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

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[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 at 202-499-4114.

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.