean precision (%CV) and accuracy (% bias) for quality control samples assayed with study samples ranged from 4.9% to 6.4% and 1.9% to 3.3%, respectively, for valbenazine, 2.7% to 4.3% and 1.2% to 3.2%, respectively, for NBI-98782, and 3.3% to 5.5% and 1.7% to 6.6%, respectively, for NBI-136110. The analytical methods are acceptable

Results

Valbenazine

Mean valbenazine plasma concentration versus time profile is presented in the following figure:

Figure 4 Mean (+SD) Plasma Valbenazine Concentration Versus Time by Renal Function



Source: Applicant's report for study NBI-98854-1701, Page 35, Figure 2

Table 7 Plasma Valbenazine Pharmacokinetic Parameters

Parameter (unit)	Statistic	Normal Renal Function (N=8)	Severe Renal Impairment (N=8)
$AUC_{0\text{-tlast}}$ (ng×hr/mL)	Mean (SD) Geom CV(%)	2300 (475) 20.8	2250 (487) 23.1
$AUC_{0\text{-}\infty}$ (ng×hr/mL)	Mean (SD) Geom CV(%)	2350 (472) 20.3	2300 (482) 22.5
C_{max} (ng/mL)	Mean (SD) Geom CV(%)	300 (79.2) 27.8	271 (101) 44.1
t_{max} (hr)	Median (Min, Max)	0.50 (0.50, 1.0)	0.75 (0.50, 1.0)
T_{lag} (hr)	Mean (SD)	0.05 (0.10)	0.03 (0.09)
$t_{½}$ (hr)	Mean (SD) Geom CV(%)	21 (4.5) 21	22 (5.5) 24
MRT (hr)	Mean (SD) Geom CV(%)	23 (2.9) 13	24 (5.1) 21
CL/F (L/hr)	Mean (SD) Geom CV(%)	17.6 (3.48) 20.3	18.2 (4.25) 22.5
Vz/F (L)	Mean (SD) Geom CV(%)	540 (150) 25	570 (210) 36

Source: Applicant's report for study NBI-98854-1701, Page 39, Table 3

Table 8 Valbenazine Renal Function Group Geometric Mean Ratios for Pharmacokinetic Exposure Parameters

Analyte Parameter (unit)	**Ratio[a,b]**	**90% Confidence Interval[c]**
Valbenazine		
$AUC_{0-\infty}$ (ng×hr/mL)	97.5%	(77.7%, 122.3%)
$AUC_{0-tlast}$ (ng×hr/mL)	97.3%	(77.1%, 122.8%)
C_{max} (ng/mL)	86.9%	(59.4%, 127.1%)

[a] All comparisons are between the severe renal impairment group versus the normal renal function group.
[b] Ratio of geometric least-squares means using log-transformed (base 10) data from analysis of variance model.
[c] Two-sided 90% confidence interval for geometric mean ratio was based on least-squares means using log-transformed (base 10) data from an analysis of variance model.

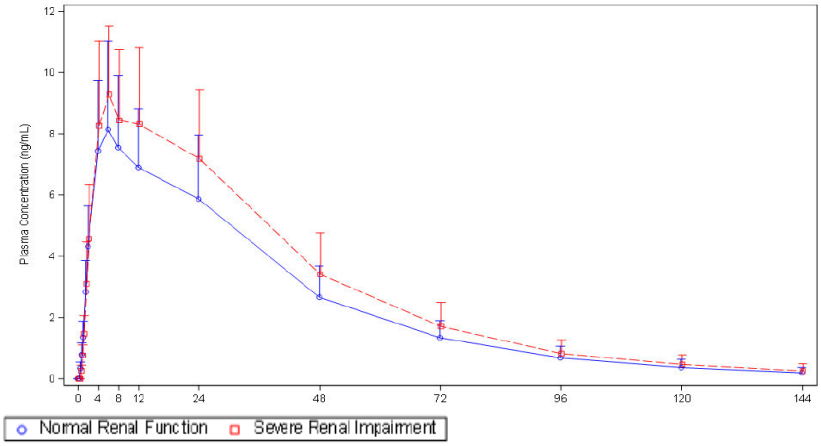
Source: Applicant's report for study NBI-98854-1701, Page 41, Table 6

The geometric mean ratio for Cmax of valbenazine was about 13% lower in subjects with severe renal impairment compared with subjects with normal renal function and the geometric mean ratios for AUC0-∞ and AUC0-tlast were about 3% lower.

NBI-98782

The mean plasma concentration time profile of the active metabolite, NBI-98782 is provided in the following figure:

Figure 5 Mean (+SD) Plasma NBI-98782 Concentration Versus Time by Renal Function Group



Source: Applicant's report for study NBI-98854-1701, Page 36, Figure 3

Table 9 Plasma NBI-98782 Pharmacokinetic Parameters

Parameter (unit)	Statistic	Normal Renal Function (N=8)	Severe Renal Impairment (N=8)
$AUC_{0\text{-}tlast}$ (ng×hr/mL)	Mean (SD) Geom CV(%)	345 (120) 36.9	421 (136) 32.7
$AUC_{0\text{-}\infty}$ (ng×hr/mL)	Mean (SD) Geom CV(%)	355 (126) 37.2	435 (144) 33.7
C_{max} (ng/mL)	Mean (SD) Geom CV(%)	8.17 (2.84) 38.3	9.90 (2.17) 20.3
t_{max} (hr)	Median (Min, Max)	6.0 (4.0, 8.0)	6.0 (4.0, 12.0)
T_{lag} (hr)	Mean (SD)	0.28 (0.10)	0.28 (0.09)
$t_{½}$ (hr)	Mean (SD) Geom CV(%)	25 (6.0) 25	28 (7.1) 25
MRT (hr)	Mean (SD) Geom CV(%)	37 (6.0) 17	39 (7.7) 19

Source: Applicant's report for study NBI-98854-1701, Page 40, Table 4

Table 10 NBI-98782 Renal Function Group Geometric Mean Ratios for Pharmacokinetic Exposure Parameters

Parameter	Ratio[a,b]	90% Confidence Interval[c]
AUC(o-∞), ng*h/mL	123.5%	(85.4%, 178.6%)
AUC(0-tlast), ng*h/mL	123.2%	(85.7%, 177.0%)
Cmax, ng/mL	125.9%	(91.4%, 173.3%)

[a] All comparisons are between the severe renal impairment group versus the normal renal function group.

[b] Ratio of geometric least-squares means using log-transformed (base 10) data from analysis of variance model.

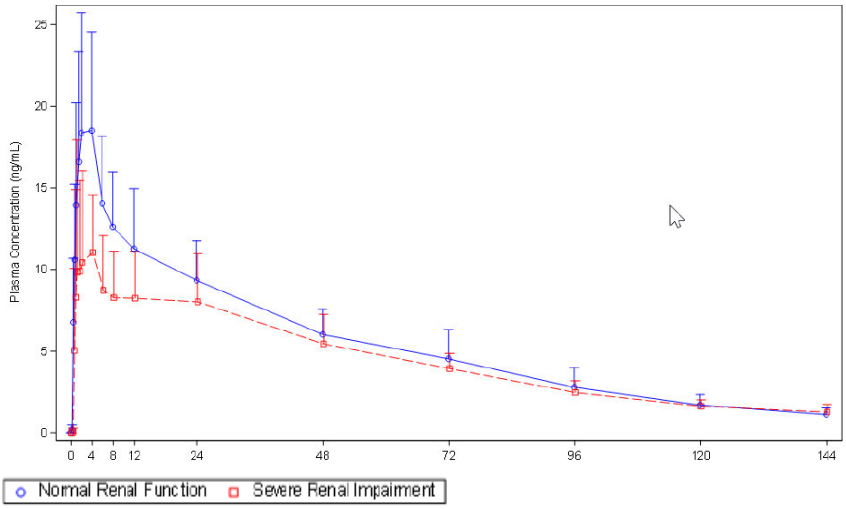
[c] Two-sided 90% confidence interval for geometric mean ratio was based on least-squares means using log-transformed (base 10) data from an analysis of variance model.

Source: Applicant's report for study NBI-98854-1701, Page 41, Table 6

The geometric mean ratios for NBI-98782 C_{max}, $AUC_{0\text{-}\infty}$, and $AUC_{0\text{-}tlast}$ were about 23% to 26% higher for subjects with severe renal impairment compared with subjects with normal renal function. This is not expected to be clinically meaningful.

The mean plasma concentration time profile for NBI-136110 (metabolite) is provided in the following figure:

Figure 6 Mean (+SD) Plasma NBI-136110 Concentration Versus Time by Renal Function Group



Source: Applicant's report for study NBI-98854-1701, Page 37, Figure 4

Table 11 Plasma NBI-136110 Pharmacokinetic Parameters

Parameter (unit)	Statistic	Normal Renal Function (N=8)	Severe Renal Impairment (N=8)
$AUC_{0\text{-}tlast}$ (ng×hr/mL)	Mean (SD) Geom CV(%)	776 (161) 21.7	639 (153) 23.0
$AUC_{0\text{-}\infty}$ (ng×hr/mL)	Mean (SD) Geom CV(%)	837 (165) 20.8	730 (151) 19.1
C_{max} (ng/mL)	Mean (SD) Geom CV(%)	19.6 (6.65) 36.6	12.9 (6.60) 48.5
t_{max} (hr)	Median (Min, Max)	3.0 (1.0, 8.0)	4.0 (0.75, 24)
T_{lag} (hr)	Mean (SD)	0.21 (0.16)	0.22 (0.09)
$t_{½}$ (hr)	Mean (SD) Geom CV(%)	37 (7.2) 22	46 (15) 34
MRT (hr)	Mean (SD) Geom CV(%)	55 (9.5) 18	70 (20) 31

Source: Applicant's report for study NBI-98854-1701, Page 40, Table 5

Table 12 NBI-136110 Renal Function Group Geometric Mean Ratios for Pharmacokinetic Exposure Parameters

Parameter	Ratio[a,b]	90% Confidence Interval[c]
AUC(o-∞), ng*h/mL	87.4%	(70.7%, 108.0%)
AUC(0-tlast), ng*h/mL	82.1%	(64.8%, 104.0%)
Cmax, ng/mL	63.1%	(40.7%, 98.0%)

[a] All comparisons are between the severe renal impairment group versus the normal renal function group.
[b] Ratio of geometric least-squares means using log-transformed (base 10) data from analysis of variance model.
[c] Two-sided 90% confidence interval for geometric mean ratio was based on least-squares means using log-transformed (base 10) data from an analysis of variance model.

Source: Applicant's report for study NBI-98854-1701, Page 41, Table 6

The geometric mean ratios for NBI-136110 C_{max} was about 37% lower for severe renal impaired compared to subjects with normal renal function. $AUC_{0\text{-}\infty}$, and $AUC_{0\text{-}tlast}$ were about 13% -18%

lower for subjects with severe renal impairment compared with subjects with normal renal function. The decrease in Cmax and AUC should not be clinically meaningful.

The CLurine values for valbenazine, NBI-98782, and NBI-136110 were lower in subjects with severe renal impairment (0.463, 3.47, and 0.505 L/hr, respectively) compared with subjects with normal renal function (1.15, 4.44, and 3.91 L/hr, respectively). This resulted in a decreased absolute (AE0-72) and relative (%AE) excretion of valbenazine and NBI-136110 in urine in subjects with renal impairment; however, absolute and relative excretion were similar between the renal function groups for NBI-98782.

Summary and conclusions
Administration of valbenazine 40 mg to subjects with severe renal impairment did not have clinically meaningful effect on C_{max} or $AUC_{0-\infty}$ of valbenazine, NBI-98782, or NBI-136110 compared to subjects with normal renal function. There was a reduction in urine clearance of valbenazine and metabolites in subjects with severe renal impairment compared with subjects with normal renal function, but this was not associated with clinically relevant changes in systemic exposure. The sponsor reported that Valbenazine was well tolerated in subjects with severe renal impairment and in subjects with normal renal function. Treatment-related TEAEs were reported in 3 subjects, including vision blurred (1 subject in the severe renal impairment group), headache (1 subject in the normal renal function group), and somnolence (1 subject in the normal renal function group and 1 subject in the severe renal impairment group).

Reviewer comment: The reviewer concurs with the sponsor's conclusion that renal impairment does not have clinically meaningful differences in exposure to valbenazine and its active metabolite, NBI98782.

PMR-3771-1

Title (Report #: XT173067): In Vitro Evaluation of NBI-136110 as an inducer of cytochrome P450 2B6 Expression in Cultured Human Hepatocytes

Objective: To evaluate the effect of NBI-136110 (0.1 to 10 μM) on the expression of cytochrome P450 (CYP) 2B6 in three cultures of cryopreserved primary human hepatocytes

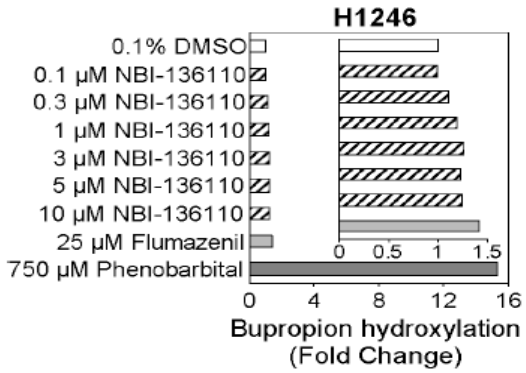
Study Design
Three preparations of cultured human hepatocytes from three livers were treated once daily for three consecutive days with DMSO (0.1% v/v, vehicle control), flumazenil (25 μM, negative control), one of six concentrations of NBI-136110 (0.1, 0.3, 1, 3, 5 or 10 μM) or the known human CYP enzyme inducer phenobarbital (750 μM). After treatment, the cells were incubated in situ with marker substrates for the analysis of human CYP2B6. NBI-136110 was evaluated for its ability to induce human CYP2B6 enzyme as measured by bupropion hydroxylation. Following the in situ incubation, the same hepatocytes from the same treatment groups were harvested with Buffer RLT to isolate RNA, which was analyzed by qRT-PCR to assess the effect of NBI-136110 on mRNA expression. The potential of NBI-136110 to cause cytotoxicity was assessed based on the release of LDH into the culture medium (a measure of cell membrane integrity) and changes observed in cell morphology.

Results

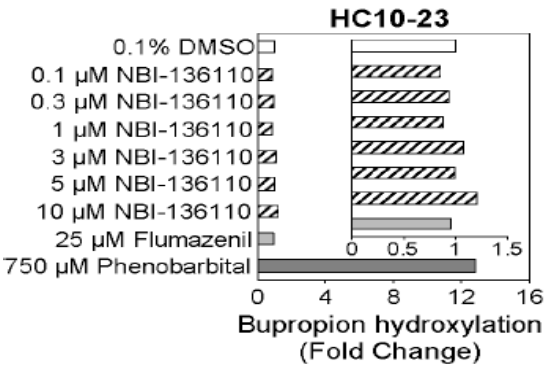
Treatment of cultured human hepatocytes once daily for three consecutive days with phenobarbital caused increases ranging from 9.44- to 15.4-fold change in bupropion hydroxylation (CYP2B6 activity). Treatment with the non-inducer, flumazenil, had little or no effect on CYP2B6 activity with changes ranging from 0.961- to 1.41-fold change. Treatment with up to 10 µM NBI-136110 caused little or no increase in CYP2B6 activity in any hepatocyte culture evaluated, with changes ranging from 0.803- to 1.26-fold change in CYP2B6 activity.

Treatment with NBI-136110 caused a maximum increase up to 2.46-fold (13.7% of the positive control response) in CYP2B6 mRNA expression in one hepatocyte preparation (H1246) and in the presence of 1 µM NBI-136110. Treatment with up to 10 µM NBI-136110 caused little or no increase in CYP2B6 mRNA expression in the remaining two hepatocyte cultures, with changes ranging from 0.633- to 1.86-fold change in CYP2B6 mRNA expression.

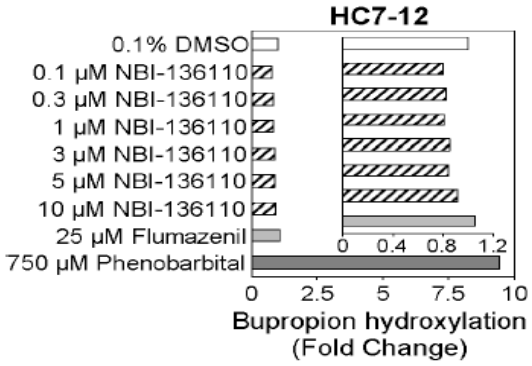
Figure 7 CYP2B6 activity: The effect of treating cultured human hepatocytes with NBI-136110 on the rate of bupropion hydroxylation activity



Fold Change	Rate ± Std Dev	n
1.00	1.68 ± 0.03	3
0.988	1.66 ± 0.16	3
1.11	1.85 ± 0.08	3
1.19	2.00 ± 0.13	3
1.26	2.11 ± 0.15	3
1.23	2.06 ± 0.22	3
1.24	2.08 ± 0.13	3
1.41	2.37 ± 0.04	3
15.4	25.8 ± 5.5	3

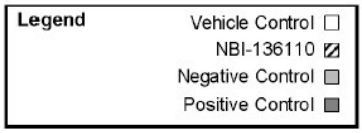


Fold Change	Rate ± Std Dev	n
1.00	6.85 ± 0.38	3
0.849	5.82 ± 0.18	3
0.936	6.41 ± 0.32	3
0.881	6.04 ± 0.36	3
1.08	7.40 ± 0.31	3
0.992	6.80 ± 0.16	3
1.21	8.28 ± 0.10	3
0.961	6.59 ± 0.16	3
12.8	87.7 ± 10.1	3



Fold Change	Rate ± Std Dev	n
1.00	2.96 ± 0.38	3
0.803	2.38 ± 0.21	3
0.826	2.45 ± 0.09	3
0.808	2.40 ± 0.07	3
0.856	2.54 ± 0.05	3
0.849	2.52 ± 0.18	3
0.912	2.70 ± 0.05	3
1.06	3.13 ± 0.17	3
9.44	28.0 ± 3.2	3

n Number of replicates
Std Dev represents standard deviation.
Fold change = Activity of test article / Activity of vehicle control
Rate is expressed in pmol/incubation/min.



Source: Applicant's report for study CT173067, Page 28, Figure 5

Table 13 CYP2B6 activity percent positive control: The effect of treating cultured human hepatocytes with NBI-136110 on the rate of bupropion hydroxylation activity

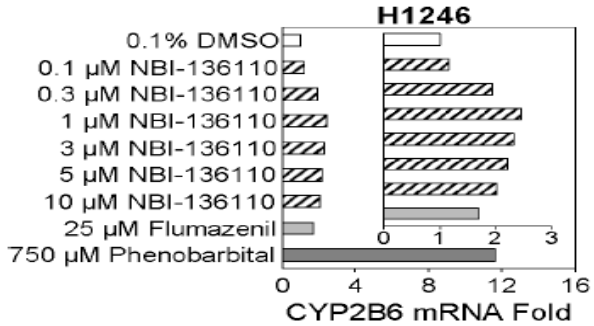
CYP2B6 Activity Fold Percent Positive Control (Bupropion hydroxylation)

Sample ID	H1246	HC10-23	HC7-12
0.1% DMSO	0	0	0
0.1 µM NBI-136110	-0.0862	-1.28	-2.34
0.3 µM NBI-136110	0.733	-0.542	-2.06
1 µM NBI-136110	1.34	-1.01	-2.28
3 µM NBI-136110	1.81	0.674	-1.71
5 µM NBI-136110	1.59	-0.0702	-1.79
10 µM NBI-136110	1.65	1.77	-1.05
25 µM Flumazenil	2.85	-0.327	0.660
750 µM Phenobarbital	100	100	100

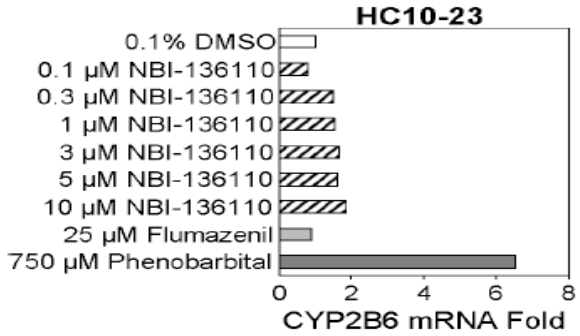
Percent positive control = ([Fold change of test article – Fold change of vehicle control]/[Fold change of positive control – Fold change of vehicle control]) × 100

Source: Applicant's report for study CT173067, Page 29, Table 3

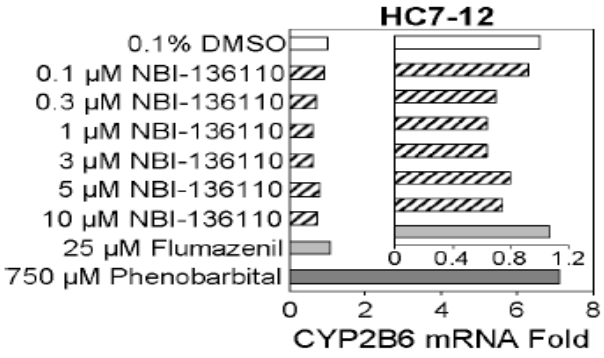
Figure 8 CYP2B6 mRNA fold change: The effect of treating cultured human hepatocytes with NBI-136110 on CYP2B6 mRNA expression



mRNA Fold Change	n
1.00	4
1.17	4
1.94	4
2.46	4
2.34	4
2.22	4
2.03	4
1.71	4
11.6	4



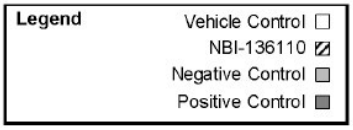
mRNA Fold Change	n
1.00	4
0.808	4
1.48	4
1.51	4
1.66	4
1.61	4
1.86	4
0.906	4
6.51	4



mRNA Fold Change	n
1.00	4
0.920	4
0.698	4
0.639	4
0.633	4
0.806	4
0.740	4
1.07	4
7.12	4

n Number of replicates

Fold change values are relative to vehicle control, normalized to GAPDH.



Source: Applicant's report for study CT173067, Page 31, Figure 6

Table 14 CYP2B6 mRNA percent positive control: The effect of treating cultured human hepatocytes with NBI-136110 on CYP2B6 mRNA expression

CYP2B6 mRNA Percent Positive Control

Sample ID	H1246	HC10-23	HC7-12
0.1% DMSO	0	0	0
0.1 µM NBI-136110	1.61	-3.49	-1.31
0.3 µM NBI-136110	8.80	8.73	-4.94
1 µM NBI-136110	13.7	9.20	-5.90
3 µM NBI-136110	12.6	12.1	-6.00
5 µM NBI-136110	11.5	11.0	-3.17
10 µM NBI-136110	9.65	15.5	-4.25
25 µM Flumazenil	6.67	-1.71	1.19
750 µM Phenobarbital	100	100	100

Percent positive control = ([Fold change of test article – 1]/[Fold change of positive control – 1]) × 100

Source: Applicant's report for study CT173067, Page 32, Table 5

Conclusions

Under the conditions examined, NBI-136110 caused little or no increase in CYP2B6 activity. Treatment with NBI-136110 caused little or no increases in CYP2B6 mRNA expression in two

of three hepatocyte cultures. A non-concentration-dependent increase (up to 2.46-fold change [13.7% of the positive control]) in CYP2B6 mRNA expression was observed in one culture.

Reviewer comments: The reviewer supports the sponsor's conclusions that the metabolite NBI-136110 does not appear to potentially be an inducer of CYP 2B6. None of the human hepatocytes showed increase in CYP 2B6 activity as measured by the rate of bupropion hydroxylation activity. Two human hepatocytes showed an increase in mRNA expression of less than 2-fold, although one of the hepatocytes showed 2.5-fold increase in mRNA expression. Therefore, looking at the totality of the data provided, it is unlikely that NBI-136110 has the potential to be an inducer of CYP2B6.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KOFI A KUMI
03/23/2020 03:49:05 PM

LUNING ZHUANG
03/23/2020 04:18:33 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209241Orig1s016

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER
LABELING REVIEW

Drug/NDA: Ingrezza (valbenazine) 40 mg and 80 mg capsules
NDA 209241/S-016
Sponsor: Neurocrine Biosciences, Inc.
Indication: Treatment of adults with tardive dyskinesia

Pending and Last Approved Supplements:

NDA	Supplement #	Type (CBE/PA)	Dated	Provides for	Status
209241	(b) (4)				
	S-016	PA	8/29/2019	Revisions to sections 2 (Dosage and Administration), 7 (Drug Interactions), 8.6 (CYP2D6 Poor Metabolizers), 8.8 (Renal Impairment), and 12.3 (Pharmacokinetics) based upon results of PMR studies 3177-2 & 3177-3. Review also includes the induction study submitted on 8/17/18 to fulfill PMR 3177-1. This submission also fulfills 3 pending PMRs: 3177-1; 3177-2; 3177-3	Pending
	S-012	PA	5/3/2019	Response to 4/3/19 901 SLC letter requesting labeling revisions due to an association between the use of Ingrezza and the development of Parkinson-like symptoms. Sponsor proposing alternative language.	Approved 7/15/2019

BACKGROUND

- This prior approval labeling supplement (PAS) was submitted on 8/29/2019.
- The last approved labeling, for comparison purposes, was labeling supplement S-012, which was approved on 7/15/2019.
- This review will only encompass pending PA supplement 16 which was submitted on 8/29/2019.
- Please note there is (b) (4)

REVIEW

Reviewed by: Kofi Kumi, Clinical Pharmacology Reviewer (Review dated 3/23/2020)

- This supplement proposes the following changes to the PI for Ingrezza:

- HL Page
  - RMC – Dosage and Administration 2.3 and 2.4
  - Dosage and Administration
    - Changed (b) (4) to “dosage” where appropriate
    - Updated last bullet language to say “The recommended dosage for known CYP2D6 poor metabolizers is 40 mg once daily. (2.3)”
  - Drug Interactions was updated
  - Use in Specific Populations
    - Renal Impairment language was removed
- Section 2.3 Dosage Recommendations for Known CYP2D6 Poor Metabolizers
  - Updated the language within this section
- Section 2.4 Dosage Recommendations for Concomitant Use with Strong CYP3A4 Inducers and Strong CYP3A4 or CYP2D6 Inhibitors
  - Updated language under “Coadministration with Strong CYP3A4 Inhibitors” and “Coadministration with Strong CYP2D6 Inhibitors”.
- Section 7 Drug Interactions
  - Table 2 was updated
- Section 8.6 CPY2D6 Poor Metabolizers
- Section 8.8 Renal Impairment
  - Language regarding severe renal impairment was updated
- Section 12.3 Pharmacokinetics
  - Language updated to include severe renal under “Studies in Specific Populations”
  - Updated title for Figure 1 to include “and Severe Renal”
  - Added “paroxetine” under Drug Interaction Studies
  - Updated title for Figure 2 to: “Effects of Strong CYP2D6 and CYP3A4 Inhibitors and CYP3A4 Inducers”
- This submission also fulfills 3 pending PMRs: 3177-1; 3177-2; 3177-3.

DISCUSSION

- Labeling negotiations (conducted via email): dated 3/5/2020 and 3/26/2020. The Sponsor agreed to our final comments and submitted labeling on 3/31/2020.
- The clinical pharmacology reviewer reviewed the studies submitted for fulfilment of PMR 3177-1, PMR 3177-2, and PMR 3177-3.
- There are other postmarketing commitments and a postmarketing requirement listed in the April 11, 2017, approval letter that are still open and pending.

CONCLUSIONS

1. This PA labeling supplement only provides for the revisions as stated above when compared to the last approved labeling (approval letter dated 7/15/2019).

2. The Sponsor has agreed to incorporate our revisions, verbatim (email agreement dated 3/31/2020).
3. I recommend that an approval letter be issued for this pending supplemental application.
4. I recommend that a PMR/PMC fulfillment letter be issued for PMR 3177-1; PMR 3177-2; and PMR 3177-3.

{See appended electronic signature page}

Simran Parihar, PharmD

{See appended electronic signature page}

Kim Updegraff, RPh, MS, RAC
Associate Director of Labeling

Attachments: 1) Annotated labeling; 2) Labeling e-mail agreement dated 3/31/2020

20 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

From:	Kim, Kristine
To:	Parihar, Simran
Subject:	RE: NDA 209241 Seq 0438 / S-016 PAS Response - (Labeling) INGREZZA (valbenazine) PMR 3177-2 CSR, PMR 3177-3 CSR
Date:	Tuesday, March 31, 2020 4:42:29 PM
Attachments:	image003.png image004.png

Dear Simran,

We have accepted all FDA-proposed language for the S-016 USPI revision, and submitted final labeling the NDA in Sequence 0441. In doing so, I made note of 2 discrepancies in the USPI that were corrected. See Highlights, Recent Major Changes and Section 2.4 Strong CYP2D6 Inhibitors (this update was for consistency with the agreed, preceding CYP3A4 inhibitor language; screenshots below. Because of these corrections, a tracked changes version of the final label was submitted, in addition to the clean copy.

Please let me know if you have any questions.

Kind regards,
Kristine

From: Parihar, Simran <Simran.Parihar@fda.hhs.gov>
Sent: Thursday, March 26, 2020 2:30 PM
To: Kim, Kristine <kkim@neurocrine.com>
Subject: [EXTERNAL] RE: NDA 209241 Seq 0438 / S-016 PAS Response - (Labeling) INGREZZA (valbenazine) PMR 3177-2 CSR, PMR 3177-3 CSR
Importance: High

Dear Kristine,

Please find our response to your comments in the label attached. We would like to secure final labeling agreement. We request that you ***accept*** all changes to the attached labeling, and submit the final label to us as soon as possible, but **no later COB Tuesday, March 31, 2020**.

Thank you,
Simran

From: Kim, Kristine <kkim@neurocrine.com>

Sent: Friday, March 20, 2020 3:45 PM
To: Parihar, Simran <Simran.Parihar@fda.hhs.gov>
Subject: NDA 209241 Seq 0438 / S-016 PAS Response - (Labeling) INGREZZA (valbenazine) PMR 3177-2 CSR, PMR 3177-3 CSR

Dear Simran,

Today we have submitted NDA 209241 Seq 0438; the submission contains the Sponsor response to the FDA-proposed revisions to the Ingrezza USPI for the updates associated with the CYP2D6 DDI and renal impairment PMRs. The revisions that we have proposed for the label incorporate the FDA recommended revisions and provide additional clarifying language (b) (4) (b) (4). I have attached the word document of the proposed revisions to facilitate any further edits that FDA may want to implement.

If you have any questions regarding this submission, please let me know.

Kind regards,
Kristine

From: Kim, Kristine
Sent: Tuesday, March 10, 2020 9:28 AM
To: Parihar, Simran <Simran.Parihar@fda.hhs.gov>
Subject: RE: NDA 209241 Seq 0383 / S-016 PAS (Labeling) INGREZZA (valbenazine) PMR 3177-2 CSR, PMR 3177-3 CSR

Dear Simran,

Yes, we will target getting our response in on or before Friday March 20th. Thank you for your understanding.

Kind regards,
Kristine

From: Parihar, Simran <Simran.Parihar@fda.hhs.gov>
Sent: Tuesday, March 10, 2020 6:34 AM
To: Kim, Kristine <kkim@neurocrine.com>
Subject: [EXTERNAL] RE: NDA 209241 Seq 0383 / S-016 PAS (Labeling) INGREZZA (valbenazine) PMR 3177-2 CSR, PMR 3177-3 CSR

Dear Kristine,

Thank you for your email below. Could you please try and get your response in on or before Friday, March 20th instead?

Thank you,
Simran

From: Kim, Kristine <kkim@neurocrine.com>
Sent: Monday, March 9, 2020 4:59 PM
To: Parihar, Simran <Simran.Parihar@fda.hhs.gov>
Subject: RE: NDA 209241 Seq 0383 / S-016 PAS (Labeling) INGREZZA (valbenazine) PMR 3177-2 CSR, PMR 3177-3 CSR

Dear Simran,

While we understand the scope of the FDA proposed USPI language revisions with respect to CYP2D6 inhibitors and poor metabolizers, we would like to request an extension to the Sponsor response timeline. This extension would enable us to have adequate time to consider further revisions to the updated dosage and administration language to ensure consistency and clarity for the prescribers. We are proposing a response be provided to the FDA by Monday, March 23 2020.

Please confirm acknowledgement of receipt of our request, and feedback as to the acceptability of our proposal.

Kind regards,
Kristine

From: Kim, Kristine
Sent: Wednesday, March 4, 2020 11:02 PM
To: Parihar, Simran <Simran.Parihar@fda.hhs.gov>
Subject: RE: NDA 209241 Seq 0383 / S-016 PAS (Labeling) INGREZZA (valbenazine) PMR 3177-2 CSR, PMR 3177-3 CSR

Dear Simran,

I am acknowledging receipt of the FDA proposed labeling language. I will provide a response by COB Monday, March 9 EST.

Kind regards,
Kristine

From: Parihar, Simran <Simran.Parihar@fda.hhs.gov>
Sent: Wednesday, March 4, 2020 9:08 PM
To: Kim, Kristine <kkim@neurocrine.com>
Subject: [EXTERNAL] RE: NDA 209241 Seq 0383 / S-016 PAS (Labeling) INGREZZA (valbenazine) PMR 3177-2 CSR, PMR 3177-3 CSR
Importance: High

Dear Kristine,

We have reviewed your submission (dated August 29, 2019) and in an effort to take a final action, we

would like to secure final labeling agreement. We request that you *accept* all changes to the attached labeling, and submit the final label to us as soon as possible, but **no later COB Monday, March 9, 2020**. Please do not delete the Agency's bracketed comments in the labeling.

We also remind you to update the Table of Contents after labeling revisions are complete.

I would like to bring your attention to the following website that compiles all of the labeling guidances. Please confirm that the final agreed-upon label conforms to the requirements listed on this FDA website. To help you, the Agency provides a 42-item checklist (scroll down to Selected Requirements of Prescribing Information (SRPI).

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm

Best,
Simran

From: Kim, Kristine <kkim@neurocrine.com>
Sent: Monday, February 24, 2020 11:30 AM
To: Parihar, Simran <Simran.Parihar@fda.hhs.gov>
Subject: RE: NDA 209241 Seq 0383 / S-016 PAS (Labeling) INGREZZA (valbenazine) PMR 3177-2 CSR, PMR 3177-3 CSR

Dear Simran,

I hope this email finds you well. I am following up with NDA 209241 S-016 PAS (Labeling) for INGREZZA (valbenazine) for reporting of PMRs 3177-2 (CYP2D6 inhibition drug interaction) and 3177-3 (renal impairment), with the action date pending on 29 February 2020. Could you please let me know if the PAS action is on track for the end of this week?

Kind regards,
Kristine

Kristine Munar Kim, MS | Executive Director, Regulatory Affairs
Neurocrine Biosciences, Inc.
12780 El Camino Real, San Diego, CA 92130, USA
t: 858-617-7785 | m: (b) (6)

From: Kim, Kristine
Sent: Monday, September 16, 2019 11:04 AM
To: Parihar, Simran <Simran.Parihar@fda.hhs.gov>
Subject: RE: NDA 209241 Seq 0383 / S-016 PAS (Labeling) INGREZZA (valbenazine) PMR 3177-2 CSR, PMR 3177-3 CSR

Dear Simran,

Thank you for providing the acknowledgement letter; I am confirming receipt. We look forward to

the FDA action on 29 Feb 2020.

Kind regards,
Kristine

From: Parihar, Simran <Simran.Parihar@fda.hhs.gov>
Sent: Monday, September 16, 2019 10:55 AM
To: Kalsi, Jasmeet (Mona) <Jasmeet.Kalsi@fda.hhs.gov>; Kim, Kristine <kkim@neurocrine.com>
Subject: [EXTERNAL] RE: NDA 209241 Seq 0383 / S-016 PAS (Labeling) INGREZZA (valbenazine) PMR 3177-2 CSR, PMR 3177-3 CSR

Thanks, Mona and Kristine!

Please find our acknowledgement letter attached for your records.

Simran

From: Kalsi, Jasmeet (Mona)
Sent: Thursday, September 12, 2019 2:25 PM
To: Kim, Kristine <kkim@neurocrine.com>
Cc: Parihar, Simran <Simran.Parihar@fda.hhs.gov>
Subject: RE: NDA 209241 Seq 0383 / S-016 PAS (Labeling) INGREZZA (valbenazine) PMR 3177-2 CSR, PMR 3177-3 CSR

Hi Kristine,

Simran Parihar (cc'd) will be handling this labeling supplement.

Thanks,
Mona

From: Kim, Kristine <kkim@neurocrine.com>
Sent: Thursday, September 12, 2019 1:53 PM
To: Kalsi, Jasmeet (Mona) <Jasmeet.Kalsi@fda.hhs.gov>
Subject: RE: NDA 209241 Seq 0383 / S-016 PAS (Labeling) INGREZZA (valbenazine) PMR 3177-2 CSR, PMR 3177-3 CSR

Hello Mona,

I wanted to follow up with this PAS submission for fulfillment of our PMRs 3177-2 and 3177-3. Specifically, I was wondering if the PAS was the appropriate designation, or if a submission with clinical data of this nature (ie, a submission that does not contain efficacy data) would be considered under a different review timeline.

Thank you,

Kristine

From: Kim, Kristine
Sent: Thursday, August 29, 2019 4:15 PM
To: Kalsi, Jasmeet (Mona) (Jasmeet.Kalsi@fda.hhs.gov) <Jasmeet.Kalsi@fda.hhs.gov>
Subject: NDA 209241 Seq 0383 / S-016 PAS (Labeling) INGREZZA (valbenazine) PMR 3177-2 CSR, PMR 3177-3 CSR

Dear Mona,

NDA 209241 Seq 0383 / S-16 Prior Approval Supplement (Labeling) for INGREZZA (valbenazine) was submitted today. This submission contains final reports for the following postmarketing requirements:

- PMR 3177-2: trial to quantify the impact of CYP2D6 inhibition on the exposures of the parent compound and major metabolites (Study NBI-98854-1703)

- PMR 3177-3: trial to assess exposure differences of the parent compound and major metabolites in patients with severe renal impairment and matching subjects with normal renal function (Study NBI-98854-1701)

Draft labeling containing proposed revisions for the label language to incorporate the findings from PMR 3177-2 and 3177-3 has also been included in this submission.

If you have any questions regarding this submission, please let me know.

Kind regards,
Kristine

Kristine M. Kim, MS | Sr. Director, Regulatory Affairs | Neurocrine Biosciences, Inc.
12780 El Camino Real, San Diego, CA 92130, USA
t: 858-617-7785 | f: 858-617-7521

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SIMRAN K PARIHAR
04/08/2020 01:07:18 PM

KIMBERLY S UPDEGRAFF
04/08/2020 01:48:12 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209241Orig1s016

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

NDA 209241/S-016

ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT

Neurocrine Biosciences, Inc.
Attention: Kristine Kim
Sr. Director, Regulatory Affairs
12780 El Camino Real
San Diego, CA 92130

Dear Ms. Kim:

We have received your supplemental new drug application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER:	209241
SUPPLEMENT NUMBER:	016
PRODUCT NAME:	Ingrezza (valbenazine) Capsule
DATE OF SUBMISSION:	August 29, 2019
DATE OF RECEIPT:	August 29, 2019

This supplemental application proposes the following revisions for the Ingrezza US prescribing information language to incorporate the findings of the studies conducted to fulfill Post Marketing Requirement 3177-2 and 3177-3.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on October 28, 2019, in accordance with 21 CFR 314.101(a)

If the application is filed, the goal date will be February 29, 2020.

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.[1]

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Failure to submit the content of labeling in SPL format may result in a refusal-to-file action.

If you have questions, please email Simran Parihar, PharmD, at simran.parihar@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Simran Parihar, Pharm.D.
Senior Regulatory Health Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SIMRAN K PARIHAR
09/16/2019 01:52:24 PM