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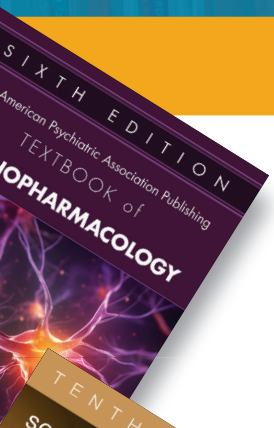

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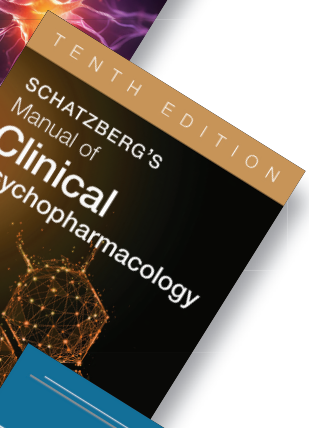

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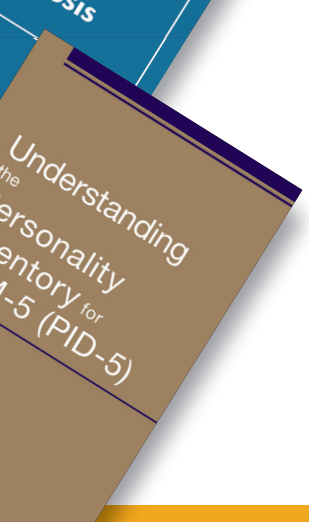

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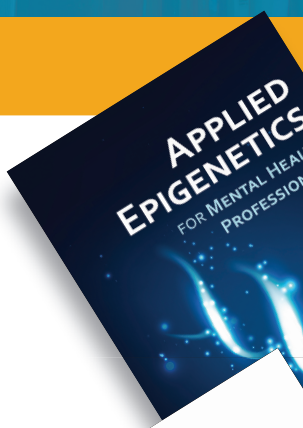

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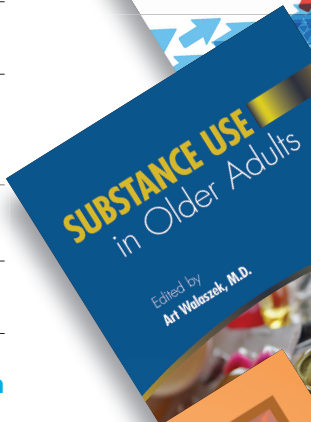

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INGREZZA® (valbenazine) capsules, for oral use

INGREZZA® SPRINKLE (valbenazine) capsules, for oral use

Brief Summary: for full Prescribing Information and Medication Guide, refer to package insert.

INDICATIONS AND USAGE

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

WARNING: DEPRESSION AND SUICIDAL IDEATION AND BEHAVIOR IN PATIENTS WITH HUNTINGTON'S DISEASE

VMAT2 inhibitors, including INGREZZA and INGREZZA SPRINKLE, can increase the risk of depression and suicidal thoughts and behavior in patients with Huntington's disease. Anyone considering the use of INGREZZA or INGREZZA SPRINKLE must balance the risks of depression and suicidal ideation and behavior with the clinical need for treatment of chorea. Closely monitor patients for the emergence or worsening of depression, suicidal ideation, or unusual changes in behavior. Inform patients, their caregivers, and families of the risk of depression and suicidal ideation and behavior and instruct them to report behaviors of concern promptly to the treating physician. Particular caution should be exercised in treating patients with a history of depression or prior suicide attempts or ideation, which are increased in frequency in patients with Huntington's disease.

CONTRAINDICATIONS

INGREZZA and INGREZZA SPRINKLE are contraindicated in patients with a history of hypersensitivity to valbenazine or any components of INGREZZA or INGREZZA SPRINKLE. Rash, urticaria, and reactions consistent with angioedema (e.g., swelling of the face, lips, and mouth) have been reported.

WARNINGS AND PRECAUTIONS

Depression and Suicidal Ideation and Behavior in Patients with Huntington's Disease

Patients with Huntington's disease are at increased risk for depression, and suicidal ideation or behaviors. VMAT2 inhibitors, including INGREZZA and INGREZZA SPRINKLE, can increase the risk for suicidal ideation and behaviors in patients with Huntington's disease. In a 14-week, double-blind, placebo-controlled trial, depression or depressed mood was reported in 4.7% of patients taking INGREZZA compared to 1.6% of patients who received placebo, and no patients taking INGREZZA reported suicidal ideation or behavior compared to 1 patient (1.6%) who received placebo. Patients with significant risk for suicidal behavior or with unstable psychiatric symptoms were excluded from this trial. Suicidal ideation (9 subjects; 7.2%) and suicide attempts (3 subjects; 2.4%) were reported in the longer open-label extension trial (N = 125). When considering the use of INGREZZA or INGREZZA SPRINKLE, the risk of suicidal ideation and behaviors must be balanced against the need for treatment of chorea. All patients treated with INGREZZA and INGREZZA SPRINKLE should be observed for new or worsening depression, suicidal ideation or behaviors. If any of these reactions occur and do not resolve, consider discontinuing treatment with INGREZZA or INGREZZA SPRINKLE.

Hypersensitivity Reactions

Hypersensitivity reactions, including cases of angioedema involving the larynx, glottis, lips, and eyelids, have been reported in the post-marketing setting in patients after taking the first or subsequent doses of INGREZZA. A case of angioedema involving the lips and face, with rash and shortness of breath was reported in a patient with Huntington's disease taking INGREZZA during a clinical study. Urticaria and rash were also reported during a clinical study in patients with Huntington's disease. Angioedema associated with laryngeal edema can be fatal. If any of these reactions occur, discontinue INGREZZA or INGREZZA SPRINKLE.

Somnolence and Sedation

INGREZZA and INGREZZA SPRINKLE can cause somnolence and sedation, which was the most common adverse reaction in placebo-controlled trials. 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 or INGREZZA SPRINKLE.

QT Prolongation

INGREZZA and INGREZZA SPRINKLE 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 and INGREZZA SPRINKLE concentrations may be higher and QT prolongation clinically significant. For patients who are CYP2D6 poor metabolizers or are taking a strong CYP2D6 inhibitor, dose reduction may be necessary. For patients taking a strong CYP3A4 inhibitor, reduce the dose of INGREZZA or INGREZZA SPRINKLE to 40 mg once daily. INGREZZA and INGREZZA SPRINKLE 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.

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with drugs that reduce dopaminergic transmission. In the post-marketing setting, NMS has been reported in patients taking VMAT2 inhibitors, including INGREZZA. Clinicians should be alerted to the signs and symptoms associated with NMS. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria, rhabdomyolysis, and acute renal failure. The diagnosis of NMS can be complicated; other serious medical illness (e.g., pneumonia, systemic infection) and untreated or inadequately treated extrapyramidal disorders can present with similar signs and symptoms. Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include (1) immediate discontinuation of INGREZZA or INGREZZA SPRINKLE; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

Recurrence of NMS has been reported with resumption of drug therapy. If treatment with INGREZZA or INGREZZA SPRINKLE is needed after recovery from NMS, patients should be monitored for signs of recurrence.

Parkinsonism

INGREZZA and INGREZZA SPRINKLE may cause parkinsonism. 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.

In a placebo-controlled clinical study in patients with chorea associated with Huntington's disease, the incidence of parkinson-like adverse events was 4.7% in patients treated with INGREZZA and 0% in placebo-treated patients. Because rigidity can develop as part of the underlying disease process in Huntington's disease, it may be difficult to distinguish between potential drug-induced parkinsonism and progression of underlying Huntington's disease. Drug-induced parkinsonism has the potential to cause more functional disability than untreated chorea for some patients with Huntington's disease.

Postmarketing safety reports have described parkinson-like symptoms in patients taking INGREZZA for tardive dyskinesia, some of which were severe and required hospitalization. In most cases, severe parkinsonism occurred within the first 2 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 or INGREZZA SPRINKLE treatment in patients who develop clinically significant parkinson-like signs or symptoms.

ADVERSE REACTIONS

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

- Depression and Suicidal Ideation and Behavior in Patients with Huntington's Disease
- Hypersensitivity Reactions
- Somnolence and Sedation
- QT Prolongation
- Neuroleptic Malignant Syndrome (NMS)
- Parkinsonism

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.

The safety of INGREZZA SPRINKLE has been established from adequate and well-controlled studies of INGREZZA. Below is a display of the adverse reactions of INGREZZA in these adequate and well-controlled studies.

Tardive Dyskinesia

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 – Tardive Dyskinesia

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

Chorea Associated with Huntington's Disease
The safety of INGREZZA was evaluated in a 14-week placebo-controlled study including 127 patients with chorea associated with Huntington's disease. Patients were 25 to 75 years of age. The mean age was 54 years. Patients were 96% Caucasian, 1% African-American, 1% Asian, and 2% Other. With respect to ethnicity, 6% were Hispanic or Latino.

Adverse Reactions Leading to Discontinuation of Treatment
A total of 8% of INGREZZA-treated patients and 6% of placebo-treated patients discontinued because of adverse reactions.

Common Adverse Reactions
Adverse reactions that occurred in the placebo-controlled study at an incidence of ≥4% and greater than placebo are presented in Table 2.

Table 2: Adverse Reactions in the Placebo-Controlled Study of 12-week Treatment Duration Reported at ≥4% and >Placebo – Chorea Associated with Huntington's Disease

Adverse Reaction	INGREZZA (n=64) %	Placebo (n=63) %
Nervous System Disorders		
Somnolence, lethargy, sedation	18.8	3.2
Akathisia	6.3	4.8
General Disorders and Administration Site Conditions		
Fatigue	14.1	9.5
Skin and Subcutaneous Tissue Disorders		
Urticaria	9.4	0
Rash	7.8	0
Gastrointestinal Disorders		
Diarrhea	4.7	1.6
Nausea	4.7	0
Psychiatric Disorders		
Insomnia, middle insomnia	6.3	1.6
Depression, depressed mood	4.7	1.6
Musculoskeletal Disorders		
Back pain	4.7	0

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, and pruritus)

DRUG INTERACTIONS

Drugs Having Clinically Important Interactions with INGREZZA and INGREZZA SPRINKLE

Table 3: Clinically Significant Drug Interactions with INGREZZA and INGREZZA SPRINKLE

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

OVERDOSAGE

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

Management of Overdosage
No specific antidotes for INGREZZA or INGREZZA SPRINKLE 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).

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

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(valbenazine) capsules

From the start.

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Remission was achieved in **59% of patients** at week 48.[2,3,4,†,‡]

SELECTIVE PHARMACOLOGY

Only INGREZZA exclusively delivers one **primary metabolite (+α)** for potent and selective inhibition of VMAT2[1,5,6,*]

THERAPEUTIC DOSE FROM DAY 1

The only VMAT2 inhibitor that offers **an effective starting dosage** you can adjust based on response and tolerability[1]

*Based on *in vitro* VMAT2 binding affinity of dihydrotetrabenazine (HTBZ) metabolites and INGREZZA's primary active metabolite, +α HTBZ. The clinical significance of *in vitro* data is unknown and is not meant to imply clinical outcomes.
†Remission defined as "complete response" by study authors.
‡Post-hoc analysis of the KINECT 4 trial, 59% (61/103) of patients who completed the trial taking INGREZZA (40 mg and 80 mg) achieved a score of 1 or less for each body part measured with AIMS at Week 48. The results are descriptive in nature.

Learn more about control made simple for your TD patients.

#1 PRESCRIBED VMAT2 INHIBITOR[7]

MOST PRESCRIBED FOR 7 YEARS AND COUNTING

Important Information

INDICATION & USAGE

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

IMPORTANT SAFETY INFORMATION

Depression and Suicidality in Patients with Huntington's Disease: VMAT2 inhibitors, including INGREZZA and INGREZZA SPRINKLE, can increase the risk of depression and suicidal thoughts and behavior (suicidality) in patients with Huntington's disease. Balance the risks of depression and suicidality with the clinical need for treatment of chorea. Closely monitor patients for the emergence or worsening of depression, suicidal ideation, or unusual changes in behavior. Inform patients, their caregivers, and families of the risk of depression and suicidal ideation and behavior and instruct them to report behaviors of concern promptly to the treating physician. Exercise caution when treating patients with a history of depression or prior suicide attempts or ideation, which are increased in frequency in patients with Huntington's disease.

CONTRAINDICATIONS

INGREZZA and INGREZZA SPRINKLE are contraindicated in patients with a history of hypersensitivity to valbenazine or any components of INGREZZA or INGREZZA SPRINKLE.

WARNINGS & PRECAUTIONS

Hypersensitivity Reactions
Hypersensitivity reactions, including cases of angioedema involving the larynx, glottis, lips, and eyelids, have been reported in patients after taking the first or subsequent doses of INGREZZA. Angioedema associated with laryngeal edema can be fatal. If any of these reactions occur, discontinue INGREZZA or INGREZZA SPRINKLE.

Somnolence and Sedation
INGREZZA and INGREZZA SPRINKLE can cause somnolence and sedation. 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 or INGREZZA SPRINKLE.

QT Prolongation
INGREZZA and INGREZZA SPRINKLE may prolong the QT interval, although the degree of QT prolongation is not clinically significant at concentrations expected with recommended dosing. INGREZZA and INGREZZA SPRINKLE 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.

WARNINGS & PRECAUTIONS (continued)

Neuroleptic Malignant Syndrome
A potentially fatal symptom complex referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with drugs that reduce dopaminergic transmission, including INGREZZA. The management of NMS should include immediate discontinuation of INGREZZA or INGREZZA SPRINKLE, intensive symptomatic treatment and medical monitoring, and treatment of any concomitant serious medical problems. If treatment with INGREZZA or INGREZZA SPRINKLE is needed after recovery from NMS, patients should be monitored for signs of recurrence.

Parkinsonism
INGREZZA and INGREZZA SPRINKLE may cause parkinsonism. Parkinsonism has also been observed with other VMAT2 inhibitors. Reduce the dose or discontinue INGREZZA or INGREZZA SPRINKLE treatment in patients who develop clinically significant parkinson-like signs or symptoms.

ADVERSE REACTIONS

The most common adverse reaction in patients with tardive dyskinesia (≥5% and twice the rate of placebo) is somnolence.

The most common adverse reactions in patients with chorea associated with Huntington's disease (≥5% and twice the rate of placebo) are somnolence/lethargy/sedation, urticaria, rash, and insomnia.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit MedWatch at **www.fda.gov/medwatch** or call **1-800-FDA-1088**.

Dosage Forms and Strengths: INGREZZA and INGREZZA SPRINKLE are available in 40 mg, 60 mg, and 80 mg capsules.

Please see the adjacent pages for Brief Summary of Prescribing Information and visit Neurocrine.com/INGREZZAPI for full Prescribing Information, including Boxed Warning.

REFERENCES: 1. INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc. **2.** Correll CU, Citrome L, Singer C, et al. Sustained treatment response and global improvements with long-term valbenazine in patients with tardive dyskinesia. *J Clin Psychopharmacol.* Published online May 20, 2024. **3.** Correll CU, Cutler AJ, Kane JM, McEvoy JP, Liang GS, O'Brien CF. Characterizing treatment effects of valbenazine for tardive dyskinesia: additional results from the KINECT 3 Study. *J Clin Psychiatry.* 2018;80(1):18m12278. **4.** Data on file. Neurocrine Biosciences, Inc. **5.** Harriott ND, Williams JP, Smith EB, Bozigian HP, Grigoriadis DE. VMAT2 inhibitors and the path to INGREZZA (valbenazine). *Prog Med Chem.* 2018;57(1):87-111. **6.** Grigoriadis DE, Smith E, Hoare SRJ, Madan A, Bozigian H. Pharmacologic characterization of valbenazine (NBI-98854) and its metabolites. *J Pharmacol Exp Ther.* 2017;361(3):454-461. **7.** Data on file as of Q3 2023. Neurocrine Biosciences, Inc.

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