CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209241Orig1s000

<u>LABELING</u>

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

----------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 dose is 40 mg once daily. After one week, increase the dose to the recommended dose of 80 mg once daily. (2.1)
- Can be taken with or without food. (2.1)
- The recommended dose for patients with moderate or severe hepatic impairment is 40 mg once daily. (2.2)
- Consider dose reduction based on tolerability in known CYP2D6 poor metabolizers. (2.2)

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

----------CONTRAINDICATIONS----------
None. (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)

----------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 (2.3, 7):

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	Reduce dose to 40 mg.
Use of strong CYP2D6 inhibitors with INGREZZA	Consider dose reduction based on tolerability.

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: May cause fetal harm. (8.1)
- Lactation: Advise not to breastfeed. (8.2)
- Renal Impairment: No dosage adjustment is necessary for patients with mild to moderate renal impairment. Use is not recommended in patients with severe renal impairment. (8.8)

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

Revised: 04/2017

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Reference ID: 4083041

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 dose for INGREZZA is 40 mg once daily. After one week, increase the dose to the recommended dose 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 dose 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

Consider reducing INGREZZA dose based on tolerability for known CYP2D6 poor metabolizers *[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

Reduce INGREZZA dose to 40 mg once daily when INGREZZA is coadministered with a strong CYP3A4 inhibitor *[see Drug Interactions (7.1)]*.

Coadministration with Strong CYP2D6 Inhibitors

Consider reducing INGREZZA dose based on tolerability when INGREZZA is coadministered with a strong CYP2D6 inhibitor *[see Drug Interactions (7.1)]*.

3 DOSAGE FORMS AND STRENGTHS

INGREZZA is available as 40 mg capsules. The white opaque body and purple cap capsule is printed with ‘VBZ’ and ‘40’ in black ink.

4 CONTRAINDICATIONS

None.

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.

6 ADVERSE REACTIONS

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

- Somnolence *[see Warnings and Precautions (5.1)]*
- QT Prolongation *[see Warnings and Precautions (5.2)]*

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.

<u>Variable and Fixed Dose Placebo-Controlled Trial Experience</u>

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.

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 (2.3)]*.
Examples:	itraconazole, ketoconazole, clarithromycin
Strong CYP2D6 Inhibitors	
Clinical Implication:	Concomitant use of INGREZZA with strong CYP2D6 inhibitors may increase the exposure (C_{max} and AUC) to valbenazine's active metabolite compared with the use of INGREZZA alone *[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:	Consider reducing INGREZZA dose based on tolerability when INGREZZA is coadministered with a strong CYP2D6 inhibitor *[see Dosage and Administration (2.3)]*.
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 2-4% and 15-20% 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

Consider reducing INGREZZA dose based on tolerability for known CYP2D6 poor metabolizers *[see Dosage and Administration (2.2)]*. 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 (2.3)]*. 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 to moderate renal impairment (creatinine clearance 30 to 90 mL/min). INGREZZA does not undergo primary renal clearance. INGREZZA is not recommended in patients with severe renal impairment (creatinine clearance <30 mL/min).

10 OVERDOSAGE

10.1 Human Experience

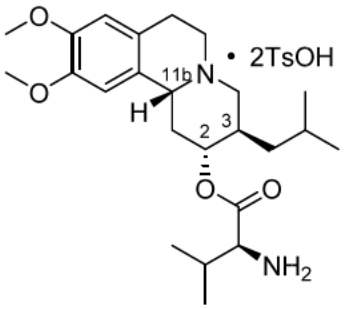
The pre-marketing clinical trials involving INGREZZA in approximately 850 subjects do not provide information regarding symptoms with overdose.

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 of valbenazine tosylate, which is equivalent to 40 mg of valbenazine free base. It also contains the following inactive ingredients: mannitol, partially pregelatinized starch, fumed silica, and magnesium stearate. The capsule shell contains gelatin, candurin silver fine, FD&C Red#40, and FD&C Blue#1.

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.

<u>Cardiac Electrophysiology</u>

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.

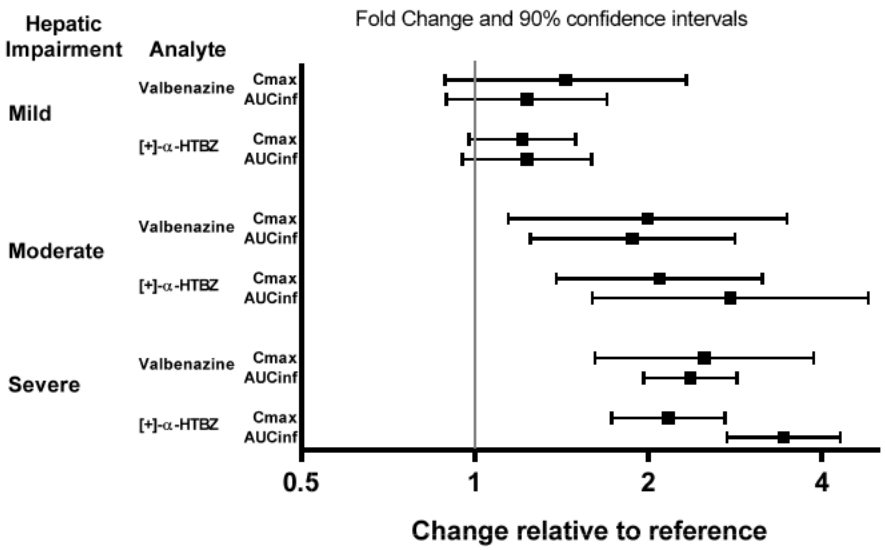
Excretion

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 impairment are summarized in Figure 1.

Figure 1: Effects of Hepatic Impairment on Valbenazine Pharmacokinetics

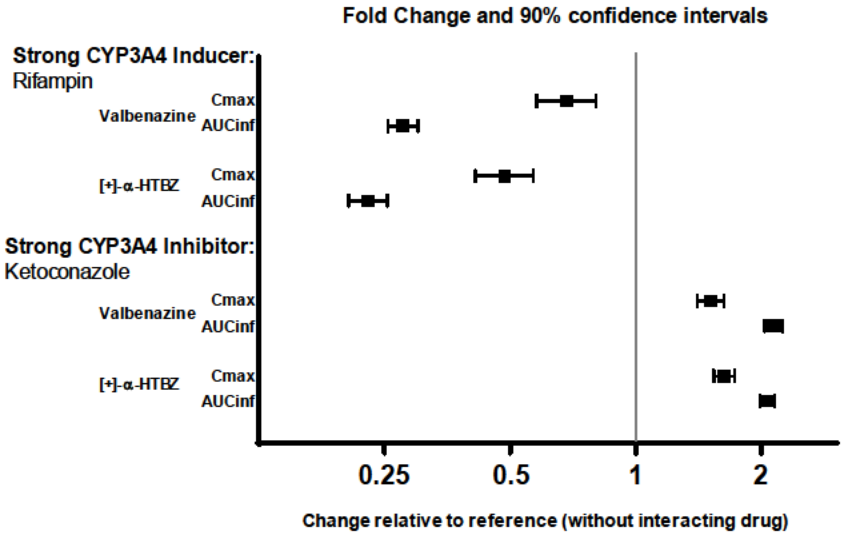


AUC_{inf}=area under the plasma concentration versus time curve from 0 hours extrapolated to infinity
[+]-α-HTBZ=[+]-α-dihydrotetrabenazine (active metabolite)

Drug Interaction Studies

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

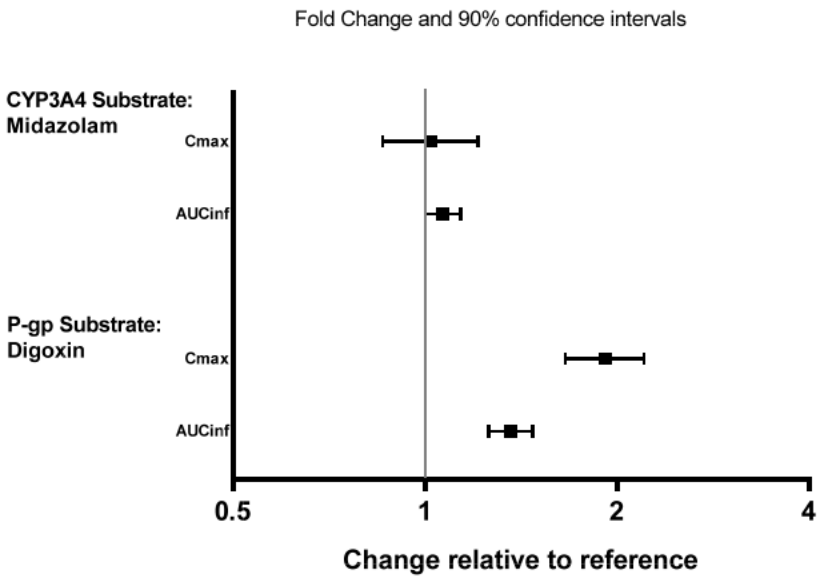
Figure 2: Effects of Strong CYP3A4 Inducers and Inhibitors on Valbenazine Pharmacokinetics



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 3, 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.

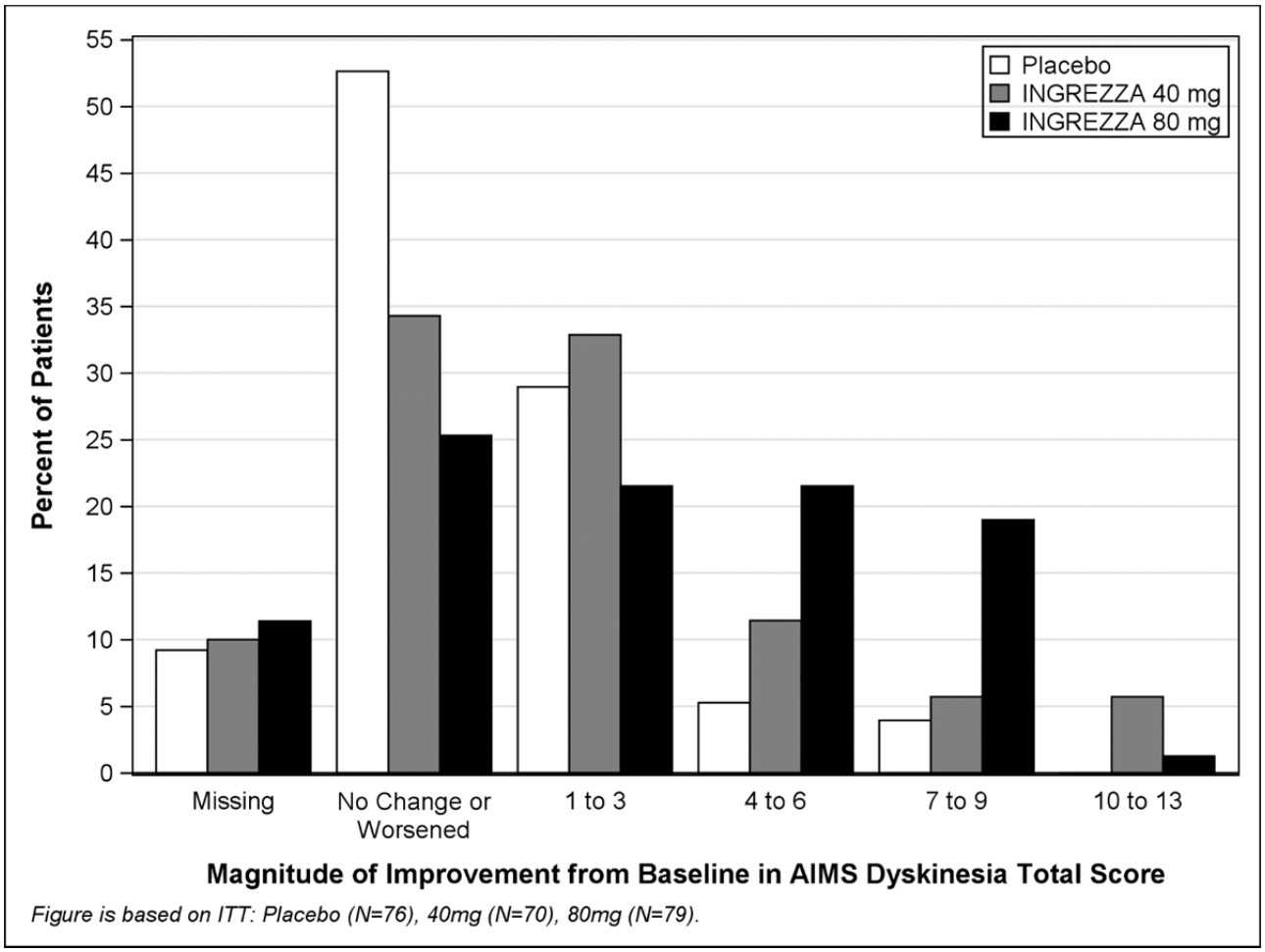
The mean changes in the AIMS dyskinesia total score by visit are shown in Figure 5. Among subjects remaining in the study at the end of the 48-week treatment (N=123 [52.6%]), following discontinuation of INGREZZA, the mean AIMS dyskinesia total score appeared to return toward baseline (there was no formal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

Table 3: 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)	

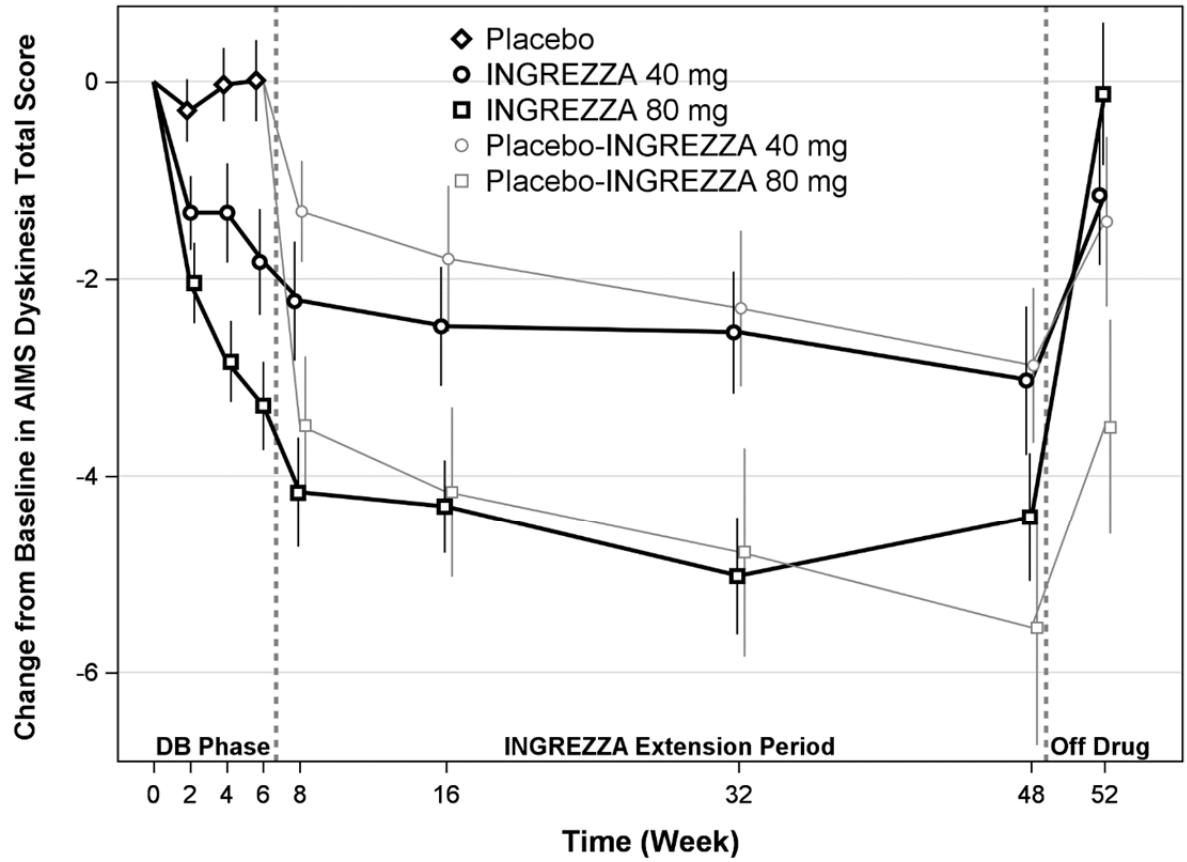
LS Mean=least-squares mean; SD=standard deviation; SEM=standard error of the mean; CI=2-sided 95% confidence interval
*Dose that was statistically significantly different from placebo after adjusting for multiplicity.
**A negative change from baseline indicates improvement.

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)



	Number of Patients							
Placebo	76	76	73	69				
INGREZZA 40 mg	70	70	64	63	59	50	37	34	34
INGREZZA 80 mg	79	77	73	70	67	58	50	43	41
Placebo-INGREZZA 40 mg					32	29	27	24	24
Placebo-INGREZZA 80 mg					33	31	27	22	22

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.

Bottle of 30: NDC 70370-1040-1

Bottle of 90: NDC 70370-1040-2

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.

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 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.

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
  - shortness of breath
  - dizziness or fainting

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
- headache
- feelings of restlessness
- dry mouth
- constipation
- 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?

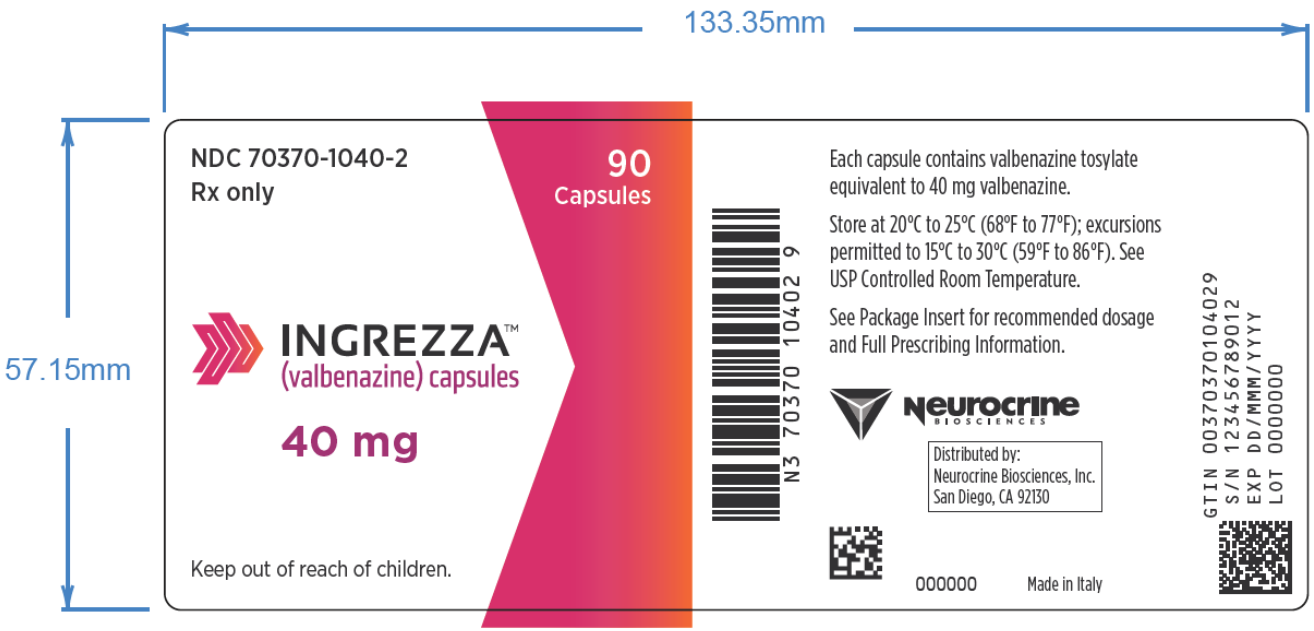
Active ingredient: valbenazine
Inactive ingredients: mannitol, partially pregelatinized starch, fumed silica, and magnesium stearate. The capsule shell contains gelatin, candurin silver fine, FD&C Red#40, and FD&C Blue#1.
Distributed by: Neurocrine Biosciences, Inc., San Diego, CA 92130, U.S.A
For more 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 Approved: 4/2017

Valbenazine Sample and Trade Packaging

05 APRIL 2017

LEFT PANEL	RIGHT PANEL
NDC 70370-1040-1 Rx only 30 Capsules “LOGO” INGREZZA™ (valbenazine) capsules 40 mg Keep out of reach of children.	Each capsule contains valbenazine tosylate equivalent to 40 mg valbenazine. 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. See Package Insert for recommended dosage and Full Prescribing Information. “LOGO” Neurocrine Biosciences Distributed by: Neurocrine Biosciences, Inc. San Diego, CA 92130 Serialization block GTIN: 00370370104012 S/N: 123456789012 EXP: DD/MMM/YYYY LOT: 0000000 Component data matrix 546268 Made in Italy



LEFT PANEL	RIGHT PANEL
NDC 70370-1040-2 Rx only 90 Capsules “LOGO” INGREZZA™ (valbenazine) capsules 40 mg Keep out of reach of children.	Each capsule contains valbenazine tosylate equivalent to 40 mg valbenazine. 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. See Package Insert for recommended dosage and Full Prescribing Information. “LOGO” Neurocrine Biosciences Distributed by: Neurocrine Biosciences, Inc. San Diego, CA 92130 Serialization block GTIN: 00370370104012 S/N: 123456789012 EXP: DD/MMM/YYYY LOT: 0000000 Component data matrix 0000000 Made in Italy

LOT: ABCD1234 Component data matrix
EXP: DD/MMM/YYYY 551427
Made in Italy.

Each capsule contains valbenazine tosylate equivalent to 40 mg valbenazine.

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.

See Package Insert for recommended dosage and Full Prescribing Information.

TO OPEN:
Step 1:
Press & hold button gently
Step 2:
Pull out medication card

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

“LOGO” INGREZZA™ (valbenazine) capsules 40 mg per capsule

NDC 70370-1040-3 Rx only

“LOGO” INGREZZA™ (valbenazine) capsules See reverse side for opening instructions

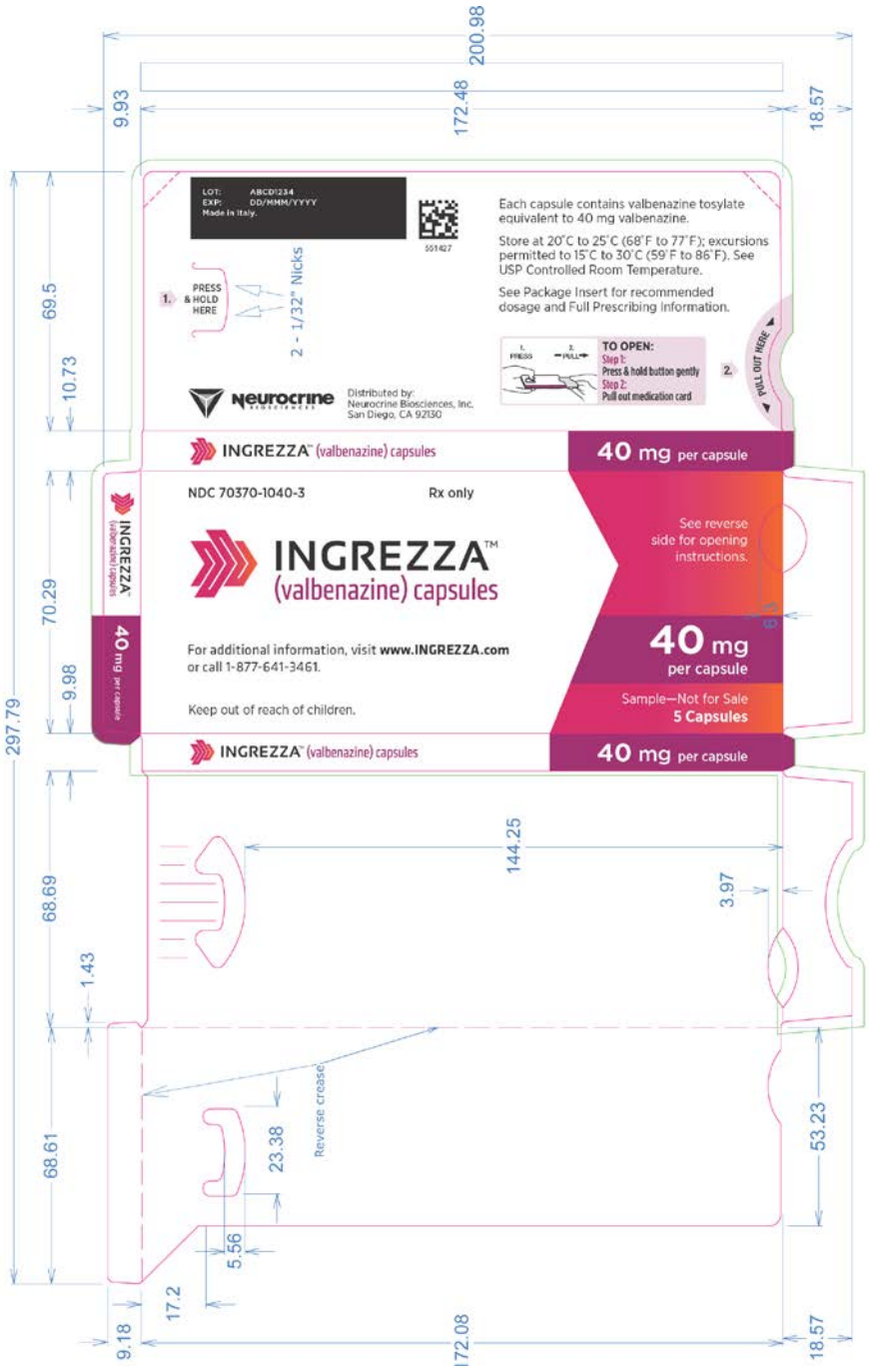
For additional information, visit www.INGREZZA.com
or call 1-877-641-3461.

40 mg per capsule

Keep out of reach of children.

Sample—Not for Sale
5 Capsules

“LOGO” INGREZZA™ (valbenazine) capsules 40 mg per capsule



BLISTER BASE

"LOGO" INGREZZA™
(valbenazine) capsules

40 mg
per capsule

LOT: ABCD1234
EXP: DD/MMM/YYYY

Push capsule through from other side.

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

BLISTER FORM SIDE

“LOGO” INGREZZA™ (valbenazine) capsules 40 mg per capsule Push to release capsule.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELLIS F UNGER
04/11/2017