For Tardive Dyskinesia

Tardive dyskinesia (TD) is a repetitive, involuntary movement disorder caused by prolonged use of medications that block the dopamine receptor, most commonly antipsychotic drugs used to treat schizophrenia, bipolar disease, and other conditions. Until April 2017, there were **no treatments** with FDA approval for TD.

Since then, two new therapies have been approved for TD, both belonging to a class of drugs known as vesicular monoamine transporter-2 (VMAT2) inhibitors. ICER's report assesses both of these new VMAT2 inhibitors, **valbenazine (Ingrezza®, Neurocrine Biosciences)** and **deutetrabenazine (Austedo®, Teva)**, as well as **tetrabenazine (Xenazine®, Lundbeck),** a VMAT2 inihibitor approved for Huntington's disease that has been used off-label for treatment of TD.

Summary

NEW ENGLAND CEPAC VOTING RESULTS

The report was subject to public deliberation during a meeting of the New England CEPAC. A majority of the independent council voted that:

- Evidence is sufficient to suggest a net health benefit of both valbenazine and deutetrabenazine in treating tardive dyskinesia. However, uncertainty remains around the long-term benefits and harms.
- Evidence is insufficient to show a net health benefit of tetrabenazine, or distinguish between valbenazine and deutetrabenazine.

VALUE AND AFFORDABILITY

To fall within ICER's threshold value range of $100,000 to $150,000 per QALY, **valbenazine would require a discount of 85-90%. Deutretrabenazine would require a discount of 90-93%.**

Assuming standard discounts, only one in five eligible Americans with TD could be treated with the new therapies before crossing ICER's budget threshold of $915 million per year. As a result, ICER is issuing an **Affordability and Access Alert** as part of its final report on VMAT2 inhibitors for treating TD.

KEY POLICY RECOMMENDATIONS

- To provide reasonable value and facilitate improved access and affordability for patients, manufacturers should reduce prices for the VMAT2 inhibitors to better align with their demonstrated short-term clinical benefits.
- Given that the new VMAT2 inhibitors are priced far beyond their relative benefits for patients, payers should use available evidence, along with patient and clinical expert input, to develop prior authorization criteria, periods of authorized treatment, and methods for feedback to clinicians regarding potential alternative management of TD.
- Professional societies should update their clinical practice guidelines rapidly following the advent of paradigm-changing treatment options like the VMAT2 inhibitors.

Clinical Analyses

ICER EVIDENCE RATINGS

How strong is the evidence that VMAT2 inhibitors improve outcomes?

Valbenazine	Evidence promising but inconclusive
Deutetrabenazine	Evidence promising but inconclusive
Tetrabenazine	Insufficient evidence

Key clinical benefits studied in clinical trials:

- Abnormal Involuntary Movement Scale **(AIMS)**: A clinician-assessed 5-point scale that measures the severity of TD symptoms. Studies of VMAT2 inhibitors focused on seven key areas of the body.
- Clinical Global Impression of Change **(CGIC)**: A 7-point clinician-assessed measure of the change in a patient's TD symptoms at the time of assessment relative to a past visit.
- Patients' Global Impression of Change **(PGIC)**: A 7-point scale reflecting patients' rating of overall improvement.

	VALBENAZINE	DEUTETRABENAZINE	TETRABENAZINE
AIMS	**Greater reduction in AIMS scores** and more patients with a substantial improvement in AIMS scores compared to placebo.	**Greater reduction in AIMS scores,** and more patients with a substantial improvement in AIMS scores compared to placebo.	Tetrabenazine may reduce the symptoms of TD. **However,** the lack of randomized controlled trials, use of non-standard and variable clinical measures, and other study design limitations severely limit any inferences that can be drawn on effectiveness, and prevent even qualitative comparisons to the other VMAT2 inhibitors.
CGIC	Conflicting study findings with **no consistent benefit** over placebo on the CGIC scale.	**Did not demonstrate a statistically significant benefit** over placebo on the CGIC scale.	
PGIC	Conflicting study findings with **no consistent benefit** over placebo on the PGIC scale.	**Did not demonstrate a statistically significant benefit** over placebo on the PGIC scale.	

Clinical Analyses

HARMS

Valbenazine: The most common side effects of valbenazine were drowsiness, fatigue, headache, decreased appetite, akathisia (a movement disorder), nausea, vomiting, and dry mouth. There was no indication of increased rates of depression and suicidal ideation compared with placebo at six weeks.

Deutetrabenazine: Drowsiness, headache, diarrhea, fatigue, insomnia, anxiety, and nasopharyngitis were the most common side effects reported for deutetrabenazine. There was no indication of increased rates of depression and suicidal ideation compared with placebo at 12 weeks.

Tetrabenazine: The most common side effects of tetrabenazine were drowsiness, fatigue, insomnia, falls, depression, agitation, parkinsonism, akathisia (a movement disorder), and anxiety. Although statistical significance was not reported, tetrabenazine resulted in substantially greater incidence of depression compared to placebo in a clinical trial for Huntington's disease and carries a black box warning for the risks of depression and suicidality.

SOURCES OF UNCERTAINTY

Data limitations: There were no randomized controlled trials of tetrabenazine for people with TD, no studies directly comparing valbenazine and deutetrabenazine, and no studies comparing any of the agents to other agents used off-label in TD treatment.

Limitations in outcome measures: There is a lack of patient-reported measures directly reflecting the burden of TD symptoms on all aspects of life, including overall quality of life.

The provider-measured AIMS scale was based on office video recordings that were centrally reviewed and may not reflect how TD is assessed in routine practice. In addition, the summation of severity score across body regions may not reflect the overall burden of symptoms.

Patient reported outcomes: Patient-reported and clinician-based results for treatment impact on quality of life measures varied for unknown reasons. Some experts suggest that individuals with underlying psychotic disorders may be unaware of their symptom severity and less able to assess the impact of treatment.

Side effect profile: Randomized trials of valbenazine and deutetrabenazine were only six and 12 weeks in duration, respectively, so the long-term comparative safety and effectiveness of these drugs remains to be determined.

Economic Analyses

LONG-TERM COST-EFFECTIVENESS AT NET PRICE

Do the new therapies meet established thresholds for long-term cost-effectiveness?

The list prices of both valbenazine and deutetrabenazine are similar to that of tetrabenazine. However, tetrabenazine was originally priced based on its "orphan drug" status in a rare disease (Huntington's disease), and TD is a far more common condition. Analyses were based on net prices calculated using the wholesale acquisition cost minus the industry-wide average discount rate for branded drugs of 27%.

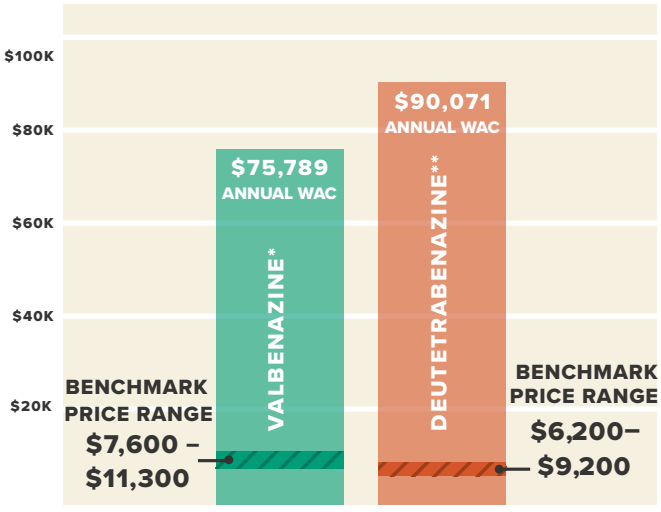
Compared to placebo, both valbenazine and deutetrabenazine **far exceed commonly accepted thresholds for long-term cost-effectiveness** of $50,000-$150,000 per quality adjusted life-year (QALY).

- **Valbenazine: $752,000 per QALY**
- **Deutetrabenazine: $1.1 million per QALY**

Tetrabenazine was not included in cost-effectiveness analyses due to the lack of comparative and rigorous data on its use in TD.

ICER'S VALUE-BASED PRICE BENCHMARKS

What is a fair price for VMAT2 inhibitors based on their value to patients and the health care system?



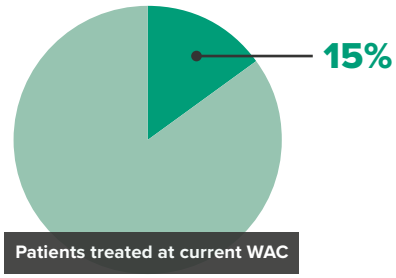
*Valbenazine: 80 mg per day
**Deutetrabenazine: 36 mg per day

To fall within ICER's threshold value range of $100,000 to $150,000 per QALY, **valbenazine would require a discount of 85-90%** and **deutetrabenazine would require a discount of 90-93%.** These discounts are greater than the expected discounts from wholesale acquisition costs (WAC).

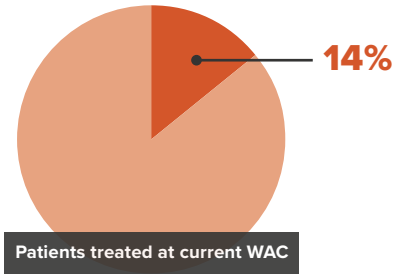
Economic Analyses

POTENTIAL SHORT-TERM BUDGET IMPACT

How many patients could be treated before crossing a $915 million budget impact threshold?



Valbenazine: At current WAC, approximately **15% of eligible patients** could be treated in a given year without crossing ICER's $915 million budget impact threshold. **21% could be treated at assumed net prices.** Conversely, if prices aligned with the value-based price benchmarks, the entire eligible cohort could be treated without crossing the threshold.



Deutetrabenazine: At current WAC, approximately **14% of eligible patients** could be treated in a given year without crossing ICER's $915 million budget impact threshold. **20% could be treated at assumed net prices.** Conversely, if prices aligned with the value-based price benchmarks, the entire eligible cohort could be treated without crossing the threshold.

ACCESS AND AFFORDABILITY ALERT

ICER is issuing an **Affordability and Access Alert** as part of its final report on VMAT2 inhibitors for treating TD. Clinical experts and patient advocates advised that the optimal clinical use should involve a trial of treatment with the new therapies for all patients with moderate-to-severe TD.

This alert is intended to signal to manufacturers, insurers, patient groups, and other stakeholders when the amount of added health care costs associated with new treatments may be difficult for the health system to absorb over the short term. This could result in displacement of other needed services or contribution to rapid growth in health care insurance costs that threaten sustainable access to high-value care for all patients.

Voting Results

The New England Comparative Effectiveness Public Advisory Council (New England CEPAC) deliberated on key questions raised by ICER's report at a public meeting on December 5, 2017. The results of the votes are presented below. More detail on the voting results is provided in the full report.

NET HEALTH BENEFIT

A majority of the Council voted that evidence is adequate to demonstrate a neth health benefit of valbenazine and tetrabenazine for patients* with TD.

Evidence was insufficient to distinguish between the agents, or to show a net health benefit of tetrabenazine.

*Patient populations defined as adults ages 18 and older with symptoms of tardive dyskinesia for at least three months and history of use of dopamine receptor blocking agents (DRBAs).

OTHER BENEFITS AND CONTEXTUAL CONSIDERATIONS

The Council also voted on other benefits and additional considerations that may be important context when considering VMAT2 inhibitors, but would not necessarily have been captured in the clinical evidence.

A majority of the Council highlighted significant patient health benefits not adequately captured by the QALY and the novel treatment approach of the VMAT2 inhibitors as key benefits.

The contextual considerations voted most important included intended use of the therapies in a disease area with high impact on quality of life and a high lifetime burden of illness, as well as significant uncertainty about the long-term risk, side effects, and durability of benefit.

Key Policy Implications

The New England CEPAC participated in a moderated policy roundtable of clinical experts, patient advocates, drug makers, and insurers to discuss how best to apply the evidence to policy and practice. None of the statements below should be taken as a consensus view held by all participants. Below are the top-line policy implications; for more information please see the full report.

MANUFACTURERS

- In order to provide reasonable value and thereby facilitate improved access and affordability for patients, prices for the VMAT2 inhibitors should be reduced to better align with their demonstrated short-term clinical benefits.
- Support studies of patients with TD to generate evidence on the relative long-term benefits and harms of individual VMAT2 inhibitors and other treatment options.
- Support studies to directly compare VMAT2 inhibitors by standardizing research protocols and outcome assessments to permit real-world, long-term outcome assessment.

SPECIALTY SOCIETIES

- Accept the responsibility to update their clinical practice guidelines rapidly following the advent of paradigm-changing treatment options like the VMAT2 inhibitors.
- Given that VMAT2 inhibitors may be prescribed by a larger group of specialist and primary care clinicians, develop educational materials to educate clinicians about TD management and to encourage close coordination among all clinicians caring for these patients.

PAYERS

- Given that the new VMAT2 inhibitors are priced far beyond their relative benefits for patients, use available evidence, along with patient and clinical expert input, to develop prior authorization criteria, periods of authorized treatment, and methods for feedback to clinicians regarding the potential for alternative management of TD.
- Leverage competitive market forces by negotiating for the best possible price in exchange for exclusive formulary placement of only one VMAT2 inhibitor. Other drugs in the class should remain available through an individual appeal process.

PATIENT ADVOCACY ORGANIZATIONS AND RESEARCHERS

- Develop outcome measures that better document the impact of TD on functional domains related to work, family, and social interactions.

REGULATORS

- Require post-approval, long-term comparative outcomes studies for treatments initially evaluated and approved in very short-term randomized trials, but for which long-term therapy would be expected.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent nonprofit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public hearings through three core programs: the California Technology Assessment Forum (CTAF), the Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) and the New England Comparative Effectiveness Public Advisory Council (New England CEPAC). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care. For more information about ICER, please visit ICER's website (www.icer-review.org).