Tirzepatide for Type 2 Diabetes

Draft Background and Scope

June 30, 2021

Background

More than 34 million Americans, or 13% of the US population, have diabetes mellitus.[1] Type 2 diabetes mellitus (T2DM), which is characterized by progressive loss of adequate insulin secretion from the pancreas and peripheral resistance to insulin, accounts for 90-95% of those cases.[1] Prevalence of T2DM increases with age and minorities bear a disproportionate burden of disease, with American Indian/Alaska Natives, Blacks, Asians, and Hispanics at greater risk of developing or having diabetes, as well as developing complications from the disease.[1,2] Obesity is a major risk factor for developing T2DM with more than 60% of people with diabetes having a body mass index (BMI) in the obese or extreme obesity range.[1,3]

The hallmark of diabetes is an abnormal elevation in blood glucose, or hyperglycemia. Chronic hyperglycemia puts patients at risk for damage to both small (microvascular) and large (macrovascular) blood vessels, resulting in damage to the eyes, nerves, and kidneys, as well as cardiovascular events and limb ischemia.[4] Diabetes is the leading cause of new blindness and end-stage renal disease, and the 7th leading cause of death in the US. In 2016, diabetes was associated with 16 million emergency department visits, 7.8 million hospitalizations, and 1.7 million hospitalizations for cardiovascular disease. Total direct and indirect costs for diabetes exceeded $327 billion in 2017, with 72% of the total considered direct costs (e.g., health care services or technologies).[5]

Management of T2DM is focused on controlling hyperglycemia, managing comorbidities, and preventing complications of disease. Treatment goals are based in part on measurements of glycated hemoglobin (HbA1c), an average measure of blood sugar over 3 months. Treatment targets vary, with less stringent control accepted in patients with higher risk of hypoglycemia, more severe comorbidities, and shorter life expectancy.[6] Cornerstones of therapy include lifestyle modifications such as diet, exercise, and weight loss, management of cardiovascular risk factors such as high cholesterol and high blood pressure.[7] Intensive lifestyle changes may be enough to control blood sugars and prevent progression in some patients; however, many patients will require pharmacologic therapy during their disease course to achieve successful management.

Metformin is recommended as initial pharmacotherapy for patients with T2DM and is recommended to be continued as long as it is tolerated and not contraindicated.[8] Combination therapy with additional agents can be considered if patients do not meet their HbA1c goal on metformin, including oral medications such as sulfonylureas, thiazolidinediones, sodium-glucose cotransporter 2 (SGLT-2) inhibitors, and dipeptyl peptidase-4 (DPP-4) inhibitors, and injectable therapies such as glucagon-like peptide 1 (GLP-1) receptor agonists and insulin. Considerations for choosing an additional agent include the presence of cardiovascular or renal comorbidities, risk of hypoglycemia, impact on weight, side effects, cost, and patient preferences.[8] Since 2008, when the Food and Drug Administration (FDA) issued recommendations for the evaluation of cardiovascular risk for new antihyperglycemic therapies, multiple cardiovascular outcome trials have been conducted, adding greater certainty in the assessment of the relative risks and benefits of each therapy.[9] For example, SGLT-2 inhibitors such as empagliflozin and GLP-1 receptor agonists such as dulaglitide and semaglutide have been recently granted FDA approval to reduce major cardiovascular adverse events (MACE).[10-12]

Although many options for therapy for T2DM exist, nearly half of patients may not have adequate glycemic control.[1] Tirzepatide (Eli Lilly), a novel, once-weekly injectable dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist combination drug, is currently in development to treat patients with T2DM. Trials are also ongoing to assess tirzepatide for the treatment of obesity and cardiovascular disease. The manufacturer is expected to file a biologics license application for FDA approval in 2021, with a decision likely in 2022.

Stakeholder Input

This draft scoping document was developed with input from diverse stakeholders, including patients and their families, clinicians, researchers, and manufacturers of the agents of focus in this review. This document incorporates feedback gathered during preliminary calls with stakeholders and open input submissions from the public.

Patient groups emphasized that the impact of diabetes is substantial in minority populations, with Native Americans and Blacks having the highest rate of disease, and that greater focus on efforts to decrease disparities in prevention and treatment of diabetes and accurate modeling of the health effects of diabetes are critical to improving health equity.

Clinicians were enthusiastic about the prospect of therapies that both improved glycemic control and resulted in substantial weight loss. However, they emphasized the importance of cardiovascular outcomes on their assessments of efficacy and were eagerly awaiting the results of such trials for tirzepatide. Cost of therapy for patients was an additional issue of great importance to both clinicians and patients and was cited as a major factor in the choice of therapy.

Manufacturers and payers highlighted additional outcomes that may be important to consider when assessing the value of therapy, including satisfaction with the delivery device and the ability of the therapy to address comorbidities related to obesity that may be impacted by weight loss (e.g., obstructive sleep apnea, nonalcoholic fatty liver disease, etc).

A revised scoping document will be posted following a three-week public comment period. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of preventive treatments.

Report Aim

This project will evaluate the health and economic outcomes of tirzepatide for type 2 diabetes. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions.

Scope of Clinical Evidence Review

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see ICER's grey literature policy).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the revised scope in a research protocol published on the Open Science Framework website.

Populations

The population of interest for this review is adults with T2DM with inadequate glycemic control despite current treatment with antihyperglycemic agent(s). Data permitting, we intend to examine the following patient subgroups including, but not limited to:

1. High risk for cardiovascular events
2. High risk for heart failure
3. Moderate-to-severe renal impairment
4. Requiring a second antihyperglycemic agent (i.e., second-line therapy)
5. Requiring a third antihyperglycemic agent (i.e., third-line therapy)
6. Overweight (BMI 25.0-29.9) or obese (≥30.0)
7. Race and ethnicity or socioeconomic status

Interventions

Our intervention of interest for this review is subcutaneous tirzepatide (Eli Lilly) added to ongoing background antihyperglycemic treatment (e.g., metformin, sulfonylureas, etc.).

Comparators

We plan to compare to ongoing background treatment (e.g., metformin, sulfonylureas, etc.) and each of the following add-on agents:

- One or more of the following injectible GLP-1 receptor agonists:
    - Dulaglutide (Trulicity®, Eli Lilly)
    - Semaglutide (Ozempic®, Novo Nordisk)
- Empagliflozin (Jardiance®, Boehringer Ingelheim and Eli Lilly), an oral SGLT-2 inhibitor

Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - Glycated hemoglobin (HbA1c) levels
    - Fasting plasma glucose
    - Body weight
    - Blood pressure
    - Estimated glomerular filtration rate (eGFR)
    - Percentage of patients achieving adequate glycemic control or normoglycemia (HbA1C of <5.7%)

- Lipid profile (e.g., Total Cholesterol, Low-Density Lipoprotein Cholesterol, High-Density Lipoprotein Cholesterol, and Triglycerides)
- Use of rescue medication (e.g., additional glucose-lowering medication)
- Hospitalization
- Health-related quality of life and activities of daily living (e.g., Diabetes Treatment Satisfaction Questionnaire (DTSQ), EuroQol 5-Dimensions Health-Related Quality of Life questionnaire (EQ-5D), Impact of Weight on Quality of Life Questionnaire–Lite (IWQOL-Lite), Short Form Health Survey (SF-36))
- Macrovascular outcomes including:
  - All-cause mortality
  - Cardiovascular mortality
  - Stroke
  - Myocardial infarction
  - Heart failure requiring hospitalization or an urgent heart failure visit
  - Other cardiovascular events
- Microvascular outcomes including:
  - Retinopathy
  - Nephropathy
  - Neuropathy
  - Other renal or eye events (e.g., chronic kidney disease progression, visual deterioration)
- Adverse events including:
  - Hypoglycemia
  - Weight gain
  - Pancreatitis
  - Urogenital infections
  - Gastrointestinal effects
  - Fractures
  - Renal effects
  - Cardiovascular events
  - Other events occurring in more than 5% of patients
  - Discontinuation (all-cause, due to adverse events)
  - Serious adverse events

Timing

Evidence on intervention effectiveness and harms will be derived from studies of at least 3 months' duration.

Settings

All relevant settings will be considered, with a focus on outpatient settings in the United States.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These general elements (i.e., not specific to a given disease) are listed in the table below.

Table 1.1. Categories of Contextual Considerations and Potential Other Benefits or Disadvantages

Contextual Consideration*
Acuity of need for treatment of individual patients based on the severity of the condition being treated
Magnitude of the lifetime impact on individual patients of the condition being treated
Other (as relevant)

*Contextual considerations refer to social or ethical priorities that shape to some extent how the value of any effective treatments for a particular condition will be judged.

Potential Other Benefit or Disadvantage*
Patients' ability to achieve major life goals related to education, work, or family life
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life
Patients' ability to manage and sustain treatment given the complexity of regimen
Health inequities
Other (as relevant)

*Potential other benefits or disadvantages are meant to reflect the broader effects of a specific treatment on patients, caregivers, and society.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

As a complement to the evidence review, we will develop an economic model to assess the lifetime cost-effectiveness of tirzepatide relative to relevant comparator treatments. The model structure will be based in part on ICER's previous T2DM model, as well as a literature review of prior published models of T2DM. The base case analysis will take a health care system perspective (i.e., focus on direct medical care costs only). Data permitting, productivity impacts and other indirect costs will be considered in a separate analysis. This modified societal perspective analysis will be considered as a co-base case when the societal costs of care are large relative to direct health care costs, and the impact of treatment on these costs is substantial. This will most often occur in cases where the incremental cost-effectiveness ratio changes by greater than 20%, greater than $200,000 per QALY, and/or when the result crosses the threshold of $100,000-$150,000 per QALY gained. The target population will consist of adults with T2DM with inadequate glycemic control despite

ongoing treatment with antihyperglycemic agent(s). Data permitting, we will consider separately modeling patient subgroups listed in the Populations section.

The model will consist of a microsimulation based on risk equations from the Building, Relating, Assessing, and Validating Outcomes (BRAVO) model that predict risk factor progression, relevant microvascular and macrovascular events, as well as all-cause and CVD-related mortality.[13] A cohort of patients with T2DM from the National Health and Nutrition Examination Survey will be simulated through the risk factor progression, clinical event and mortality risk equations over a lifetime time horizon, modeling patients from treatment initiation until death. In addition, cost-effectiveness will be estimated for shorter time horizons (e.g., five years). We will apply a 3% discount rate to costs and outcomes.

Key model inputs will include clinical probabilities (changes in HbA1c and weight and relative changes in clinical event rates), quality of life values, and health care costs. Probabilities, costs, and other inputs will differ to reflect varying effectiveness between interventions. Treatment effectiveness of tirzepatide and the comparators will be estimated using the network meta-analysis described above.

Health outcomes and costs will be dependent on time spent in each equation-driven health state, clinical events, adverse events (AEs), and direct medical costs. The health outcome of each intervention will be evaluated in terms of major adverse cardiovascular event (MACE) avoided, life-years gained, quality-adjusted life years (QALYs) gained, and equal value of life years gained (evLYG). Quality of life weights will be applied to each equation-driven health state, including quality of life decrements for serious adverse events. The model will include direct medical costs, including but not limited to costs related to drug administration, drug monitoring, condition-related care, and serious adverse events. In addition, productivity changes and other indirect costs will be included in a separate analysis. The model outputs will be averaged across all patient-level simulations for each intervention strategy (tirzepatide and its comparators) to produce cohort-based findings. Relevant cohort-based pairwise comparisons will be made between tirzepatide and the comparators, and results will be expressed in terms of the incremental cost per QALY gained, cost per evLYG, cost per life-year gained, and cost per MACE avoided.

In separate analyses, we will explore the potential health care system budgetary impact of tirzepatide over a five-year time horizon, utilizing published or otherwise publicly available information on the potential population eligible for treatment and results from the economic model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact and will allow assessment of any need for managing the cost of such interventions. More information on ICER's methods for estimating potential budget impact can be found here.

Identification of Low-Value Services

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see ICER's Value Assessment Framework). These services are ones that would not be directly affected by tirzepatide, as these services will be captured in the economic model. Rather, we are seeking services used in the current management of type 2 diabetes beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient. To date, we have not received any suggestions.

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