October 4, 2019

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: Draft Scoping Document on Oral Semaglutide for Type 2 Diabetes: Effectiveness and Value

Dear Dr. Pearson:

On behalf of the Institute for Patient Access, I thank you for the opportunity to provide comments regarding ICER's draft evidence report titled "Oral Semaglutide for Type 2 Diabetes: Effectiveness and Value," released September 11, 2019.

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 health care. 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 physicians committed to shaping a patient-centered health care system. IfPA is a 501(c)(3) public charity nonprofit organization.

Draft Evidence Report Comments

Several methodological issues in the draft evidence report for oral semaglutide are likely biasing the results toward an overly restrictive cost-effectiveness result. These issues include:

- Not adequately accounting for the additional patient benefits that a once-daily oral formulation provides
- Not adequately accounting for the co-morbidities associated with Type 2 diabetes
- Underestimating the full costs Type 2 diabetes impose on patients and their caregivers
- Not adequately accounting for the well-documented heterogeneity across Type 2 diabetes patients.

In addition, as documented in the draft evidence report, the results of the cost-effectiveness model contain an unacceptable level of uncertainty.

Each of these issues, detailed below, leads ICER's conclusions to underestimate the cost-effectiveness of oral semaglutide, potentially introducing inappropriate access obstacle for patients.

The Report Does Not Adequately Account for the Benefits of a Once-Daily Oral Formulation

Current evidence demonstrates that, as a pill rather than an injection, oral semaglutide improves patients' adherence and willingness to take the medicine that is most appropriate for them. Oral semaglutide should, therefore, improve overall health outcomes and decrease overall disease management costs.

Injectable drugs are often an obstacle to patient adherence. In describing the introduction of oral semaglutide, the *American Journal of Managed Care* noted that the entire purpose of the drug is to

> … address an unmet need in patients with T2D [Type 2 diabetes] and CV [cardiovascular] risk who are overweight, as the GLP-1 receptor agonist class has been shown to help patients achieve significant weight loss. However, not all patients are willing to use an injectable drug, even one only needed once a week.
>
> An ACC panel discussion reviewed case studies on when to prescribe GLP-1 receptor agonists or SGLT2 inhibitors, and cardiologists said there are cases in which GLP-1 receptor agonists are indicated, but patients will not take an injectable drug. In one scenario described during the ACC session, an obese female patient was prescribed an SGLT2 inhibitor instead, but the physician commented that while this would control her blood sugar, it would not provide the same weight loss benefits.[1]

The draft evidence report fails to adequately incorporate these benefits, thereby underestimating the cost effectiveness of this drug.

The Report Does Not Adequately Account for Co-Morbidities

A number of serious and complex co-morbidities are associated with Type 2 diabetes. The existence of these co-morbidities significantly limits the reliability of the results derived from the cost-effectiveness model.

Cardiovascular disease, for example, is a common comorbidity of Type 2 diabetes. Cardiovascular disease imposed over $555 billion in costs in 2015, and is projected to impose $1.1 trillion in costs by 2035.[2] Oral semaglutide is associated with a lowered rate of adverse cardiovascular outcomes for patients with Type 2 diabetes who also had high cardiovascular

[1] Caffrey Mand DiGrande S (2019) "Novo Nordisk Seeks Oral Semaglutide Approval, CV Indications on New Drug and Injectable" *the American Journal of Managed Care*, March 21; https://www.ajmc.com/newsroom/novo-nordisk-seeks-oral-semaglutide-approval-cv-indications-on-new-drug-and-injectable-.

[2] https://healthmetrics.heart.org/wp-content/uploads/2017/10/Cardiovascular-Disease-A-Costly-Burden.pdf

risks, and it improves patient adherence and patient willingness to use a GLP-1 receptor.[3] Therefore, an additional benefit from oral semaglutide is that it will reduce the costs associated with cardiovascular disease. Similar benefits are derived from other co-morbidities associated with Type 2 diabetes.

While these benefits are significant, it can take years for patients or the health care system to fully realize them. In other words, it is difficult to "reliably predict" the full benefits from oral semaglutide to include the benefits gained by reducing the co-morbidities associated with Type 2 diabetes.

The draft evidence report admits that these concerns are a significant limitation to the cost-effectiveness model:

> The overarching limitation of this model is the complexity of T2DM, its large number of co-morbidities, and its patient-specific clinical management. This complexity demands a patient-level microsimulation. Yet, it is extremely challenging to expect regression equations to reliably predict any one patient's actual outcomes, therefore we undertook a large number of sensitivity and scenario analyses in order to avoid depending on a single deterministic output.

Sensitivity analyses, however, do not adequately address this limitation. In reality, the public health effects of oral semaglutide cannot yet be fully understood, and accurate lifetime cost-effectiveness estimates are simply unknowable at present.

The Report Underestimates the Costs Associated with Diabetes

Diabetes was the seventh leading cause of death in the United States as of 2015.[4] The draft evidence report notes that the estimated total direct and indirect costs of diabetes were $245 billion; on a per-patient basis, there were $7,900 in annual health expenditures directly attributable to diabetes.

These cost estimates are as of 2012, however. The costs are undoubtedly higher today.

To get a sense of how much these costs could have grown, as of 2007, the estimated costs of diabetes were $174 billion.[5] Thus, the American Diabetes Association is estimating that the direct and indirect costs of diabetes grew 41 percent between 2007 and 2012.

While there are no estimates for how much these costs have increased over the past seven years, applying the past five-year growth rate over a seven-year timeframe (a conservative assumption) would imply that the direct and indirect costs of diabetes could be more than $345 billion today.

The implications of this growth are not immaterial. A 41 percent increase in the economic costs of diabetes meaningfully changes the cost effectiveness of oral semaglutide. Without accounting

[3] https://www.nejm.org/doi/full/10.1056/NEJMoa1607141.
[4] https://www.cdc.gov/diabetes/data/statistics-report/deaths-cost.html.
[5] http://care.diabetesjournals.org/content/36/4/1033.

for these higher costs, the report underestimates the economic burden that Type 2 diabetes imposes on society.

The Report Fails to Fully Account for Patient Heterogeneity

Current treatments are not effective for all patients. Given the high cost of diabetes, there is a significant value to a medicine that can effectively treat patients who have not achieved adequate control with current therapies for Type 2 diabetes. As the draft evidence report notes, oral semaglutide has properties that can make it more appropriate for many patients. Nevertheless, the report does not account for the value that is created when patients who did not have an effective option now do.

The Analysis Contains an Excessive Amount of Uncertainty

While uncertainty is inherent with all models, the base case results of the long-term cost effectiveness model are plagued with an excessive amount of uncertainty. When discussing the base case results, the draft evidence report states:

> we urge caution when interpreting these findings as ***they are highly uncertain.*** The uncertainties are reflected both in statistical variance in the model input parameters and risk equations, as shown in the probabilistic sensitivity analyses, and in the additional uncertainties from the NMA ***caused by concerns about whether effect modification could result from differences in the underlying CVOTs***. (emphasis added)

The best interests of patients cannot be served when a medicine's cost effectiveness is based on "highly uncertain" findings. Due to this uncertainty, it is not possible to know whether the estimated cost-effectiveness thresholds are overly restrictive, thereby denying patients access to a medicine that would provide value to them.

Given the number of patients living with Type 2 diabetes in the United States, such errors will be excessively costly to the health care system. If the uncertainties that plague the base case model cannot be reduced, ICER should delay its analysis until such time that the results can be modeled with an acceptable level of uncertainty.

Conclusion

Comparing the efficacy of a treatment when robust post-marketing data does not yet exist is always problematic. It offers an understanding of the drug's benefits that is, by definition, constrained, increasing the uncertainty of any cost-effectiveness evaluation. The sheer number of times the draft evidence report notes "significant uncertainties" raises serious red flags regarding the accuracy of the cost-effectiveness results.

As a result, IfPA is concerned that the report provides an inaccurate picture of the benefits that oral semaglutide could offer patients living with Type 2 diabetes.

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