Semaglutide and Tirzepatide for Obesity

Draft Background and Scope

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Background

Obesity is a complex, chronic disease that affects both physical and mental health, and can result in an increased risk for other conditions such as diabetes, hypertension, liver disease, sleep apnea, cancer, and cardiovascular disease. Severe obesity can shorten life expectancy by up to 14 years, similar to the effect of smoking.[1] The prevalence of obesity has been increasing, and currently around 40 percent of the US population is considered obese.[2] There are both racial and ethnic differences in obesity prevalence, with Black and Hispanic adults having higher rates of obesity.[3] Obesity is costly to the healthcare system, with an estimated $172 billion in medical costs annually attributed to the disease.[4]

Obesity is typically defined using body mass index (BMI, weight in kilograms, height in meters squared), a measurement of weight relative to height. An individual is considered overweight at a BMI of ≥25; obesity is defined as a BMI ≥30, and individuals with a BMI ≥40 are considered to have severe obesity. There are multiple factors that affect a person's risk of developing obesity, including variations in genes that affect metabolic processes, appetite regulation, and body fat distribution, and environmental factors such as physical activity, diet, and socioeconomic status.[5] Obesity can start in childhood and thus can have lifelong effects on an individual's education, work, and social interactions. People with obesity also face substantial social stigma from the disease, with discrimination in workplace, education, and healthcare settings and resulting in high rates of depression and anxiety.[6]

There are multiple modalities for treating obesity including lifestyle modifications (e.g., diet, physical activity, and behavioral modifications), anti-obesity medications (AOMs), and bariatric surgery, alone or in combination. Lifestyle modifications generally result in five to ten percent loss of body weight; however, a substantial number of individuals not only do not achieve long-term, sustained weight loss,[7] but regain weight as well.[8] In adults with obesity or overweight with weight-related complications who require additional weight loss after lifestyle modifications, clinical practice guidelines recommend adding pharmacologic agents.[9] Various AOMs are available for chronic use, including oral agents such as phentermine-topiramate and naltrexone-bupropion and injectable drugs targeting glucagon-like peptide-1 (GLP-1) receptors. For those with severe obesity,

bariatric surgery has been shown to result in durable and substantial weight loss and a lower incidence of diabetes and cardiovascular events.[10] Weight loss can lead to improvement in metabolic markers (e.g., fasting glucose, cholesterol, blood pressure), depression, and quality of life, as well as a decreased risk of developing obesity-related complications (e.g., diabetes, hypertension, sleep apnea, hyperlipidemia, asthma) and death.[11,12]

The approval of semaglutide (Wegovy), a GLP-1 receptor agonist (GLP-1 RA), and tirzepatide (Zepbound), a combination GLP-1 RA/glucose-dependent insulinotropic polypeptide (GIP) RA, have dramatically altered the landscape of AOMs. Both are weekly injections that mediate weight loss primarily through decreasing appetite. Not only are semaglutide and tirzepatide associated with substantial weight loss (mean 15-20%) but can also result in improvements in obesity-related complications. For example, treatment with semaglutide is associated with a reduction in cardiovascular events and decrease in progression of chronic kidney disease; treatment with tirzepatide can improve obstructive sleep apnea.

The promise of the class of GLP-1 RAs for weight loss and to prevent or reverse obesity-related complications, coupled with the large eligible population for treatment and the current high cost of the drugs, has led to the need for an assessment of their value to patients and to a healthcare system with limited resources. Although ICER reviewed treatments for obesity in 2022,[13] additional data have since been published for some AOMs that may affect their clinical and economic value. Thus, this ICER report will focus on the comparative effectiveness and value of semaglutide (oral and injectable) and tirzepatide for the treatment of obesity.

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, data from ICER's 2022 obesity report,[13] and open input submissions from the public. 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.

We heard from stakeholders that obesity is a lifelong disease, often starting in childhood, and both genetic and environmental factors lead to difficulty losing weight and maintaining weight loss over a lifetime. Thus, lifelong treatment will likely be necessary, as with other chronic diseases. There is also stigma and bias associated with obesity that can affect individuals' mental health, self-esteem, and their willingness to engage with the healthcare system for treatment.

Patient advocacy groups and clinical experts emphasized that one of the main limitations of access to GLP-1 RAs is economic – namely, insurance coverage is variable and out-of-pocket costs are high for individuals without insurance coverage. The high cost of therapy also affects adherence, as some individuals are not able to afford to stay on the drugs long-term, which may lead to discontinuation and then regain of weight. Clinical experts stated that although some individuals may respond to older, cheaper medications, those are not as effective as GLP-1 RAs and thus are mainly offered when GLP-1 RAs are cost-prohibitive or when they are not available.

We heard from clinical experts that there is variability in response to AOMs. There are individuals who are hyperresponders and lose large amounts of weight on low doses of medication; on the other hand, individuals with higher BMI at baseline may not have as robust a response to medication. There may also be differences in response based on sex, race, and ethnicity, with women tending to respond better to medication and Black participants losing less weight relative to their White counterparts. Finally, we heard that there is excitement about the use of GLP-1 RAs for treatment for diseases other than obesity and Type 2 diabetes, including substance use disorder and Alzheimer's disease.

Report Aim

This project will evaluate the health and economic outcomes of semaglutide (subcutaneous and oral) and tirzepatide for individuals with obesity, excluding those with established type 2 diabetes, who are seeking medical management for weight loss. 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 innovation, 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 (https://osf.io/7awvd/).

Populations

The population of focus for this review is adults with obesity or adults with overweight in the presence of at least one weight-related comorbid condition, who are actively seeking medical management for weight loss; adults with established diabetes are excluded.

Data permitting, we will seek to examine the following patient subgroups, including but not limited to: sex at birth, race and ethnicity, BMI categories, use and intensity of lifestyle interventions, and prior bariatric surgery.

Interventions

The full list of interventions is as follows:

- Semaglutide, subcutaneous administered weekly
- Semaglutide, oral administered daily
- Tirzepatide, subcutaneous administered weekly

Each of these may be administered in combination with lifestyle modification (e.g., reduced calorie diet and increased physical activity) or alone.

Comparators

We intend to compare these interventions to lifestyle modification alone and to each other.

Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - Weight reduction
    - Weight re-gain
    - Quality of life
    - Mental health outcomes (e.g., anxiety and depression)
    - Obesity-related complications, including but not limited to:
        - Cardiovascular events
        - Sleep apnea
        - Diabetes requiring treatment
        - Heart failure
        - Hyperlipidemia requiring treatment
        - Hypertension requiring treatment
        - End-stage kidney disease
        - Cirrhosis
        - Symptomatic degenerative joint disease
        - Joint replacement surgery
        - Infertility
        - Cancer
        - Mortality
    - Adverse events including
        - Gastrointestinal events (e.g., nausea, vomiting, diarrhea, constipation, etc.)
        - Muscle loss
        - Serious adverse events
        - Adverse events leading to treatment discontinuation
- Other Outcomes
    - Body composition
    - Chronic kidney disease (CKD)
    - Metabolic-associated liver disease
    - Polycystic ovarian syndrome

Timing

Evidence on effectiveness will be derived from studies with at least 26 weeks duration and evidence on harms from studies of any duration.

Settings

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

Benefits Beyond Health and Special Ethical Priorities

Our reviews seek to provide information on benefits beyond health and special ethical priorities 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. Benefits Beyond Health and Special Ethical Priorities

Benefits Beyond Health and Special Ethical Priorities*
There is substantial unmet need despite currently available treatments.
This condition is of substantial relevance for people from a racial/ethnic group that have not been equitably served by the healthcare system.
The treatment is likely to produce substantial improvement in caregivers' quality of life and/or ability to pursue their own education, work, and family life.
The treatment offers a substantial opportunity to improve access to effective treatment by means of its mechanism of action or method of delivery.

*Benefits beyond health and special ethical priorities shape to some extent how the value of any effective treatments for a particular condition will be judged and are meant to reflect the broader effects of a specific treatment on patients, caregivers, and society. For additional information, please see the ICER Value Assessment Framework.

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

Scope of Comparative Value Analyses

A detailed economic model analysis plan with proposed methodology, model structure, model parameters, model inputs, and model assumptions will be published on July 24, 2025. This scoping document provides early thoughts about the overall model structure.

As a complement to the evidence review, we will develop an economic model to assess the lifetime cost-effectiveness of semaglutide (both subcutaneous and oral forms) and tirzepatide as add-on to lifestyle modifications compared to lifestyle modifications alone. The model structure will be based in part on a literature review of prior published models of interventions for obesity.[14-17] Analyses will be conducted from the health care system perspective and the modified societal perspective. The base case analysis will take a health care system perspective (i.e., focus on direct medical care costs only). Societal impacts (e.g., patient productivity) and other indirect costs will be considered in a separate modified societal perspective analysis. This analysis will be considered as a co-base case

when (a) direct data on indirect costs are available, (b) the societal costs of care are large relative to direct health care costs, and (c) 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 percent, greater than $200,000 per evLY or QALY, and/or when the result crosses the threshold of $100,000-$150,000 per evLY or QALY gained. If direct data are lacking on patient and/or caregiver productivity, we will implement a method to capture the potential impacts of semaglutide and tirzepatide on productivity (patient and caregiver) as well as certain other impacts (e.g., patient time in treatment).

The target population will consist of adults who have a body mass index (BMI) of equal to or greater than 30 kilogram per square meter (kg/m^2) or BMI of equal to or greater than 27 kg/m^2 and previously diagnosed with at least one of the weight related comorbidities and without diabetes. The Markov model developed for the 2022 ICER obesity review will be adapted to include health states or events that reflect a broad range of obesity-related outcomes, such as major adverse cardiovascular events (MACE), heart failure (HF), diabetes, chronic kidney disease (CKD), metabolic dysfunction-associated steatohepatitis (MASH), hip or knee replacement, and obstructive sleep apnea (OSA).[13] A cohort of patients will transition between states during predetermined cycles over a lifetime time horizon, modeling patients from treatment initiation until death.

Key model inputs will include clinical probabilities, quality of life values, and health care costs. Probabilities, costs, and other inputs will differ to reflect varying effectiveness between interventions. Treatment effectiveness will be estimated using clinical trials and network meta-analyses where appropriate.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events (AEs), and direct medical costs. The health outcome of each intervention will be evaluated in terms of weight or BMI reduction, presence of weight-related outcomes, equal value of life years gained (evLYG), quality-adjusted life years (QALYs) gained, and life-years gained. Quality of life weights will be applied to each health state, including quality of life decrements for serious adverse events and clinical events not captured via health states. 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, patient and caregiver productivity changes and other indirect costs will be included in a separate analysis, as available data allow. Relevant pairwise comparisons will be made between each of the interventions and placebo, and results will be expressed in terms of the marginal cost per evLYG, cost per QALY gained, cost per life-year gained, and cost per key clinical outcome avoided (e.g., cost per cardiovascular event avoided).

In separate analyses, we will explore the potential health care system budgetary impact of semaglutide and 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 semaglutide or tirzepatide (e.g., CPAP for OSA treatment), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of obesity 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.

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