REPORT AT A GLANCE: **OBESITY MANAGEMENT**

OCTOBER 2022

THEMES AND RECOMMENDATIONS

	Evidence Rating	Annual Net Price	Annual Health-Benefit Price Benchmark
Semaglutide	B+ (when compared to lifestyle modification)	$13,618	$7,500 – $9,800
Liraglutide	B (when compared to lifestyle modification)	$11,760	$3,800 – $4,900
Phentermine/ Topiramate	C++ (when compared to lifestyle modification)	$1,465	$3,600 – $4,800
Bupropion/ Naltrexone	C++ (when compared to lifestyle modification)	$2,095	$1,800- $2,400

"The vast majority of people with obesity cannot achieve sustained weight loss through diet and exercise alone. As such, obesity, and its resulting physical health, mental health, and social burdens is not a choice or failing, but a medical condition. The development of safe and effective medications for the treatment of obesity has long been a goal of medical research that now appears to be coming to fruition. With a condition affecting more than 40% of adults in the US, the focus should be on assuring that these medications are priced in alignment with their benefits so that they are accessible and affordable across US society." **– ICER's Chief Medical Officer, David Rind, MD**

THEMES AND RECOMMENDATIONS

- All stakeholders have an important role to play in ensuring that people living with obesity have access to effective medications as a core benefit of health care insurance coverage.
- Manufacturers should set the price for new treatments for obesity in proportion to their demonstrated benefit to patients and society, with adjustments for residual uncertainty about long-term benefits and the large size of the potential population of people to be treated. Similarly, payers should ensure that pharmaceutical benefit designs developed in conjunction with employers and other plan sponsors ensure access to approved therapies among individuals with obesity.
- All stakeholders should take steps that make effective treatment options for people living with obesity available in a way that will help reduce health inequities.
- Manufacturers should develop patient assistance programs at a level commensurate with other chronic disease conditions to support access to medications among racial and ethnic groups where the burden of obesity is increased, payer coverage is low, and inability to afford out-of-pocket payments is common. Likewise, payers should design coverage criteria that are sensitive to racial and ethnic variability in the clinical applicability of BMI thresholds.

Clinical Analyses

KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

Obesity is a common chronic disease that increases the risk of other conditions such as diabetes mellitus, cancer, and heart disease as well as death. Individuals with overweight and obesity also face considerable social stigma that can have both direct (e.g., mental health, wellbeing) and indirect consequences (e.g., engagement with health care providers). Body mass index (BMI) is commonly used to assess for obesity because it is easy to measure and correlates with body fat measurements. In 2015, the number of adults in the United States (US) with overweight or obesity was estimated to be 79 million and 70 million, respectively. The prevalence of obesity surpassed 40% of US adults in 2018, but among some racial and ethnic groups obesity is even more prevalent with higher proportions for Hispanic adults and highest proportions among non-Hispanic Black women. The direct medical costs attributable to obesity are staggering, estimated to be $260 billion in the US in 2016. Given the high of obesity and its many adverse clinical and cost consequences, cost-effective treatments for this chronic condition are imperative.

Interest in medications to reduce weight and improve health in individuals with obesity has increased due to more non-surgical alternatives and data suggesting that newer medications have an acceptable safety profile and may be more effective in promoting weight loss. Limitations of medications for weight loss include side effects that lead to patient discontinuation, and weight regain when stopped. Under a chronic disease framework, clinical experts concluded that long-term anti-obesity medication use would likely be needed, particularly to prevent complications of obesity such as heart disease. This Report reviews four medications approved by the US Food and Drug Administration (FDA): semaglutide (Wegovy®, Novo Nordisk, June 2021), liraglutide (Saxenda®, Novo Nordisk, 2014), phentermine/topiramate (Qysmia®, Vivus, 2012), and bupropion/naltrexone (Contrave®, Currax Pharmaceuticals, 2014). Semaglutide and liraglutide are glucagon-like peptide-1 (GLP-1) receptor agonists that are also approved for diabetes mellitus and given by subcutaneous injection, whereas phentermine/topiramate and bupropion/naltrexone are combination oral agents that work via other mechanisms. Other promising therapies (e.g., tirzepatide) are still under investigation and are therefore not included in the scope of this review.

For adults without pre-existing diabetes mellitus and either a BMI ≥30 kg/m2 or ≥27 kg/m2 with at least one weight-related comorbid condition (such as hypertension or dyslipidemia), the four interventions added to usual care all reduced body weight compared to usual care alone, which included standard diet and activity and lifestyle recommendations. Indirect mean and categorical weight loss reduction comparisons across the drugs as well as direct head-to-head evidence between two of the agents (semaglutide and liraglutide) suggest that semaglutide and phentermine/topiramate achieve greater weight loss than liraglutide and bupropion/naltrexone. Semaglutide and liraglutide improved blood sugar and blood pressure compared to how they compare to phentermine/topiramate and bupropion/naltrexone is less certain. In addition, none of these drugs have assessed long-term outcomes in adults without pre-existing diabetes mellitus, and thus there is uncertainty around long-term benefits such as cardiovascular morbidity and mortality. Adverse events were common among all interventions, but few serious harms were noted. All interventions had greater discontinuation due to adverse events than for placebo, though semaglutide appears to have lower rates than the other drugs. For all interventions, there is uncertainty about whether sustained weight loss leads to decreased clinical endpoints, and if weight regain occurs over time despite continued therapy.

Given the strength of the evidence on weight loss

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outcomes in the trials and uncertainty around long-term outcomes for adults without pre-existing diabetes mellitus and with obesity or overweight with at least one comorbid condition, Table 1 presents the ICER evidence ratings comparing each intervention with lifestyle modification to lifestyle modification alone and comparing semaglutide and the other interventions with lifestyle modification.

Table 1, Evidence Ratings for Treatment of Adults with Obesity

Intervention	Comparator	Evidence Rating
Semaglutide	Lifestyle modification	B+
Liraglutide	Lifestyle modification	B
Phentermine/ Topiramate	Lifestyle modification	C++
Bupropion/ Naltrexone	Lifestyle modification	C+
Semaglutide	Liraglutide	C+
	Phentermine/topiramate	C+
	Bupropion/naltrexone	C++

Information about ICER's Evidence Rating Matrix may be found here.

Economic Analyses

LONG-TERM COST EFFECTIVENESS

At current prices and with commonly accepted cost-effectiveness benchmarks, results suggest that phentermine/topiramate in addition to lifestyle modification is cost effective compared with lifestyle modification alone. The cost effectiveness of treatment of obesity with semaglutide or liraglutide in patients without diabetes mellitus exceeds commonly used thresholds. Bupropion/naltrexone is cost effective only at higher thresholds.

The health-benefit price benchmark for semaglutide is $7,500 to $9,800 per year; this would require a discount from the wholesale acquisition cost of 44-57%.

In summary, among the agents we reviewed, greater weight loss was seen with semaglutide and with phentermine/topiramate; less weight loss was seen with liraglutide and with bupropion/naltrexone. Although few serious harms were noted for all the interventions, semaglutide may have lower rates of discontinuation and, along with liraglutide, may have additional cardiovascular benefits that extend beyond weight loss effects. Phentermine/topiramate is substantially less expensive than semaglutide and liraglutide, meets commonly accepted cost-effectiveness thresholds and is actually cost-saving when prescribed generically. Bupropion/naltrexone

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is cost effective only at higher thresholds, but is cost effective when prescribed generically. Semaglutide requires substantial discounts from the wholesale acquisition cost to meet typical thresholds, but it is more effective, less burdensome, and more cost effective than liraglutide.

POTENTIAL BUDGET IMPACT

At semaglutide's current net price, approximately 0.1% of the 142 million adult patients across the US with overweight or obesity eligible for treatment with semaglutide could be treated within five years without crossing the ICER potential budget impact threshold of $777 million per year.

ICER is issuing an access and affordability alert for semaglutide in the management of overweight and obesity. The purpose of an ICER access and affordability alert is to signal to stakeholders and policy makers that the amount of added health care costs associated with a new service may be difficult for the health system to absorb over the short term without displacing other needed services, creating pressure on payers to sharply restrict access, or causing rapid growth in health care insurance costs that would threaten sustainable access to high-value care for all patients.

Public Meeting Deliberations

VOTING RESULTS

For adults without pre-existing diabetes and either a BMI ≥30 kg/m2 or ≥27 kg/m2 with at least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes, or dyslipidemia):

- All panelists (15-0) found that the evidence is **adequate** to demonstrate a net health benefit of semaglutide added to lifestyle modification compared to lifestyle modification alone.
- All panelists (15-0) found that the evidence is **adequate** to demonstrate a net health benefit of liraglutide added to lifestyle modification compared to lifestyle modification alone.
- A majority of panelists (14-1) found that the evidence is **adequate** to demonstrate a net health benefit of phentermine/topiramate added to lifestyle modification compared to lifestyle modification alone.
- A majority of panelists (10-5) found that the evidence is **adequate** to demonstrate a net health benefit of bupropion/naltrexone added to lifestyle modification compared to lifestyle modification alone.
- By votes ranging from 10-5 to 15-0, a majority of panelists found that the evidence is **adequate** to demonstrate a net health benefit of semaglutide compared to liraglutide, phentermine/topiramate, or buprioprion/naltrexone.

During their deliberations, panel members also weighed the therapy's other potential benefits, disadvantages, and contextual considerations. Voting highlighted the following as particularly important for payers and other policymakers to note:

Public Meeting Deliberations

- Magnitude of the lifetime impact on individual patients with obesity;
- Patients' ability to achieve major life goals related to education, work, or family life;
- Society's goal of reducing health inequities.

After reviewing the clinical evidence and considering the treatments' other potential benefits, disadvantages, and contextual considerations noted above, the New England CEPAC evaluated the long-term value of semaglutide at its current pricing:

- A majority (11-4) of panelists found that semaglutide added to lifestyle modification represents "low" long-term value for money.
- A majority (12-3) of panelists found that semaglutide added to lifestyle modification represents "low" long-term value for money when compared to phentermine/topiramate.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent nonprofit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public hearings through three core programs: the California Technology Assessment Forum (CTAF), the Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) and the New England Comparative Effectiveness Public Advisory Council (New England CEPAC). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care.

For more information about ICER, please visit ICER's website (www.icer.org).