



ONCE-DAILY

INGREZZA[®]
(valbenazine) capsules

KINECT 4:

A phase 3, 1-year, open-label trial of valbenazine in adults with tardive dyskinesia

Marder SR, Singer C, Lindenmayer JP, et al.
J Clin Psychopharmacol. 2019;39(6):620-627.

Important Information

INDICATION & USAGE

INGREZZA[®] (valbenazine) capsules is indicated for the treatment of adults with tardive dyskinesia.

IMPORTANT SAFETY INFORMATION

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.

Please see additional Important Safety Information throughout and accompanying full [Prescribing Information](#).

Background: KINECT 3 pivotal trial

FDA approval of INGREZZA® (valbenazine) capsules was based on positive results from the KINECT 3 pivotal study. KINECT 3 was a phase 3, randomized, double-blind, placebo-controlled, parallel, fixed-dose study evaluating the efficacy and safety of INGREZZA 40 mg or 80 mg, administered once daily for the treatment of adults with tardive dyskinesia (TD).^{1,2}

KINECT 3 study design included

- 6-week double-blind, placebo-controlled treatment period: Patients randomized 1:1:1 to INGREZZA 40 mg, INGREZZA 80 mg, or placebo^{1,2}
- 42-week double-blind treatment extension period, for up to 48 weeks of treatment. Patients receiving placebo were re-randomized 1:1 to INGREZZA 40 mg or INGREZZA 80 mg^{1,2}
- Patients initially randomized or re-randomized to the 80 mg group received 40 mg for the first week^{2,3}
 - Investigators could decrease the 80 mg dose once at any time during the study due to tolerability. Patients were discontinued if the new dose was not tolerated
- 4-week washout, for a total duration of up to 52 weeks¹

^a Videos were scored by blinded central AIMS video raters. Raters were blind to treatment and study visit.

^b Dose that was statistically significantly different from placebo to control for multiple comparisons.

^c Nominal *P* value when controlled for multiple comparisons.

KINECT 3 primary endpoint and results

- Primary efficacy endpoint was change in AIMS dyskinesia score (sum of items 1–7) from baseline to Week 6 for INGREZZA 80 mg vs placebo^{1,2,a}
- INGREZZA reduced TD severity at 6 weeks, with results you can start to see as early as 2 weeks^{1–3}
 - Mean change from baseline to Week 6 was –3.2 for INGREZZA 80 mg vs –0.1 for placebo ($P \leq 0.001$)^b. Reduction in TD severity was also seen with INGREZZA 40 mg (–1.9, $P < 0.01$)^c
 - AIMS score reduction by $\geq 50\%$ from baseline was observed in more patients taking INGREZZA vs placebo
- INGREZZA provided continued reduction of TD severity through 48 weeks^{1,4}

KINECT 4 study objective

KINECT 4 was a phase 3, open-label study conducted to further evaluate the long-term safety and tolerability of INGREZZA 40 mg or 80 mg, administered once daily. In addition, long-term effectiveness of treatment was assessed.⁵

Study population

In this long-term, open-label study, INGREZZA was studied in a broad population of adult patients with various underlying diagnoses and treatment regimens.⁵

KEY INCLUSION CRITERIA	SELECT STUDY DEMOGRAPHICS
<ul style="list-style-type: none">• Stable psychiatric status• 18 to 85 years of age	<ul style="list-style-type: none">• Of the 167 participants who entered the study, 103 (61.7%) completed 48 weeks of treatment and a 4-week washout period• Mean age was 57.4 years of age
Patients had one of these diagnoses <ul style="list-style-type: none">• Schizophrenia• Schizoaffective disorder• Mood disorder	<ul style="list-style-type: none">• 73% had a diagnosis of schizophrenia or schizoaffective disorder• 27% had a mood disorder
Diagnosis of DRBA-induced TD for ≥ 3 months before screening <ul style="list-style-type: none">• Moderate to severe TD based on qualitative assessment at screening	<ul style="list-style-type: none">• 88.3% were taking antipsychotics• 65% were taking antidepressants• 27% were taking anticholinergics

DRBA, dopamine receptor blocking agent.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS & PRECAUTIONS

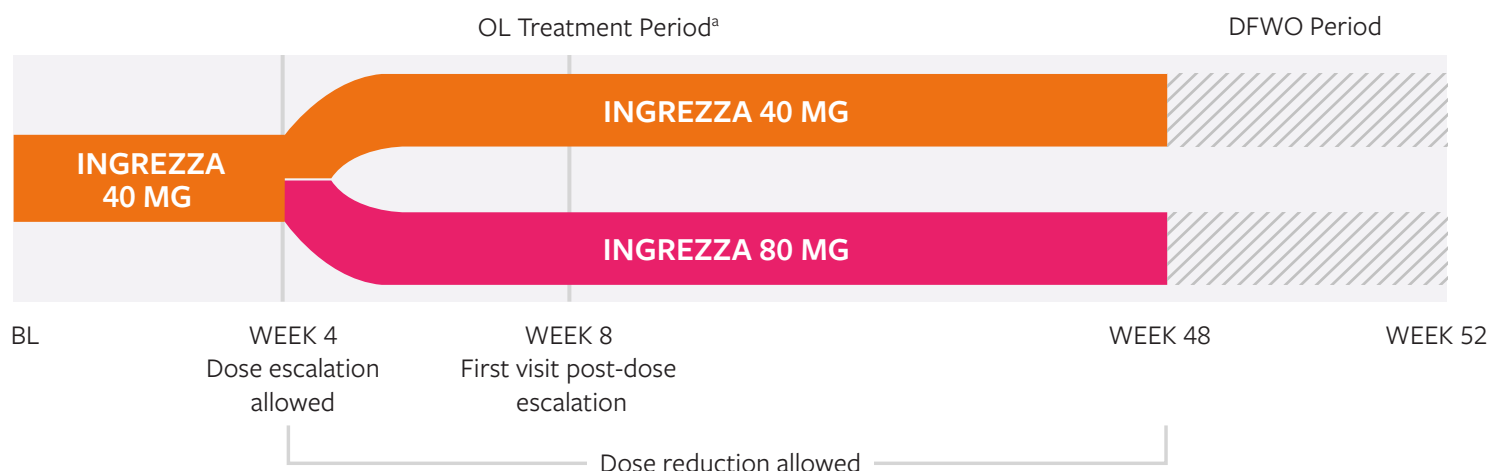
Somnolence

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.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.

KINECT 4 methodology

In the KINECT 4 study, eligible patients entered a 48-week treatment period with once-daily INGREZZA followed by a 4-week washout period.⁵



^a Postbaseline visits during OL treatment period were at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48.
BL, baseline; OL, open-label; DFWO, drug-free washout.

All patients received INGREZZA 40 mg for 4 weeks. The dosage was then escalated to 80 mg once daily based on individual patient tolerability and clinical response to be reflective of real-world care.⁵

- At the end of Week 4 (first postbaseline visit), the dose was escalated to 80 mg if both of the following conditions were met: (1) Clinical Global Impression of Change-TD (CGI-TD) score of ≥ 3 and (2) acceptable safety and tolerability with 40 mg, based on investigator's judgment⁵
- A dose reduction to 40 mg was permitted once any time after dose escalation due to tolerability. Patients were discontinued if the 40 mg dose was not tolerated⁵

KINECT 4 allowed patients to maintain the 40 mg dose after 4 weeks based on tolerability and treatment response⁵

- 27.6% of patients were maintained on the 40 mg dose for tolerability or because they already experienced an adequate response

Assessments^{5,b}

SAFETY ANALYSES	EFFICACY MEASURES ASSESSED
<ul style="list-style-type: none"> • Treatment-emergent adverse events (TEAEs) • Psychiatric status • Treatment-emergent akathisia or parkinsonism • Emergence of suicidal ideation or behavior • 12-lead electrocardiogram (ECG) • Vital signs and laboratory assessments 	<ul style="list-style-type: none"> • Abnormal Involuntary Movement Scale (AIMS) change from baseline^{c,d} • Clinical Global Impression of Change-TD (CGI-TD) • Patient Global Impression of Change-TD (PGIC) • AIMS response rates^e

^b All study assessments were analyzed descriptively.

^c AIMS was scored at baseline and at Weeks 8, 12, 24, 36, 48, and 52 by site raters, who were study investigators (generally psychiatrists).

^d For continuity with earlier valbenazine studies, AIMS was also scored by consensus between 2 central AIMS video raters (movement disorder neurologists) at limited visits (baseline, Week 8 [first visit after dose escalation], and Week 52 [after washout]). Raters were blinded to treatment and study visit.

^e AIMS response defined as $\geq 50\%$ improvement from baseline in the total score (sum of items 1-7).

Long-term safety profile

In the KINECT 4 study, the majority of TEAEs were mild or moderate in intensity and few led to premature discontinuation.⁵

Treatment emergent adverse reactions (TEAEs) reported in ≥3% of all patients⁵

Adverse Events	INGREZZA 40 MG (n=163) (%)	All INGREZZA treated ^a (n=153) (%)	INGREZZA 40 MG (n=35) (%)	INGREZZA 80 MG (n=107) (%)
Urinary tract infection	1.2%	8.5%	8.6%	8.4%
Headache	4.3%	5.2%	5.7%	5.6%
Nasopharyngitis	1.2%	4.6%	2.9%	3.7%
Suicidal ideation	0.6%	4.6%	8.6%	3.7%
Constipation	0.6%	3.9%	5.7%	1.9%
Fall	0.0%	3.9%	2.9%	2.8%
Fatigue	3.7%	3.9%	8.6%	2.8%
Hypertension	0.0%	3.9%	0.0%	3.7%
Somnolence	3.7%	3.9%	0.0%	3.7%
Back pain	0.6%	3.3%	2.9%	2.8%
Dizziness	0.6%	3.3%	0.0%	4.7%

BL TO WEEK 4

WEEK 4 TO 48

^a Includes 11 patients who had a dose reduction from 80 mg to 40 mg after Week 4.
BL, baseline.

- After Week 4, <15% of all participants had serious TEAEs (13.7%) or TEAE leading to discontinuation (11.8%)⁵

**Psychiatric status generally remained stable during the clinical study.⁵
No clinically important changes in akathisia or parkinsonism.⁵**

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS & PRECAUTIONS (continued)

QT Prolongation

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

Parkinsonism

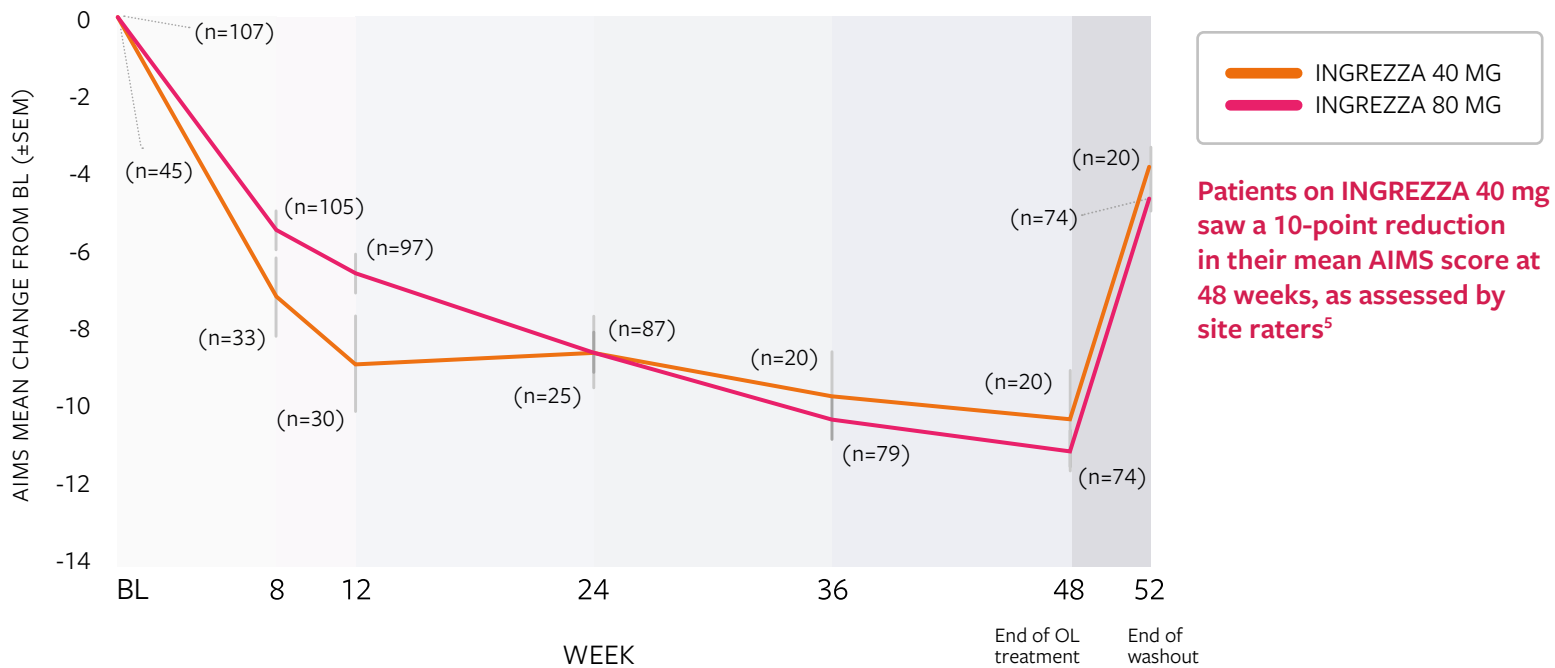
INGREZZA may cause parkinsonism in patients with tardive dyskinesia. Parkinsonism has also been observed with other VMAT2 inhibitors. Reduce the dose or discontinue INGREZZA treatment in patients who develop clinically significant parkinson-like signs or symptoms.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.

Long-term effectiveness

In the KINECT 4 study, sustained TD improvements were observed with INGREZZA 40 mg. The effectiveness of INGREZZA 80 mg was also studied.⁵

Mean change from baseline in AIMS dyskinesia total score by site raters^{5,a}

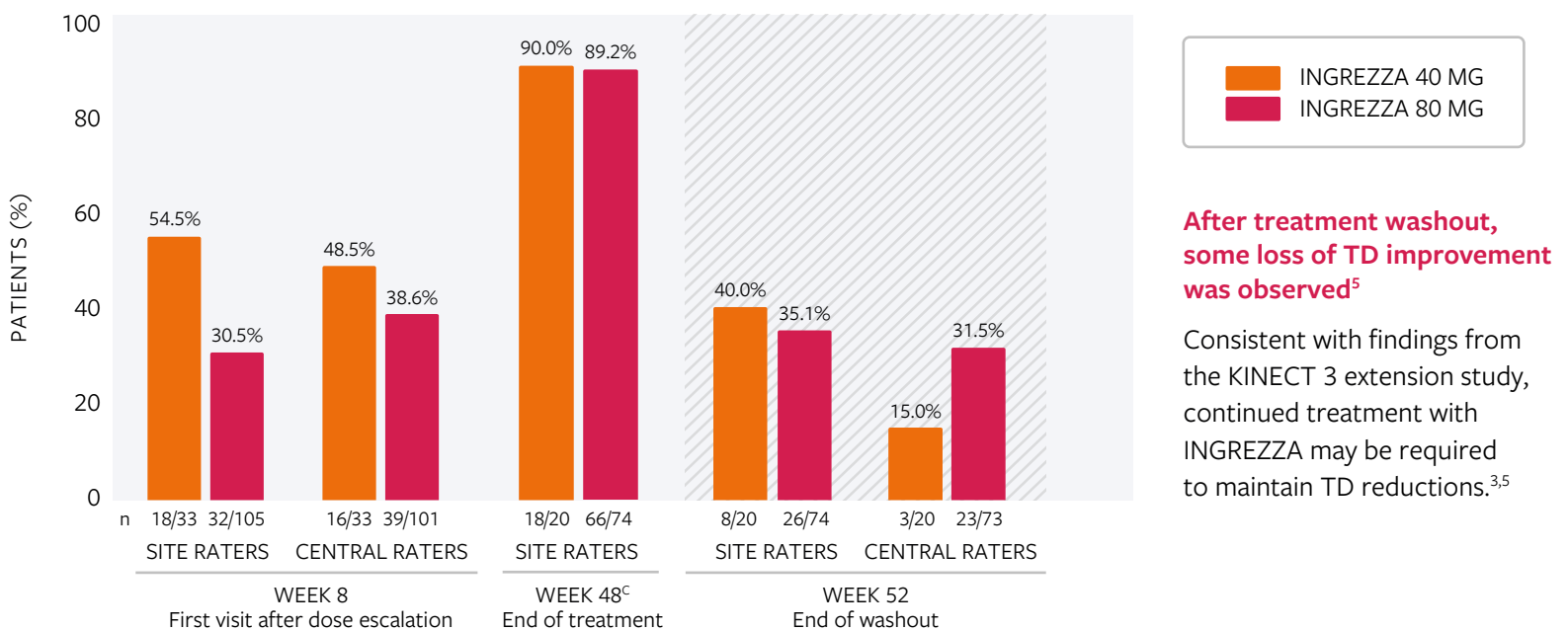


Patients who received 80 mg in the KINECT 4 study followed a different dosing schedule than those in the KINECT 3 pivotal study. In KINECT 3, patients had a dose increase from 40 mg to 80 mg after Week 1. In KINECT 4, patients had a dose increase from 40 mg to 80 mg after Week 4. The impact of this on long-term effectiveness is not known.

^a Analyses were based on observed cases, with no imputation of missing data. Data are not shown for 11 participants who had a dose reduction from 80 mg to 40 mg after Week 4. AIMS, Abnormal Involuntary Movement Scale; BL, baseline; OL, open-label; SEM, standard error of the mean.

- Mean AIMS total score change from baseline to Week 8 was -4.5 for INGREZZA 40 mg and -3.5 for INGREZZA 80 mg, as assessed by central video raters⁵

AIMS response rates by central video and site raters^{5,b}



^b AIMS response defined as $\geq 50\%$ improvement from baseline in the total score (sum of items 1-7). Data are not shown for 11 participants who had a dose reduction from 80 mg to 40 mg after Week 4.

^c Per study protocol, Week 48 AIMS was not evaluated by central AIMS video raters. AIMS, Abnormal Involuntary Movement Scale.

KINECT 4: Summary of findings

Long-term treatment with INGREZZA[®] (valbenazine) capsules 40 mg may be appropriate for some patients

Maintain or adjust back to INGREZZA 40 mg based on your patient's individual treatment needs⁵

Even at the lowest dose, long-term effectiveness of once-daily INGREZZA was observed through 48 weeks⁵

- INGREZZA demonstrated sustained improvements in TD
- ~49% and 55% of patients on INGREZZA 40 mg achieved rigorous thresholds of TD improvement at 8 weeks, as measured by AIMS response by central video raters and site raters, respectively³

Long-term tolerability with no new safety concerns demonstrated with INGREZZA⁵

- Majority of TEAEs were mild or moderate in intensity and few led to premature discontinuation
- Psychiatric stability was generally maintained throughout the study

³ AIMS response defined as $\geq 50\%$ improvement from baseline in the total score (sum of items 1-7).

IMPORTANT SAFETY INFORMATION (continued)

ADVERSE REACTIONS

The most common adverse reaction ($\geq 5\%$ and twice the rate of placebo) is somnolence. Other adverse reactions ($\geq 2\%$ and $>$ Placebo) include: anticholinergic effects, balance disorders/falls, headache, akathisia, vomiting, nausea, and arthralgia.

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.

Please see accompanying INGREZZA full [Prescribing Information](#)

REFERENCES: 1. INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc; 2020. 2. Hauser RA, Factor SA, Marder SR, et al. KINECT 3: a phase 3 randomized, double-blind, placebo-controlled trial of valbenazine for tardive dyskinesia. *Am J Psychiatry*. 2017;174(5):476-484. 3. Data on file. Neurocrine Biosciences, Inc. 4. Factor SA, Remington G, Comella CL, et al. The effects of valbenazine in participants with tardive dyskinesia: results of the 1-year KINECT 3 extension study. *J Clin Psychiatry*. 2017;78(9):1344-1350. 5. Marder SR, Singer C, Lindenmayer JP, et al. A phase 3, 1-year, open-label trial of valbenazine in adults with tardive dyskinesia. *J Clin Psychopharmacol*. 2019;39(6):620-627.