KEY FINDINGS

	tirzepatide (Eli Lilly)
Evidence Rating	B+: the evidence provides high certainty that tirzepatide delivers at least a small net health benefit when added to background therapy, with the possibility of a substantial net health benefit
Estimated Annual Price	Placeholder price: $4,643.50 (based on injectable semaglutide)
Annual Health-Benefit Price Benchmark	$5,500-$5,700
Change from Annual Price Required to Reach Threshold Price	N/A: discounts not presented due to placeholder price

"Tirzepatide has a novel GIP and GLP-1 receptor agonist mechanism of action, When compared to injectable semaglutide in one head-to-head trial, tirzepatide showed a greater decrease in HbA1c levels, weight, triglycerides, and blood pressure. However, studies of cardiovascular outcomes with tirzepatide have not been concluded, and therefore there is still uncertainty on its true comparative clinical effectiveness in relation to other available treatment options. Nonetheless, based on the available evidence, economic modeling can suggest a fair price range for tirzepatide, and the manufacturer and payers should work together to ensure that a fair price is set and linked to fair, evidence-based insurance coverage terms that do not pose unnecessary burdens to patients."

– ICER's Senior Vice President for Health Economics, Jon Campbell, PhD, MS

THEMES AND RECOMMENDATIONS

- All stakeholders have a responsibility to ensure that effective new treatment options for patients with T2DM are introduced in a way that will help reduce health inequities. For example, manufacturers should ensure that that the set price for new treatments is in fair alignment with added benefits for patients; payers should ensure that benefit designs do not result in out-of-pocket costs that inappropriately limit access in vulnerable populations; health systems and clinicians should develop programs that prioritize decreasing health inequities in the delivery of diabetes care.
- The prior authorization process should be transparent and not place undue burden on clinicians and patients to ensure timely and equitable access to T2DM medications.
- Given available evidence, it is not unreasonable for payers to consider tirzepatide as part of the GLP-1 RA class or as a separate class for the purposes of coverage.
- Payers should consider removing metformin as step therapy before use of GLP-1 RAs and SGLT-2 inhibitors in certain patients, in line with clinical guidelines. If step therapy is employed, access to both GLP-1 RAs and SGLT-2 inhibitors should be preserved.
- Prices for GLP-1 RAs and SGLT-2 inhibitors are high and coupon programs by manufacturers do not adequately address affordability; development and marketing of generic drugs should not be delayed or denied.

Summary

- Especially given the increased burden of T2DM in minority populations, the lack of racial and ethnic diversity in current T2DM clinical trials is unacceptable and future trials should be more reflective of the broader T2DM *population.*
- More research is needed to generate quality-of-life data and data for use in economic evaluations regarding the societal costs of diabetes.

Clinical Analyses

KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

Type 2 diabetes mellitus (T2DM) is characterized by the progressive loss of adequate insulin secretion from the pancreas and peripheral insulin resistance. It affects more than 34 million Americans, with minorities bearing a disproportionate burden of disease. Chronic exposure to high blood glucose levels may damage both small (microvascular) and large (macrovascular) blood vessels, and can result in complications such as blindness, chronic kidney disease (CKD), and atherosclerotic cardiovascular disease (ASCVD). Consequently, the annual costs associated with T2DM exceeded $300 billion in 2017.

Patients with T2DM described the struggle of managing their disease, including struggles with glycemic control, losing weight, managing comorbidities and disease complications, and the expense of medications. Early and comprehensive education about diabetes self-management, along with access to and affordability of medications, were identified as critical factors in the success of managing T2DM over a patient's lifetime.

A measurable short-run goal of treating T2DM is glycemic control, with a goal glycated hemoglobin (HbA1c) of <7.0% in most patients. Beyond lifestyle modifications, metformin is recommended as first-line therapy based on its efficacy and safety. Additional therapy is indicated if glycemic goals are not met with metformin alone. For patients with or at high risk of ASCVD, heart failure, or CKD, sodium glucose transporter-2 (SGLT-2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RA) are preferred due to favorable cardiovascular and renal outcomes data.

Even with current treatment options, nearly half of T2DM patients may not have adequate levels of glycemic control. Tirzepatide (Eli Lilly), a novel, once-weekly injectable dual glucose-dependent insulinotropic polypeptide (GIP) receptor and GLP-1 RA combination drug, has been developed to treat patients with T2DM. A biologics license application with priority review was submitted to the FDA for T2DM on October 27, 2021, with a decision expected in mid-2022.

We compared the clinical and cost effectiveness of tirzepatide added on to background therapy compared with background therapy alone, or injectable semaglutide (Ozempic®, Novo Nordisk) or empagliflozin (Jardiance®, Boehringer Ingelheim and Eli Lilly) added on to background therapy. Treatment with tirzepatide 15 mg resulted in a statistically significant decrease in HbA1c of 2.5% and in weight of 10.9 kg compared with background therapy. Gastrointestinal symptoms were the most common adverse events; severe hypoglycemia was rare.

Tirzepatide also showed a greater reduction in HbA1c,

Clinical Analyses

weight, triglycerides, and blood pressure when compared head-to-head with injectable semaglutide in a Phase 3 randomized controlled trial. However, the tirzepatide group had a greater incidence of gastrointestinal side effects, severe adverse events, and discontinuation compared with semaglutide.

Due to a lack of head-to-head trials, tirzepatide and empagliflozin were compared through a network meta-analysis. Tirzepatide had a greater decrease in HbA1c, weight loss, lipids, and blood pressure compared with empagliflozin, though there was more uncertainty in these estimates given the indirect comparison. The point estimate decreases in HbA1c and weight loss fell in between the point estimates observed when comparing tirzepatide to injectable semaglutide and comparing tirzepatide to background therapy alone. We did not have data to compare adverse events between tirzepatide and empagliflozin.

Based on data from cardiovascular outcomes trials, semaglutide and empagliflozin have FDA indications for prevention of cardiovascular events. Empagliflozin has also been shown to improve outcomes in patients with CKD. The cardiovascular outcomes trial for tirzepatide is ongoing; however, data from SURPASS-4, a cardiovascular safety trial, showed no increase in cardiovascular events and a trend towards cardiovascular benefit.

Although tirzepatide shows an impressive impact on glucose-lowering and weight loss, given the established cardiovascular benefits of semaglutide and empagliflozin, establishing whether tirzepatide has similar benefit is imperative to reducing uncertainty in its comparative effectiveness. Additionally, although GLP-1 RAs have longer-term safety and cardiovascular data, the impact of the addition of GIP inhibition is currently unknown. Finally, the lack of head-to-head comparison makes it more difficult to fully assess whether tirzepatide provides superior benefit to empagliflozin.

Thus, compared to background therapy alone, we judge the net health benefits of tirzepatide to be incremental or better (B+). For tirzepatide compared with semaglutide, although tirzepatide had greater impact on glycemic control and weight, the lack of definitive cardiovascular outcomes data causes us to judge tirzepatide to have comparable or incremental net health benefits (C+). For tirzepatide compared with empagliflozin, the indirect comparison and lack of definitive cardiovascular or renal outcomes data, causes more uncertainty about the relative benefit (whether it has comparable, small or even substantial health benefit compared with empagliflozin), and thus we judge tirzepatide to have comparable or better net health benefits (C++).

Table 1. Evidence Ratings

Treatment	Comparator	Evidence Rating
Tirzepatide	Background therapy	B+
	Injectable semaglutide	C+
	Empagliflozin	C++

Economic Analyses

LONG-TERM COST EFFECTIVENESS

We developed an individual, patient-level, Monte Carlo-based microsimulation of costs, quality of life, clinical events, and mortality associated with T2DM among US adults using the United Kingdom Prospective Diabetes Study Outcomes Model 2 equations. Patients, with data from multiple National Health and Nutrition Examination Survey (NHANES) surveys, were simulated through the modeling steps for each comparator versus tirzepatide. The base-case analysis took a health care sector perspective and thus focused on direct medical care costs only. Costs and outcomes were discounted at 3% per year. All modeled therapies were informed by changes in intermediate outcomes: HbA1c, body weight, LDL, and SBP, predictors in the UKPDS-OM2 risk engine. Modeled cardiovascular and renal outcomes for therapies with existing long-term trials were adjusted to trial data using trial-based hazard ratios. We adjusted tirzepatide's modeled composite MACE outcomes based on SURPASS-4 trial's pooled dosing analysis hazard ratio and its uncertainty. Where possible, we compared the treatment-specific modeled events to that of comparable time horizons from long-term trials.

Tirzepatide had the highest average lifetime discounted quality-adjusted life-years (QALYs) of all considered therapies, however the QALY 95% credible ranges for active comparators overlapped. Equal value of life years (evLY) gained was not reported given no average increased survival when comparing tirzepatide with injectable semaglutide. Using a placeholder price equal to injectable semaglutide, the incremental costs per QALY gained for tirzepatide were around or under $100,000 versus all comparators with mean differences in health gains and costs being smallest in comparison to injectable semaglutide. Uncertainty analyses suggested a wide range of plausible cost-effectiveness estimates for tirzepatide.

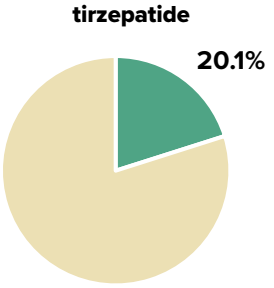
ICER's Health Benefit Price Benchmarks (HBPBs) are defined as the target prices for a drug that would meet but not surpass benchmarks tied to incremental cost-effectiveness ratios of $100,000 and $150,000 per QALY or per evLY gained. Page 1 of this RAAG illustrates the annual HBPBs for tirzepatide plus background therapy as compared to semaglutide plus background therapy, ranging from an annual price for tirzepatide of $5,500 to $5,700. Price reductions or discounts from a list price to reach a HBPB point estimate or range is not applicable for tirzepatide as its list price is currently not available. HBPBs based on evLY gained are not reported given no modeled tirzepatide survival gains versus injectable semaglutide.

In summary, tirzepatide improves blood glucose levels and results in weight loss to a greater extent than other diabetes medications. Although early results are promising, definitive data are needed to understand tirzepatide's impact on cardiovascular and renal outcomes. Additionally, because T2DM is more prevalent among minorities, health gains from a successful treatment that has consistent benefits across racial subgroups would provide proportionally greater benefit to those racial groups. Studies have not adequately enrolled minority populations to demonstrate such a consistent effect. Based on current evidence and when compared to injectable semaglutide, the estimated annualized health benefit price benchmark range for tirzepatide is $5,500 to $5,700. This range factors in assumptions about long-term cardiovascular benefits that have not yet been directly demonstrated yet in clinical trials. ICER did not issue an Access and Affordability Alert for tirzepatide due to the fact that pricing is not yet known; however, patients and clinicians expressed concern about the overall affordability of T2DM drugs.

Economic Analyses

POTENTIAL BUDGET IMPACT

Assuming the tirzepatide placeholder price of $4,643.50 per year, only 20.1% of the eligible patients could be treated within five years (assuming 20% uptake each year) without crossing the ICER potential budget impact threshold of $734 million per year.



Percent of eligible patients with type 2 diabetes that could be treated in a given year before crossing the ICER potential budget impact threshold

Public Meeting Deliberations

VOTING RESULTS

- A majority (13-0) found the evidence is **adequate** to demonstrate that a net health benefit when tirzepatide is added to background therapy when compared to background therapy alone.
- A slight majority (7-6) found that the evidence is **not adequate** to demonstrate a net health benefit when tirzepatide added to background therapy is compared to injectable semaglutide.
- A majority (10-2, 1 abstention) found that the evidence is **not adequate** to demonstrate a net health benefit when tirzepatide added to background therapy is compared to empagliflozin.

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

- Magnitude of the lifetime impact on individual patients of type 2 diabetes;

Consistent with ICER's process, the New England CEPAC did not vote on long-term value for money because the manufacturer has not yet announced a price for tirzepatide.

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).