New Drug Overview
Ingrezza (valbenazine)

INTRODUCTION

- Tardive dyskinesia (TD) is an iatrogenic condition that results from the long-term use of dopamine receptor blocking agents (DRBAs), predominantly antipsychotics/neuroleptics (first generation antipsychotics [FGAs], also known as typical antipsychotics, as well as second-generation antipsychotics [SGAs], which are also known as atypical antipsychotics) and metoclopramide *(Rana et al 2013).*
- While the pathophysiology of TD is not well-understood, the most prominent theory suggests chronic exposure to neuroleptics results in dopamine-2 (D2) receptor up-regulation with postsynaptic dopamine receptor supersensitivity *(Waln and Jankovic 2013).*
- Prospective studies of patients treated with FGAs suggest that the annual incidence of TD is between 3 to 8%. With SGAs, the mean annual incidence is estimated at 2.1 to 4.2%. Although TD prevalence has been less studied with metoclopramide, the published data indicate a prevalence ranging from 1 to 10% (*Waln and Jankovic 2013).*
- The lower incidence of TD with SGAs compared to FGAs is hypothesized to be a result of pharmacologic differences in dopamine and serotonin receptor affinity. SGAs tend to have lower D2 receptor occupancy and higher serotonin receptor activity than FGAs *(Howland et al 2011, Vijayakumar and Jankovic 2016).*
- TD is characterized by rapid, repetitive, stereotypic movements mostly involving the oral, buccal, and lingual area (Muller et al 2015). Movements may include tongue thrusting, lip smacking or pursing, grimacing and chewing movements, piano-playing finger movements, trunk and pelvic thrusting, flexion/extension of the ankles or toes, irregular respirations, and various vocalizations (*Rana et al 2013*).
- TD can affect the ability of patients to perform activities of daily living as well as make it more difficult for them to engage in the community or workplace, given the visibility of involuntary movements and societal stigma related to mental illness *(FDA Ingrezza Medical Review*).
- According to the Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV), TD develops during exposure to a DRBA for ≥ 3 months (or one month in patients ≥ 60 years of age) or within four weeks of withdrawal from an oral medication (or within eight weeks of withdrawal from a depot medication). The disorder should persist for at least one month after discontinuation of an offending drug to qualify as TD (*Waln and Jankovic 2013*).
- The first step in the treatment of TD is to discontinue the offending agent via slow taper. Sudden withdrawal of the offending drug should be avoided, as symptoms of TD could worsen. In patients with psychiatric conditions which require continued use of a neuroleptic, switching from an FGA to an SGA could be considered. Quetiapine and clozapine are the preferred SGAs due to their low receptor occupancy and fast dissociation from D2 receptors (*Vijayakumar and Jankovic 2016*).
- Ingrezza (valbenazine), a vesicular monoamine transporter 2 (VMAT2) inhibitor approved by the Food and Drug Administration (FDA) on April 11, 2017, was granted fast track status, priority review, and breakthrough therapy designation *(FDA Web site).*
  - Valbenazine is the first and only drug approved by the FDA for TD.
  - The mechanism of action of valbenazine is thought to be mediated through the reversible inhibition of VMAT2, a transporter that regulates monoamine uptake from the cytoplasm to the synaptic vesicle for storage and release. In other words, by modulating the pre-synaptic packaging and release of dopamine into the synapse, striatal dopamine depletion can be achieved (*Hauser et al 2017, Jankovic 2016*).
  - Valbenazine is the third VMAT2 inhibitor approved by the FDA; Xenazine (tetrabenazine) and Austedo (deutetrabenazine) were the first VMAT2 inhibitors approved in August 2008 and April 3, 2017, respectively. Both are indicated in the treatment of Huntington's chorea (*Austedo product information 2017, Xenazine product information 2015*).
  - Unlike tetrabenazine and deutetrabenazine, valbenazine does not carry a boxed warning for increased risk of depression and suicidal thoughts or behavior (*Austedo product information 2017, Xenazine product information 2015).*
  - Valbenazine is currently being studied as a potential treatment for Tourette's syndrome (phase 2) *(Ingrezza Web site).*
- Medispan class: Psychotherapeutic and Neurological Agents – Misc.; Movement Disorder.

INDICATION

- Valbenazine is indicated for the treatment of adults with TD *(Ingrezza prescribing information 2017*).

Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise

CLINICAL EFFICACY SUMMARY

- The FDA approval of valbenazine was based on the results from the KINECT 3 trial, a 6-week, phase 3, double-blind, placebo-controlled, multicenter, randomized clinical trial with 224 patients with moderate to severe TD *(Hauser et al 2017, FDA Ingrezza Medical Review).*
  - In this trial, 66.1% of patients had schizophrenia or schizoaffective disorder, while 33.9% had a mood disorder. Additionally, 85.5% received concomitant antipsychotics (16.7% on FGAs and 76.7% on SGAs).
  - The mean baseline Abnormal Involuntary Movement Scale (AIMS) dyskinesia score was 10.0 (range 0 to 20) between the treatment groups.
  - Patients were randomized 1:1:1 to receive valbenazine 40 mg once daily, valbenazine 80 mg once daily, or placebo.
  - The primary endpoint was the AIMS dyskinesia score, which was a modified version of the AIMS score. The AIMS dyskinesia score included 7 items rating involuntary movements in the orofacial region, extremities, and trunk on a scale from 0 (no dyskinesia) to 4 (severe dyskinesia). The original AIMS consists of a 12-item rating scale that includes the 7 aforementioned items as well as three items rating global severity, patients awareness, and distress associated with movements, and 2 items concerning problems with teeth and dentures. AIMS has been validated and widely used to assess the presence and severity of TD.
    - The AIMS dyskinesia score was evaluated by remote central video raters (movement specialists) via recordings for each patient visit. These raters were blinded to the patient's identity, visit number, and treatment arm.
    - The AIMS dyskinesia score was reduced from baseline to six weeks by 3.2 in the valbenazine 80 mg group compared to 0.1 in the placebo group ($p < 0.001$). In the valbenazine 40 mg group, the AIMS dyskinesia score decreased by 1.9 compared to 0.1 in the placebo group ($p = 0.002$).
  - The percentage of patients who achieved an AIMS response (defined in the trial as a reduction of ≥ 50% from baseline score) was 40.0% in the 80 mg group ($p < 0.001$) and 23.8% in the 40 mg group ($p = 0.02$), compared to 8.7% in the placebo group.
  - The key secondary endpoint of mean Clinical Global Impression of Change - Tardive Dyskinesia (CGI-TD) score was used by site investigators to rate the overall change in TD from baseline at Week 6. CGI-TD scores ranged from 1 (very much improved) to 7 (very much worse). The mean CGI-TD score did not reach statistical significance for either valbenazine dosage group when compared to placebo ($p = 0.056$ and $p = 0.074$ for valbenazine 80 mg and 40 mg, respectively).
  - Another secondary endpoint was Patient Global Impression of Change (PGIC), which characterized the patient's perception of improvement in their TD symptoms. The mean PGIC score at Week 6 was slightly worse in both valbenazine treatment groups compared to placebo, but the differences did not reach nominal statistical significance.
  - With the exploratory endpoint of improvement in tardive dyskinesia impact scale (TDIS) score, both doses of valbenazine were numerically superior to placebo at Weeks 4 and 6, however, the differences did not reach statistical significance.
  - The most common adverse effects (AE) observed with valbenazine (both dosage groups combined) vs. placebo were somnolence (5.3% vs. 3.9%), akathisia (3.3% vs. 1.3%), and dry mouth (3.3% vs. 1.3%). Suicidal ideation was the most common AE in the placebo group (5.3% vs. 2.6% in both valbenazine groups combined).
  - The results from the long-term extension study (KINECT 3 Extension) were presented in the form of a poster at the 55th Annual Meeting of the American College of Neuropsychopharmacology in December 2016 *(Grigoriadis et al 2016)*.
    - Subjects who completed the 6-week trial were eligible to participate in the 42-week extension period (with a 4-week washout period at the end of the 48-week period). Those initially randomized to placebo were re-randomized 1:1 to valbenazine 80 or 40 mg/day; those initially randomized to valbenazine 80 or 40 mg/day continued at the same dose.
    - The primary and secondary endpoints (ie, AIMS dyskinesia score change from baseline to Week 48 and CGI-TD score at Week 48, respectively) remained the same in the extension period.

- At Week 48, mean changes from baseline (of the six week trial) were -4.8 and -3.0for valbenazine 80 and 40 mg/day, respectively (p-value not provided).
- At Week 48, 52.4% and 28.3% of patients on valbenazine 80 mg/day and 40 mg/day, respectively, were AIMS 50% responders (p-value not provided).
- CGI-TD scores demonstrated clinically meaningful global improvement for both treatment groups (p-value not provided).
- The PGIC and TDIS scores showed improvement in patient perception from Week 8 to Week 48 in both valbenazine groups, however, the FDA stated that the patient's awareness of their treatment with active drug and attrition bias could have confounded these results.
- After the 4-week treatment washout period (at week 52), TD severity began reverting towards baseline levels, and responder rates were lower than those observed at week 8.

CLINICAL GUIDELINE

- **American Academy of Neurology (AAN)** Evidence-based guideline: Treatment of tardive syndromes (TS) *(Bhidayasiri et al 2013)*
  - Level A recommendations (recommendation must be done; high confidence in the evidence with high benefit and low risk)
    - None
  - Level B recommendations (recommendation should be done based on benefit/risk profile)
    - Ginkgo biloba extract (EGb-761) for schizophrenia only
    - Clonazepam, for short-term use
  - Level C recommendations (recommendation may or might be done; lowest recommendation level considered useful within the scope of practice)
    - Amantadine for short-term use
    - Tetrabenazine
  - Level U (available evidence is insufficient to support or refute efficacy of an intervention)
    - Withdrawal of DRBAs
    - Switching from typical to atypical antipsychotics
    - Acetazolamide plus thiamine
    - Typical antipsychotics
    - Atypical antipsychotics
    - Electroconvulsive therapy
    - Reserpine or α-methyldopa
    - Bromocriptine
    - Anticholinergic agents (other than galantamine)
    - Biperiden discontinuation
    - Antioxidants (vitamin E, vitamin B6, melatonin, selegiline, yi-gan san)
    - Baclofen
    - Levetiracetam
    - Nifedipine
    - Buspirone
    - Botulinum toxin
    - Pallidal deep-brain stimulation

SAFETY SUMMARY

- **Contraindications**
  - None

- **Warnings/precautions**
  - Somnolence
  - QT prolongation
    - Valbenazine should be avoided in patients with congenital long QT syndrome or with arrhythmias associated with a prolonged QT interval.

- **Adverse effects**

Table 1. AEs reported in ≥ 2% of patients

AE	Valbenazine (n = 262)	Placebo (n = 183)
Somnolence (somnolence, fatigue, sedation)	10.9%	4.2%
Anticholinergic effects (dry mouth, constipation, disturbance in attention blurred vision, urinary retention)	5.4%	4.9%
Balance disorders/falls (fall gait disturbance, dizziness, balance disorder)	4.1%	2.2%
Headache	3.4%	2.7%
Akathisia	2.7%	0.5%
Vomiting	2.6%	0.6%
Nausea	2.3%	2.1%
Arthralgia	2.3%	0.5%

- **Drug Interactions**
  - Concomitant use of monamine oxidase inhibitors (MAOI) is not recommended, as this could result in increased synaptic levels of monoamine oxidase, which can lead to serotonin syndrome.
  - Concomitant use with strong Cytochrome P450 (CYP) 3A4 inducers is also not recommended, as this could lead to decreased levels of valbenazine.
  - Valbenazine dose may need to be decreased when given concomitantly with strong CYP3A4 and CYP2D6 inhibitors.

DOSING AND ADMINISTRATION

Table 2. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Ingrezza (valbenazine)	Capsules	Oral	Daily	A lower dose should be administered in patients with moderate to severe hepatic failure

See the current prescribing information for full details

CONCLUSION

- The approval of valbenazine has provided the first FDA-approved treatment option for TD.
  - Valbenazine was granted priority review, accelerated approval, breakthrough therapy designation by the FDA.
- Prior to the approval of valbenazine, tetrabenazine, a VMAT2 inhibitor FDA-approved for Huntington's chorea, was used off-label to treat TD.
- The first step in the treatment of TD is to discontinue the offending agent by slow taper. The patient can switch to quetiapine and clozapine (SGAs of choice) if needed.
- The KINECT 3 trial demonstrated a significant reduction in AIMS dyskinesia score at -3.2 in the valbenazine 80 mg/day group and -1.9 in the valbenazine 40 mg/day group, however, there were no significant improvements in the CGI-TD score or patient-perceived improvement in function or QOL.
- The extension trial continued to demonstrate reductions in AIMS dyskinesia score at week 48, from baseline in both dosage groups.
- The 2013 American Academy of Neurology (AAN) evidence-based guidelines for the treatment of tardive syndromes (TS) did not make any level A (highest level of evidence for efficacy) treatment recommendations. Gingko biloba and clonazepam were recommended in the level B category, amantadine and tetrabenazine were recommended in the level

C category, and a large number of other agents/therapies were recommended in the level U (insufficient evidence) category.

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Publication Date: September 8, 2017