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

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 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.

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.

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.

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