



October 30, 2017

Submitted electronically to: publiccomments@icer-review.org

Steven D. Pearson, MD, President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Re: Feedback on ICER's Vesicular Monoamine Transporter 2 Inhibitors for Tardive Dyskinesia: Effectiveness and Value report

Dear Dr. Pearson:

On behalf of the Institute for Patient Access, I thank you for the opportunity to provide feedback on the Institute for Clinical and Economic Review's draft report evaluating the effectiveness and value of vesicular monoamine transporter 2 (VMAT2) inhibitors.

About the Institute for Patient Access

The Institute for Patient Access (IfPA) is a physician-led policy research organization dedicated to maintaining the primacy of the physician-patient relationship in the provision of quality healthcare. To further that mission, IfPA produces educational materials and programming designed to promote informed discussion about patient access to approved therapies and appropriate clinical care. IfPA was established in 2012 by the leadership of the Alliance for Patient Access, a national network of more than 800 physician advocates committed to patient access. IfPA is a 501(c)(3) public charity non-profit organization.

Several past ICER reports have elicited comments from IfPA, largely due to concerns about how these reports may shape health plan coverage policies and impact patients' ability to access treatment. While this letter focuses on concerns specific to ICER's analysis of TD treatments, IfPA finds it necessary to point out several concerning trends across ICER's reports.

In particular, ICER repeatedly attempts to evaluate the cost-effectiveness of a therapy before all the necessary data is available. Such was the case with ICER's draft report on therapies for atopic dermatitis, which were not even priced and publicly available when ICER completed its analysis. Timing is once again a factor in the data available for assessing TD therapies' cost-effectiveness, as detailed in the following pages.

Another recurring concern is whether cost-effectiveness studies and the QALY metric in particular are appropriate and accurate for diseases that are inherently qualitative. A disease such as a cancer, for example, presents finite data points, whether that be the exact size of a tumor or the duration of a patient's remission. Other diseases are not so easily quantified. How does one assign a value to the embarrassment and stigma of, as with TD, having one's face

contort uncontrollably in public? How does one quantify the discomfort of poorly tolerated treatments for psoriasis or the pain and daily inconveniences of rheumatoid arthritis? Treatments for some disease states simply do not lend themselves to economic number crunching.

Finally, despite ICER's laudable efforts to engage patients and advocacy groups, the framework used to evaluate these patients' therapies has no meaningful way to incorporate their insights. While ICER may relay the patient community's input in its reports, the calculations that result in ICER's benchmark value prices are not designed to quantify patient feedback as a numerical value that impacts the analysis' final findings.

Thus, in addition to considering the concerns outlined in the following pages, we urge you also to consider these broader trends and their impact on patient access.

Feedback on Draft Report

IfPA is concerned that ICER's draft evidence report, dated October 2, 2017, undervalues the benefits that tardive dyskinesia (TD) patients can receive from VMAT2 inhibitors. This undervaluation arises because of the reasons described below.

1. The base model does not incorporate the benefit of TD patients' improved adherence to their antipsychotic medicines.

As is widely recognized, the physical and psychological impairment caused by TD leads some patients to discontinue their antipsychotic drugs.¹ The draft report acknowledges the costs of poor drug adherence, stating that "sub-optimal adherence or deliberate dose-reduction have been shown to increase the risks of psychotic exacerbation and relapse" (p. 40).

Since TD is associated with lower adherence rates to antipsychotic medicines, it logically follows that medicines that control TD could increase patients' adherence to their antipsychotic medicines. The draft report, however, overlooks potential adherence benefits because they have "not been evaluated in clinical studies to date, and so real-world data will be needed to assess these effects."

Increased adherence is a fundamental potential benefit of controlling TD. It is inappropriate to assume away this important benefit simply because the novelty of these medicines has provided insufficient opportunities to study the issue. If, as the draft report states, "real-world data will be needed to assess these effects," then ICER should abstain from evaluating the cost-effectiveness of these medicines until such data has been produced.

Relegating the important impact of adherence to the scenario analysis, as the report does, is insufficient. Such core issues should be incorporated into the base case results. Further, the scenario analysis employs arbitrary assumptions to "account" for non-adherence, so the results cannot be relied upon as a reasonable estimate of the impact that VMAT2 inhibitors will have on patients' adherence to their antipsychotic medicines.

¹ See for example: Susman E (2016) "New Drug Eases Tardive Dyskinesia in Pivotal Trial: Tremors related to treatment for schizophrenia quieted by VMAT2 inhibitor" *MedPage Today*, April 21; <https://www.medpagetoday.com/meetingcoverage/aan/57467>.

2. The cost-effectiveness model is biased against VMAT 2 inhibitors.

Two issues limit the applicability of the QALY methodology used by the draft report to evaluate VMAT2 inhibitors.

First, while improved clinical outcomes are an important benefit of these therapies, so is the enhancement of patients' quality of life. With respect to the draft report, these quality of life benefits are the primary benefit evaluated.

However, as documented in a review of the literature that examined the limitations of the QALY methodology, "the QALY system could lead to an innate preference for life saving over life enhancing treatments because preventative or basic long-term care measures generally score lower on QALY calculations than more dramatic treatments. This places certain interventions at a disadvantage – ***for example those in mental healthcare***, where treatment modalities largely fall into the remit of life enhancing measures."²

Therefore, there is reason to suspect that the QALY methodology underestimates the benefits from VMAT2 inhibitors for patients living with TD.

Second, as noted by Hyry et al. (2014), cost-effectiveness assessments are flawed with respect to rare diseases because the small population size, by definition, raises the costs per patient.³ While TD is not officially a rare disease, its population size (approximately 500,000 patients) is small compared with many other diseases. This size limitation significantly constrains the applicability of the methodology used in the draft report to effectively evaluate the benefits of VMAT2 inhibitors.

3. There is an association between tardive dyskinesia and more severe psychopathology.

Studies have also found that patients living with TD tend to experience psychological disorders with higher severity than do patients who are not living with TD.

For example, in a 2008 study, Ascher-Syanum et al. found that patients with tardive dyskinesia "had significantly more severe psychopathology, were less likely to experience symptom remission, had more severe extrapyramidal side effects, and had lower levels of quality of life and functioning, lower productivity, and fewer activities (all $p < .001$) across the 3-year follow-up."⁴

These clinical outcomes impose real costs on patients living with TD that the draft report does not adequately discuss, let alone quantify as a benefit of the medicines that more effectively manage a patient's TD. The value to patients from these medicines that treat TD cannot be fully

² Pettitt DA, Raza S, Naughton B, Roscoe A, Ramakrishnan A, Ali A, Davies B, Dopson S, Hollander G, and Smith JA (2016) "The Limitations of QALY: A Literature Review" *Journal of Stem Cell Research & Therapy*, March 29; <https://www.omicsonline.org/open-access/the-limitations-of-qaly-a-literature-review-2157-7633-1000334.php?aid=70859> (emphasis added).

³ Hyry H.I., Stern A.D., Cox T.M., and Roos J.C.P. (2014) "Limits on use of health economic assessments for rare diseases" *QJM: An International Journal of Medicine*, Vol. 107, Issue 3,1, March; <https://academic.oup.com/qjmed/article/107/3/241/1570371/Limits-on-use-of-health-economic-assessments-for>.

⁴ Ascher-Syanum H, Zhu B, Faries D, Pen X, Kinon BJ, and Tohen M (2008) "Tardive dyskinesia and the 3-year course of schizophrenia: results from a large, prospective, naturalistic study." *J Clin Psychiatry*, Octo; 69(10); <https://www.ncbi.nlm.nih.gov/pubmed/19192441>.

understood without incorporating the potential impact that these medicines can have on improving these clinical outcomes.

4. ICER's assumption that there is no association between tardive dyskinesia and increased mortality is likely overstated.

As part of the key model assumptions made in the draft report, ICER states that TD does “not have a direct effect on mortality.” This may be too strong of an assumption. Chong et al. (2009) examined the mortality rate of 608 Asian patients that were diagnosed with schizophrenia over six years.⁵ The study found that while age was a factor, there was “a robust association with increased mortality rate and TD, but we failed to find any significant association with any specific cause of death and TD.”

A study in a Japanese medical journal back in 1989 also found that schizophrenic inpatients with TD had a significantly higher mortality rate than the inpatients that were not diagnosed with TD.⁶

Studies have not universally found a link between TD and a higher mortality rates. However, considering the severity of the outcome, this increased risk potential warrants consideration in the cost-effectiveness assessment when evaluating the potential benefits from new medications for TD – even if there is only a low probability that patients living with TD face an increased mortality risk.

Conclusions

For the above reasons, we have reservations regarding the conclusions of the draft ICER report, and its potentially negative impact on patient access to VMAT2 inhibitors. We encourage ICER to, at a bare minimum, amend the draft report to account for the considerations raised in this letter. Ideally, ICER will reserve judgement on the cost effectiveness of VMAT2 inhibitors until the information deficits identified in these comments are filled with more comprehensive clinical data.

If IfPA can provide further detail or aid the Institute for Clinical and Economic Review in incorporating any of the above recommendations into its final draft, please contact us.

Sincerely,



Brian Kennedy
Executive Director

⁵ Chong SA, Tay JA, Subramaniam M, Pek E and Machin D (2009) “Mortality rates among patients with schizophrenia and tardive dyskinesia” *J Clin Psychopharmacol* Feb; 29(1);5-8; <https://www.ncbi.nlm.nih.gov/pubmed/19142099>.

⁶ Yagi G, Takamuja M, Kauba S, Kanijima K (1989) “Mortality rates of schizophrenic patients with tardive dyskinesia during 10 years: a controlled study” *Keio Journal of Medicine*; 38: 70–72.



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Submitted electronically to: publiccomments@icer-review.org

*Re: ICER's Vesicular Monoamine Transporter 2 Inhibitors for Tardive Dyskinesia:
Effectiveness and Value report*

Dear Dr. Pearson:

On behalf of the Movement Disorders Policy Coalition, I thank you for the opportunity to provide feedback on the Institute for Clinical and Economic Review's draft evidence report "Vesicular Monoamine Transporter 2 Inhibitors for Tardive Dyskinesia: Effectiveness and Value."

The Movement Disorders Policy Coalition, comprised of more than a dozen patient advocacy organizations, serves as a platform from which stakeholders, including health care providers and patients, can inform policy impacting patient access to approved therapies and appropriate clinical care. Members advocate on behalf of millions of people affected by the wide range of neurological conditions classified as movement disorders, including those with tardive dyskinesia (TD).

TD is a complex disease characterized by jerky, involuntary movements of the face and body. The loss of physical control in patients with TD can cause those affected to feel embarrassed and may make those around them feel uncomfortable. ICER's draft report goes so far as to classify TD as "extremely debilitating... result[ing] in social isolation." The physical manifestations of TD can lead to compromised mental, emotional and social functioning. The influence of TD on these multi-dimensional domains of being meets the definition of health-related quality of life, an important concept with intangible value, as defined by the federal Office of Disease Prevention and Health Promotion.

Unfortunately, there is no known cure for TD. That is precisely why treatments that improve the quality of life for patients who suffer from this complex disease are significant.

As referenced in ICER’s draft report, TD is primarily caused by prolonged use of antipsychotic medications and can lead to “decreased compliance with the drugs given to treat the underlying condition.” As noted, some patients may try to address their TD by discontinuing their antipsychotics, which can result in ultimately losing control of both conditions.

In an ever-evolving and increasingly expensive health technology arena, we all want to obtain the maximum value for health care investments. But ICER’s approach struggles to adequately account for the qualitative nature of a disease such as TD. How can we quantify the value of fewer uncomfortable stares, less awkward public encounters and improved social functioning for those afflicted with TD?

The Movement Disorders Policy Coalition respects the need for payers to balance limited dollars with treatment value, but it is critical to consider more than just the bottom line. TD patients and caregivers understand the value of reduced stigma and improved quality of life.

The Movement Disorders Policy Coalition released a white paper this month that highlights the impact of movement disorders. It reads, “research has produced innovative drugs in recent years, providing a source of hope and relief to patients and families facing movement disorders.” In addition to the other known health benefits of vesicular monoamine transporter 2 inhibitors, one such source of hope and relief is TD patients’ increased adherence to antipsychotic medicines. The potential benefit of this outcome is great, but time is necessary for data about adherence and effect to be collected and assessed. It would be prudent for ICER to withhold judgement about the cost effectiveness of this treatment until this dynamic can be studied.

Therapeutic options have historically been limited for patients with TD and other movement disorders. As new options emerge, however, health plan policies that restrict access can make them difficult for patients to obtain. ICER’s findings could be used by health plans to justify their restrictive policies—further impeding patient access to vesicular monoamine transporter 2 inhibitors. A lack of access means a lack of options, interfering with the ability of a doctor and patient to determine and carry out a personalized course of treatment.

In closing, the Movement Disorders Policy Coalition respectfully requests that ICER take the outlined concerns into consideration as it formulates a final report. If our members can provide additional information to assist ICER in incorporating any of the positions discussed herein, please contact me .

Sincerely,

Gavin Clingham
Movement Disorders Policy Coalition



October 29, 2017

Institute for Clinical and Economic Review
Two Liberty Square
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Boston, MA 02109

Dear Members of the New England Comparative Effectiveness Public Advisory Council:

Mental Health America (MHA) would like to thank the Institute for Clinical and Economic Review (ICER) for its work in integrating evidence from the literature and stakeholder input within a thoughtful draft report on VMAT2 inhibitors for treating tardive dyskinesia (TD).

MHA appreciates that ICER has limited published research on the different aspects of TD to draw from, including limited data on prevalence, disutility, impact on adherence, and impact on employment and related role fulfillment. ICER noted the gaps in evidence well, and included meaningful contextual considerations from a number of sources. ICER also took into account some of this uncertainty in its sensitivity and scenario analyses. MHA urges ICER to integrate more of the contextual considerations, as appropriate, into the quantitative sections that are likely most helpful to decision-makers—rather than noting them separately in qualitative sections.

MHA recommends to ICER, in particular, that it helps readers understand the utility decrement sensitivity analyses in the context of the study it came from, and the stakeholder input offered. Much of the feedback from stakeholders revolved around the impacts of TD on the lives of individuals, especially those aspects that may be difficult to capture in clinical research. The utility decrement (UD) estimate comes from a well-conducted study, but is derived from this single study that was determining the UD, to answer a specific question about the different perspectives of patients, family members, and providers on the treatment options that existed at the time.¹ It is possible that the UD questions may have been asked differently in the context of different study aims, or if conducted today. The sensitivity analyses recognize this possible limitation, as do the sections on stakeholder input. It would be helpful for ICER to note more directly how to understand the sensitivity analyses in the context of the stakeholder input, and the Depression Bipolar Support Alliance (DBSA) survey in particular, even if that is to say that there is no relationship between the two. This could help more meaningfully integrate the quantitative and qualitative sections of the report.

¹ Lenert LA, Ziegler J, Lee T, Sommi R, Mahmoud R. Differences in health values among patients, family members, and providers for outcomes in schizophrenia. *Medical Care*. 2000 Oct 1;38(10):1011-21.

MHA also reiterates its previous request for ICER to conduct three additional sensitivity/scenario analyses. Even though some of these points are acknowledged in the qualitative section, they are not integrated into the quantitative sections –which are likely of the greatest use to decision-makers:

1. Benefits of disenrollment from public payers

Medicaid and disability Medicare are the largest payers of behavioral health services in the United States. Social determinants from poverty and disability can lead to behavioral health conditions, and behavioral health conditions create burdens that can lead to poverty and disability. Effective treatment and management of behavioral health conditions, on the other hand, can break this reinforcing cycle and allow individuals to reach a level of participation in community life that allows them to purchase commercial insurance and no longer require public benefits.

From a health care payer perspective, this is different than the increases in productivity that ICER currently evaluates. With Medicaid and disability Medicare, increases in productivity beyond a threshold uniquely reduce health care costs for the public payer as the individual disenrolls entirely.

Such a scenario analysis would benefit the field. By making such analyses common practice, it can shift the paradigm for how CMS and state Medicaid agencies view costs and benefits – away from trimming health care costs and toward making critical investments that alleviate poverty and disability.

2. Benefits for individuals for family being treated

ICER currently models productivity benefits when feasible, which matter to the employers that contract with the health care payer. In many cases however the treatment is rendered to a family member covered by the employer-sponsored plan, not to the employee themselves. For example, in TD, the spouse or child of a covered individual may receive treatment related to bipolar disorder or schizophrenia. In this case, the productivity benefits accrue indirectly – effectively managed bipolar disorder or schizophrenia in the family member can allow for a more productive individual.

Currently, employer benefits managers may believe that such considerations are important in selecting a health plan, but often lack rigorous quantitative methods to incorporate these considerations in cost-benefit determinations. A scenario analysis of how TD treatment for a family member of a working individual would affect that individual's productivity could help employers begin to better integrate the indirect effects of health care on worker productivity in health care purchasing decisions.


3. Benefits related to changing social norms

Many individuals experiencing early symptoms of schizophrenia, and even full psychosis, often do not receive effective treatments for months or years. In part, this is due to lack of awareness but it is also sometimes due to the implications of giving a diagnosis of schizophrenia and

initiating treatment. The availability of effective treatments for TD may decrease reticence to identify schizophrenia in adolescence and therefore could mean intervening early, because the perceived negative side-effects associated with treatment initiation will be lessened.

If people do identify and intervene more readily, this would make the underlying treatments dramatically more effective, as NIMH's Recovery After an Initial Schizophrenia Episode (RAISE) repeatedly finds – the earlier treatment begins, the better the prognosis. Scenario analyses of effects on earlier intervention for decreases in stigma associated with schizophrenia treatment may help understand how the availability of new treatments alters social norms over the long-term, a concept that has broad applicability outside TD treatment as well.

MHA thanks ICER for its consideration on how additional scenario analyses could enrich the field's understanding of costs and benefits. For additional information, please do not hesitate to contact us.

A handwritten signature in black ink, appearing to read 'Nathaniel Counts', written over a light blue horizontal line.

Nathaniel Counts, J.D.
Senior Policy Director
Mental Health America
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Comments to the Institute for Clinical and Economic Review (ICER) Preliminary Findings on Effectiveness and Value Review for Tardive Dyskinesia Treatment

October 30, 2017

On behalf of the National Alliance on Mental Illness (NAMI), I am pleased to submit the following comments on ICER's preliminary findings on its effectiveness and value review of available treatments for tardive dyskinesia. As the nation's largest organization representing people living with serious mental illness, NAMI is grateful for this opportunity to share our views.

At the outset, NAMI would like to reiterate concerns regarding the overall scope of this important ICER review. These concerns were initially raised as part of comments NAMI previously submitted on August 16 of this year. First, this ICER review continues to restrict its focus to clinical effectiveness and economic impact. As a result, the review fails to consider the social impacts of living with TD, the impact on family caregivers and how TD contributes to other medical co-morbidities. Again, NAMI remains concerned that the scope of this review excludes consideration of social impacts associated with TD.

As previously noted, involuntary muscle movements in the mouth and face region, facial grimacing, lip smacking and other symptoms associated with TD carry enormous social stigma. This in turn leads to further social isolation and exacerbation of the negative symptoms associated with psychotic disorders such as schizophrenia. Likewise, in the case of mood disorders such as bipolar disorder the social isolation resulting from TD can further exacerbate symptoms of depression and lack of self-worth. Finally, this social isolation is often associated with sedentary lifestyle, a poor diet and other factors that result in co-morbid chronic medical conditions associated with serious mental illness.

The limited scope of this review means that the findings of this review fail to capture this patient experience for individuals living with TD.

NAMI would like to raise the following additional concerns with the final report. These concerns (which in several instances have been previously raised) relate to the design and scope of the review, which in turn drive the findings themselves.

1. These findings raise the serious prospect that individuals experiencing moderate to severe TD that are diagnosed with schizophrenia, schizoaffective disorder and bipolar disorder will face enormous challenges accessing both Valbenazine and Deutetrabenazine

NAMI is extremely concerned that the very high incremental cost utility, lifetime horizon for both Valbenazine and Deutetrabenazine as compared to the same for placebo will result in both public and private payors refusing to offer access to these promising therapies for which there is no FDA approved alternative. As noted in previous comments to ICER, these new therapies to treat TD amount to a “game changer” for patients that have been living with this condition for years. To see a promising therapy taken from them after many years will be extremely frustrating.

2. In describing “stopping/changing” of antipsychotic treatment, this ICER review ignores the risk associated with such an approach and the lack of evidence supporting its effectiveness

In real life clinical practice, reducing, replacing, or removing antipsychotic treatment can jeopardize recovery and stability for people living with a serious mental illness. Interrupting treatment also increases the risk of an episode of acute psychosis, mania and suicidal ideation. Further, it fails to recognize the importance of choice and autonomy for individuals and the value of shared decision-making between prescriber and patient. It is troubling that ICER continues to integrate this into the review as an acceptable treatment option for TD patients.

3. The measures used in the final report are based almost exclusively on blinded video recorded expert central scoring

The AIMS (Abnormal Involuntary Movement Scale) is a widely accepted measure for assessing symptoms and therapeutic improvement for patients living with TD. It is important that this review measured AIMS at baseline and follow-up. Unfortunately, the review then used a substantially less reliable process for assessing outcomes – a blinded “expert” review of videotaped interactions between clinicians and their patients with central scoring. In NAMI’s view, this raises questions about whether or not the “experts” reviewing videotaped interviews are assessing the performance of the clinicians in accurately diagnosing and prescribing treatment or, instead, the symptoms and outcomes for the patients themselves.

NAMI is always concerned when studies rely exclusively on clinician-reported outcomes. While many clinicians may have expertise in diagnosis and treatment, they too often have only brief interactions with their patients (in psychiatry, a “medication assessment” can be as brief 10 to 15 minutes). In this case, it appears that the principal outcome measure is based on review of videotaped interviews. It appears that this review never afforded the opportunity for the “experts” convened by ICER to talk directly with clinicians prescribing treatments for TD in order to assess their opinion about the value of a breakthrough treatment to help their patients. Why was no weight given in the review to the judgment of a clinician who is finally able to prescribe a disease-modifying therapy for a patient that has lived with TD for years?

4. There is a nearly complete absence of patient-reported outcomes or attempts to measure the patient experience of living with TD

For NAMI, this is the most serious flaw in the ICER review; namely, the complete absence of any patient-reported outcomes. NAMI understands that in the latter stages of this review ICER undertook a survey instrument for people living with TD and their family members. NAMI was grateful for the opportunity to provide input on this survey instrument. Unfortunately, this patient survey came after ICER had already designed and executed this review, rather than seeking input from patients and their families upfront. As noted above, this review could have benefited from upfront input integrating the direct experience of people living with a moderate to severe facial tick or an involuntary movement disorder.

NAMI is hopeful that the planned December 5 meeting will include presentations from people living with TD, as well as opportunities for response to formal presentations of findings from people living with TD (or in the alternative, the perspective of family caregivers). It is critical that this voice be part of ICER's final deliberations.

5. QALYs as a major outcome measure has significant limitations in capturing the experience of living with TD

NAMI recognizes that ICER has traditionally relied on QALYs as a critical measure in assessing value, effectiveness and utility when comparing competing clinical interventions. However, in the case of TD, the use of QALYs significantly fails to capture the complexities of the patient experience. The final results accurately note that the risk of mortality associated directly with TD is rare. We know that an adult diagnosed with moderate to severe TD can live the disorder for decades. Further, being able to effectively control symptoms to the point of maintaining successful employment, peer and family relationships and other aspects of community integration are of high value to patients. Unfortunately, QALYs are largely ineffective in capturing these high value goals to patients. As a result, the ICER fails to effectively capture this patient experience.

At the same, the innovative therapies to treat TD that are in the ICER review are, in NAMI's view, penalized severely in this review for precisely the same reason – that many patients are faced with the prospect of relying on these therapies not as a curative intervention, but as a way of effectively managing their symptoms to promote recovery and integration. With ICER now finalizing and publishing these findings, NAMI would like to express our strong disappointment that this report is likely to be used by payors – both public and private – to block access to innovative therapies that people living with TD have been waiting for decades.

Respectfully Submitted,
Andrew Sperling
Director of Legislative Advocacy
National Alliance on Mental Illness
www.nami.org

October 30, 2017

To: ICER

From: Charles Yonan, PharmD., Sr. Director HEOR
Neurocrine Biosciences, Inc

Subject: ICER Response Final Draft

Modeling and Clinical Report team,

We appreciate you incorporating many of our suggestions from August into the current draft. We also appreciate the acknowledgement of missing data which, if present, would more accurately inform and be used as inputs for the model. That said, we are questioning some of the model inputs and are offering alternates to be considered.

Most of the comments are primarily based on results of the one-way sensitivity analyses shown in Table 5.6 (for valbenazine/INGREZZA[®]) and Table 5.7 (for deutetrabenazine/Austedo[®]) of ICER's draft evidence report on VMAT2 inhibitors for TD (Oct. 2, 2017). The base case incremental cost-effectiveness result for valbenazine (\$754,440 per QALY) seems to be most sensitive to the following clinical parameters: the tardive dyskinesia (TD) utility decrement and the proportion of responders to placebo. We also comment on the annual discontinuation risk because it was calculated differently for each comparator.

Topic – TD disutility assumption – (Page 57)- The report states that “a utility decrement of 0.095” was applied “to those patients with moderate to severe TD.”

As we and others have stated this utility decrement woefully underrepresents the burden of TD and thus undervalues a safe and effective treatment (e.g., valbenazine). Attempting to assign a disutility value that was derived from a study that did not concurrently assess TD severity is biased and underestimates the impact of TD. The Lenert et al. (2004) study did not provide an appropriate estimate of the disutility associated with TD as it was obtained from a sample of the general population. As noted on pg. 6 of ICER's report, the impact of TD is not likely to be correctly assessed by people who are not affected.

To offer a credible alternative, we are analyzing data from the Medical Expenditure Panel Survey to estimate the impact of TD (ICD9 code 333.xx) on patients' health-related quality of life. Our preliminary results show that the mean EQ-5D index score (utility) for respondents with TD is 0.625 and the mean utility for propensity-score matched respondents without TD is 0.750 (a difference of 0.125). The EQ-5D data was collected in 2000–2003. In addition to EQ-5D utilities, we also examined the SF-12 scores, which were collected from 2000–2015. Respondents with TD scored lower on both the Physical Component (38.4 vs. 41.8) and Mental Component (47.3 vs. 48.1) Scores. We plan to convert the SF-12 scores to utilities using published algorithms. This will allow us to present the TD utility decrement based on a larger sample and for a greater number of years. We will be submitting these analyses for upcoming conferences (AMCP, ISPOR). We argue that the TD disutility of 0.095 used in the current

model is too small to correctly capture the impact of TD. We suggest the utility decrement of at least double the value used is more appropriate, as supported by our recent analyses.

Topic: Proportion of Responders to Placebo (Pages 48–49)

The proportion of responders to placebo is a key parameter determining the distribution of patients in the discontinued-improved and discontinued-not improved health states over time. Although the incremental cost per QALY (vs. placebo) results for valbenazine and deutetrabenazine were not directly compared (as noted on of page 19 of the report), we would still like to point out the difference between the placebo values for valbenazine (8.7%) and deutetrabenazine (12.0%). The treatment-placebo differences for valbenazine and deutetrabenazine are 31.3% and 21.1%. This should be captured as a differentiating data point favoring valbenazine. Although a larger placebo effect should work against an inferior product, in this model it seems to work to its advantage via improved TD without treatment/costs. Within the current draft of the model, every year patients discontinue treatment (8.7% of the valbenazine and 12.0% of the deutetrabenazine) yet maintain their improved status. This methodology inappropriately disadvantages valbenazine. We request that you revise the methodology so that placebo transitions from “response no treatment” to “moderate TD” (comparable in both medications).

Topic: Discontinuation rates-(Pages 48–49; Page 48, Table 5.2; Page 54 Table 5.6)

The first-year discontinuation risk for valbenazine (19.0%) “was calculated based on the discontinuation rate from the longest reported observation period from open label studies, subtracting the discontinuation rate from the clinical trial, and then extrapolating to one year.” Unfortunately, the authors have combined “risks” and “rates” and, as a result, incorrectly computed the annual discontinuation risk, which should be 18.3% for valbenazine. It appears that the authors annualized the difference between the 6-week risk reported by Remington (6.0%) and the 6-month risk reported by Hauser (13.6%).

This method is incorrect, because risks occurring over different time periods cannot be combined (subtracted, in this case). Instead, the authors should have converted the risks to rates and then calculated the annual discontinuation risk from the rate difference:

- Rate computed from Remington: 0.024364.
- Rate computed from Hauser: 0.04125.
- Rate difference: 0.016887.
- Annualized discontinuation risk: 18.3%.

The first-year discontinuation risk for deutetrabenazine (13.0%) “was equal to the exposure-adjusted incidence rate reported in Anderson et al. (2017), which only included discontinuations after a “washout period.” The Anderson et al. (2017) abstract notes that the exposure-adjusted incidence rate (per patient-years) for discontinuations was 18 per 212.4 person years (≈ 0.085 per person-year). However, there is insufficient information given in the abstract and in the report for us to replicate or verify these calculations. However, as noted above, the differences in discontinuation risks, which were due to adverse events, may reflect differences between the participants of those trials. One key difference in the study populations was the exclusion of anticholinergics in the deutetrabenazine trials. This significantly changes the “risk” for adverse events/discontinuation.

Please provide a justification for using such high first-year discontinuation probabilities, which are higher than those used for the preliminary results presented in August. Please also provide a justification for assuming that the probabilities are 50% smaller during subsequent years, rather than some larger proportion. We ask that you consider reducing the first-year Valbenazine discontinuation risk as well as reducing the discontinuation risk in subsequent years by 75%.

According to our modeling efforts, we would expect the following to be reasonable scenarios:

- 2x disutility-could result in reduction of Valbenazine cost/QALY~ 50%
- Placebo transitions from response no treatment to moderate TD (equal to Valbenazine)-could reduce Valbenazine cost/QALY ~20%
- Proposed discontinuation in first year and 75% reduction in subsequent years-could reduce Valbenazine cost/QALY ~6%
- Combination of the above:
 - 2x disutility, and Placebo transitions to moderate TD at 5% annually, 75% reduction in discontinuation in years 2+

Subject: Response to Draft Evidence Report - Other Benefits and Contextual Considerations

We appreciate your collaboration with patient/advocacy groups to create your list of questions for “Other Benefits and Contextual Considerations”. In this response, we provide our interpretations of the literature along with current or forthcoming data relevant to the considerations.

This intervention provides significant direct patient health benefits that are not adequately captured by the QALY. Correct. The body regions most impacted by TD symptoms are the face/mouth/jaw, limbs and trunk. Recent surveys as well as interim data from our RE-Kinect study show that some of the most bothersome sequelae of tardive dyskinesia (TD) include inability to eat, difficulty breathing, and difficulty in movement/walking. ICER’s current utility degradation is based off non-TD sufferers reporting and absolutely does not account for the physical impact of symptoms. The report does recognize the potential impact on socialization and ability to work or go to school but underrepresents the impact on the patient and/or caregiver.

This intervention offers reduced complexity that will significantly improve patient outcomes. Correct. Valbenazine is effective and well tolerated with a single daily dose. Additionally, modeling shows there may be a synergistic relationship with antipsychotics that may allow for optimization of the antipsychotic treatment. With regards to outcomes, we believe valbenazine can (and already has) significantly improve outcomes in many patients. Given ICER’s recognition of the importance of patient-centric outcomes, the individual health state will influence the impact of treatment. As we have previously stated, highly functioning patients with limited comorbidities should benefit more than individuals with limited capacity and high comorbidity burdens. We will analyze data from our RE-Kinect study early next year to explore this further.

This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories. Possibly. Our data analyses, and those of other groups, show that the main risk for the “average” TD patient is determined by cumulative antipsychotic exposure rather than ethnicity or gender. The hope is that our educational efforts

will result in renewed interest in the screening and diagnosis of TD while reducing the human and societal burden of TD. Additionally, we hope that the body of evidence for valbenazine and evaluations like the ICER report will allow for similar access to an effective and well tolerated treatment for TD.

This intervention will significantly reduce caregiver or broader family burden. We believe it can. Currently there are few data available regarding caregiver burden. One of the key cohorts in our RE-Kinect study is the patient caregiver. In the study, we gather data on the burden of providing care for the patient with TD. We will analyze and present this data early next year.

This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients who have failed other available treatments. Correct. The term “failed” can imply either intolerance or lack of efficacy (or both). The ICER draft evidence report acknowledges the lack of evidence for available “off label” treatments. The mechanism of action for valbenazine is novel and allows for single daily dosing as well as a favorable NNT/NNH profile. Other VMAT2 inhibitors are tethered to a pharmacologic risk profile (e.g. black box warning and contraindications) due to other deleterious active metabolites.

This intervention will have a significant impact on improving return to work and/or overall productivity. Possibly, if the TD symptoms resulted in either a physical limitation or self-isolation of the patient. These are a few of the many deleterious outcomes highlighted in recent TD patient/caregiver surveys. Some of our clinical trial patients have commented on the reduction of symptoms “allowing me to return to school/work”. There will be a case study (*by Josiassen*) published soon to support this. Subsequent real-world studies (retrospective and prospective) will assist in confirming this benefit.

Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention. As stated previously, there are several components that should be considered to determine “value”: 1) the location and severity of the symptoms being treated; 2) the social impact of the location and severity of symptoms; 3) the physical impact of the location and severity of symptoms; 4) the societal impact of the location and severity of symptoms; 5) the relative healthcare burden of the location and severity of symptoms; 6) the caregiver burden; 7) the impact of the treatment on all the above; and 8) the impact of the treatment on any comorbidities, especially the underlying mental illness.

This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life. Yes (with regards to QOL and possibly length of life if the symptoms manifest in ADL sequelae). For all the reasons stated previously, the physical and social impact of the symptoms can be very significant.

This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness. Yes. The symptoms are brought about by prolonged exposure to antipsychotics and tend to be permanent if not treated. The condition becomes chronic in most patients with TD lasting for decades. The risk of lifetime burden of illness is increasing because of the use of these agents in younger patients with conditions other than schizophrenia.

This intervention is the first to offer any improvement for patients with this condition. Correct. Valbenazine is the first and most effective treatment approved for patients with TD.

Compared to surveillance with no maintenance therapy, there is significant uncertainty about the long-term risk of serious side effects of this intervention. Incorrect. Our development program has assessed long term efficacy and safety. We have completed 3 long term extension studies with valbenazine for 1 year or longer. The Kinect 3 LTE, Kinect 4 and 1506 roll-over studies all evaluated durability of effect and safety for a year or more. It is estimated there are >350 patient years of moderately long-term exposure from those three trials (i.e., subjects treated for > 3 months up to 2 years). Given the estimated TD patient population of 100-300k within the ICER report, this is a substantial accumulation of data with no additional safety signals emerging.

Compared to surveillance with no maintenance therapy, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention. Incorrect. As stated in the previous question. The valbenazine development program has assessed long term efficacy and safety. The Kinect 3 LTE, Kinect 4 and 1506 roll-over study all evaluated durability of effect and safety for a year or more. It is estimated there are >350 patient years of moderately long-term exposure from those three trials (i.e. subjects treated for > 3 months up to 2 years). The data supports persistent and durable effectiveness.

There are additional contextual considerations that should have an important role in judgments of the value of this intervention. Agree. As stated previously, there are several components that should be considered to determine “value”: 1) the location and severity of the symptoms being treated; 2) the social impact of the location and severity of symptoms; 3) the physical impact of the location and severity of symptoms; 4) the societal impact of the location and severity of symptoms; 5) the relative healthcare burden of the location and severity of symptoms; 6) the caregiver burden; 7) the impact of the treatment on all the above; and 8) the impact of the treatment on any comorbidities especially the underlying mental illness.

We appreciate your consideration of our suggestions. We believe that valbenazine is a significant advance in treating a terrible drug induced movement disorder - tardive dyskinesia. We have been transparent regarding our upcoming data sets that will support our suggestions. Unfortunately, they will emerge weeks or months after the final report. We expect that ICER will include these data sets and revise their analysis to more accurately acknowledge the benefit of treating TD with Valbenazine.

Finally, we are including updated references for you as attachments:

1. Updated pricing letter,
2. S.Caroff, S.Aggarwal, C.Yonan *Treatment of tardive dyskinesia with tetrabenazine or valbenazine: a systematic review J. Comp. Eff. Res 2017 Oct*
3. AMCP format dossier,
4. S.Marder, J.Kane, S.Factor, R.Jimenez, D.Thai-Cuarto, G.Liang, *KINECT 4: A Phase 3, One-Year, Open-Label Trial of Valbenazine in Participants with Tardive Dyskinesia abstract ACNP 2017*

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October 27, 2017

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RE: Teva's Response to ICER's "Vesicular Monoamine Transporter 2 Inhibitors for Tardive Dyskinesia: Effectiveness and Value Draft Evidence Report" (dated October 2, 2017)

Dear ICER Evaluation Team members,

Teva appreciates the opportunity to provide comments to ICER on its draft evidence report on treatment options for tardive dyskinesia. These include:

- **Black box warning:** Deutetrabenazine (Austedo®, Teva) labeling carries a "black box" warning for depression and suicidality in patients with Huntington's disease. This specific context of "in patients with Huntington's disease" is missing in multiple statements throughout the report and should be corrected to reflect the FDA-approved labeling for Austedo. These are noted in the detailed comments below.
- **The use of a cost-utility model for assessment of value for treatment of tardive dyskinesia is premature, given the state of the scientific evidence for this indication. Further research is needed in this area to develop reliable and valid metrics using a patient-centric approach.**

ICER's cost utility approach does not capture the full patient experience. The utilities used were not elicited from a relevant patient population. Further, tardive dyskinesia (TD) is primarily a functional disability, and quality of life literature in this area is scarce; therefore, QALYs are not an appropriate measure for evaluating treatments for TD. A cost-effectiveness approach in the base-case, taking into account reduction in symptoms and improvement in functional measures would be more suitable for this condition. We note that ICER does address this alternative approach, albeit briefly, in the present draft.

Until large-scale quality of life studies are conducted among TD patients and functional measures are further developed to capture the extent of disability suffered by TD patients, the cost effectiveness of deutetrabenazine cannot be evaluated properly. The extant evidence for the TD population is not sufficiently mature to substantiate use of QALYs or a cost-utility framework alone.

- **ICER’s current approach to calculating direct healthcare utilization costs fails to include the full scope of costs incurred due to having TD**

A large study conducted by Ascher-Svanum et al 2008 (737 patients with TD, 1,538 patients without TD) reported that the proportion of patients with paid employment was significantly higher for those without TD versus with TD (23.2% vs 17.7%, p=0.014), and that mean income was significantly higher for patients without TD. Estimates of lost productivity should be applied to patients in the Moderate/Severe TD state (as in scenario analyses [Table H6, page 126]).

ICER should also highlight social stigma by including the impact of TD treatments on productivity in the base-case model. Boumans et al 1994 demonstrated that patients with orofacial dyskinesia were less likely to be selected for a job (Boumans et al 1994). Although ICER makes a nod to productivity loss in a scenario analysis losses [Table H6, page 126], given the condition is primarily a functional disability, inclusion of productivity loss in the base-case is warranted.

These studies highlight the limitations of ICER’s value framework for functional disorders. As information on patient-reported outcomes develops, new data should be considered in further evaluations. Additional comments on model inputs are detailed below.

- **Use of anticipated real-world compliance and persistence rates with VMAT2 inhibitors in the evaluation:** As the majority of patients with TD have underlying psychiatric conditions, the rate of adherence to medications in this patient population is low (Kane et al 2013). This should also be considered in the economic models of any medication use in this patient population.
- **Appropriateness of including tetrabenazine in the evaluation:** Currently, tetrabenazine is not FDA approved for the treatment of TD.

Detailed comments:

Page number	Comment
8	The report states, “Deutetrabenazine (Austedo®, Teva) contains deuterium, a naturally occurring form of hydrogen, which slows metabolism and clearance. Approved for Huntington’s disease in April of 2017, it is dosed twice daily and carries the same warnings and contraindications as tetrabenazine.” Please note that deutetrabenazine (Austedo) was approved for the treatment of chorea associated with Huntington’s disease. In addition, the FDA-approved labeling for Austedo does not carry the same warnings and precautions as tetrabenazine. This statement should be revised to correct this information. Any reference to the boxed warning throughout this report should include the context of “in patients with Huntington’s disease.”
9	Pricing for deutetrabenazine 24 mg should also be displayed in Table 2.1

Page number	Comment
31	For Table 4.7, the baseline AIMS in mITT population was 9.5 in placebo group, 9.6 in the 12mg group, 9.4 in 24mg group, and 10.1 in the 36mg group; this currently reads "NR"
32	Table 4.8, ARM-TD, LS Mean AIMS Change from Baseline for deutetrabenazine should have † for the cell value -3.0 (i.e., p value≤0.05); the reported p= 0.019.
35	The following statement needs to be corrected to accurately reflect the FDA-approved labeling for Austedo for use with patients diagnosed with tardive dyskinesia: "a boxed warning for depression and suicidality was added to the deutetrabenazine labelling for HD and continued for its TD indication (see tetrabenazine harms below). ^{55,56} "
40	The statement, "However, both valbenazine and deutetrabenazine appear to be well tolerated in the TD clinical trials, despite the addition of a "black box" warning for deutetrabenazine for depression/suicidality (in all likelihood..." is incorrect as noted above and should be revised. The boxed warning was not added to Austedo labeling specifically for the TD indication.
42	The following statement should be revised as it is not consistent with the FDA-approved labeling for patients with tardive dyskinesia, "this is a new therapy with a black box FDA warning for depression and suicidality that requires ongoing use, and important adverse effects could become apparent over time."
45	ICER should adjust average age of onset and age of treatment to be more specific to US payers; this is especially relevant for a lifetime model. For example, see Loughlin et al 2017
45	ICER's report should reduce the duration of the placebo effect. Currently, patients enter the model based on response rates observed in AIM-TD. Response to treatment remains constant for all responders, and patients do not improve or decline beyond their initial response to therapy while remaining in the "improved TD" state. Patients can only leave the Improved TD state via discontinuation of the study drug. In contrast, in the placebo group, 12% of the population maintains benefit for the lifetime duration, meaning they are guaranteed to never transition to Moderate/Severe TD. The impact of this modeling flaw is exacerbated in scenario analyses, where placebo responders never discontinue their baseline disorder medication, and in turn do not incur added costs or reduced quality of life associated with uncontrolled underlying conditions. The placebo effect should not extend beyond trial period, as the basis for placebo effect is sense of hope for improvement (Dumitriu, et al., 2010) which should decrease post blinding (Benedetti, et al, 2005).

Page number	Comment
49	The draft report states that ICER modeled the effects and costs of the highest doses reported in clinical trial (36mg per day) because those doses were “generally associated with the highest effects”; however, with 24 mg dosing, 35% of patients experienced \geq 50% improvement in AIMS score (Anderson et al 2017), which is greater than 33% improvement observed for the higher dose. The efficacy and corresponding price for the 24 mg dose should then be used in the model for consistency.
50	ICER’s current approach to calculating healthcare utilization costs is not comprehensive. ICER should consider additional incremental healthcare utilization costs. See, for example, Carroll, et al., 2017 where, post-diagnosis, TD patients had significantly greater annual all-cause healthcare costs versus matched non-TD patients as shown in Figure 3 (\$10,199 vs \$2,605). Also, any discussion of the cost of TD treatments should appropriately account for real world rates of antipsychotic drug treatment modification or dose reduction and effects on patient quality of life and healthcare costs.
50	For utility estimation, the state of the science here is not well-advanced, and it would be advised to consider using a CEA, rather than CUA, model for this indication. Alternatively, Briggs et al (2008) utilities for extrapyramidal symptoms may be considered until evidence supporting the perspective of patients with tardive dyskinesia may be further developed.

Sincerely,

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on behalf of Teva Pharmaceuticals

References

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