

WHAT IS TYPE 2 DIABETES?

Type 2 diabetes mellitus (T2DM) is a condition where cells do not respond adequately to insulin and so there are high glucose (sugar) levels. In the United States approximately 30 million individuals have DM, of whom 95% have T2DM. Patients with DM are at increased risk for damage to larger and smaller blood vessels, which can lead to many complications including heart attacks, strokes, blindness, kidney failure, and infections and amputations of limbs. Control of glucose levels can reduce many of these complications, and some newer drugs for diabetes seem to reduce these complications even beyond just controlling blood glucose.

TREATMENT OPTIONS

Standard management of T2DM may include lifestyle changes (such as diet and exercise), and medications to regulate blood glucose levels. Newer medications for T2DM include dipeptidyl peptidase-4 inhibitors (DPP-4i), sodium-glucose cotransporter 2 inhibitors (SGLT-2i) and glucagon-like peptide 1 receptor agonists (GLP-1 RA).

Oral semaglutide (**Rybelsus**[®], Novo Nordisk), was recently approved for the treatment of adults with T2DM; an injectable form of semaglutide has been available since 2017. Semaglutide is a GLP-1 RA. For this report, adding oral semaglutide was compared to ongoing background therapy with medications such as metformin, and to three alternatives for add-on therapy: liraglutide (**Victoza**[®], Novo Nordisk, an injectable GLP-1 RA), sitagliptin (**Januvia**[®], Merck, a DPP-4i), and empagliflozin (**Jardiance**[®], Boehringer Ingelheim, an SGLT-2i).

KEY REPORT FINDINGS

- Adding oral semaglutide delivers a substantial net health benefit compared to ongoing background therapy alone, reducing blood glucose, weight, major adverse cardiovascular events (MACE), and probably kidney disease.
- Adding oral semaglutide results in better control of blood sugar than the other options, and better weight reduction than any of the options except empagliflozin.
- There is high certainty that semaglutide produces at least a small net health benefit compared to sitagliptin as an add-on therapy, reducing blood sugar, weight, MACE, and perhaps kidney disease more than sitagliptin.
- Compared to liraglutide, the evidence for an added benefit of oral semaglutide is judged to be promising but still inconclusive.
- There is insufficient evidence to distinguish the net health benefit of oral semaglutide from that of empagliflozin. Semaglutide is better at reducing blood glucose and empagliflozin is better at reducing hospitalizations for heart failure.
- Oral semaglutide (like other GLP-1 RA) causes GI side effects and so is less well tolerated than empagliflozin and sitagliptin. It is uncertain how this will affect patient willingness to take oral semaglutide outside of a clinical trial.
- For oral semaglutide, clinical experts suggested there are a large number of eligible patients who will likely receive treatment. As such, ICER is issuing an Access and Affordability Alert.

KEY POLICY RECOMMENDATIONS

- Manufacturers with new diabetes agents should seize the opportunity to come to market with a lower list price to benefit patients.
- Manufacturers should strive to provide high quality head-to-head evidence on the comparative effectiveness of emerging treatment options for patients with diabetes.
- Given the high rate of gastrointestinal side effects with oral semaglutide, real world evidence on adherence should be studied and reported.

Clinical Analyses

ICER EVIDENCE RATINGS

How strong is the evidence that oral semaglutide improves outcomes in patients with Type 2 diabetes with no treatment beyond ongoing background treatment to address blood sugar levels?

Adding oral semaglutide vs. ongoing background therapy alone:

- High certainty of a substantial net benefit.

Oral semaglutide vs. sitagliptin:

- There is a moderate certainty of a small or substantial net benefit, with a high certainty of at least a small net benefit.

Oral semaglutide vs. liraglutide:

- Moderate certainty of a comparable, small, or substantial net health benefit, with a small likelihood of worse net health benefit.

Oral semaglutide vs. empagliflozin:

- There is a low certainty in judging the relative net health benefit.

KEY CLINICAL BENEFITS AND HARMS STUDIED IN CLINICAL TRIALS

How effective are these therapies?

Compared to ongoing background therapy, semaglutide, liraglutide, and empagliflozin reduced rates of MACE while sitagliptin had no effect on cardiovascular events. There were no

statistically significant differences in the rate of MACE when semaglutide was compared to liraglutide or empagliflozin. Finally, empagliflozin demonstrated a statistically significant reduction in the rate of hospitalization for heart failure compared to semaglutide.

HARMS

Oral semaglutide may increase gastrointestinal side effects such as nausea, vomiting, and diarrhea. Patients treated with oral semaglutide may also be at increased risk of retinopathy (vision impairment).

SOURCES OF UNCERTAINTY

Measurement of effectiveness: The most important outcomes to patients were not assessed in head-to-head trials, so these comparisons are indirect.

Adherence to therapy: There were higher rates of gastrointestinal side effects with oral semaglutide, which may result in higher rates of discontinuation in the real world than it did in clinical trials settings. In addition, oral semaglutide must be taken on an empty stomach, which may also interfere with adherence in real world settings.

Rates of harms: The available clinical trial data provided limited data on the rate of rare harms such as thyroid cancer with semaglutide and severe genital/urinary infections and amputations with empagliflozin.

Economic Analyses

LONG-TERM COST-EFFECTIVENESS

Do these treatments meet established thresholds for long-term cost-effectiveness?

Based on current evidence, it is difficult to draw conclusions on oral semaglutide’s long-term cost effectiveness. The ultimate value of oral semaglutide will be determined by its long-term effectiveness when used in the real world and its actual net price.

At its estimated net price, oral semaglutide is likely to meet usual cost-effectiveness thresholds compared with background therapy alone but is unlikely to meet these thresholds compared with empagliflozin.

VALUE BASED PRICE BENCHMARKS

What is a fair price for oral semaglutide based on its value to patients and the health care system?

	Oral semaglutide vs. ongoing background therapy
Annual WAC	\$9,404
Estimated Net Price	\$6,103
Annual Price to Achieve \$100,000 - \$150,000/ QALY Threshold	\$5,983-\$6,396
Change from WAC Required to Reach Threshold Prices	-32% discount to -36% discount
Estimated Net Price within or below range?	YES

Oral semaglutide’s estimated annual net price of \$6,103 falls within ICER’s value-based price benchmark range of approximately \$6,000-\$6,400 per year.

Additionally, to reach alternative thresholds of between \$100,000 and \$150,000 per Life Year (LY) gained, oral semaglutide could be priced between \$6,400-\$7,100 per year.

Economic Analyses (continued)

POTENTIAL SHORT-TERM BUDGET IMPACT

How many patients can be treated before crossing ICER's \$819 million budget impact threshold?

Oral semaglutide: At the public meeting, clinical experts stated their belief that, because primary care providers are often uncomfortable prescribing injectable GLP-1 receptor agonists, oral semaglutide would be an attractive alternative for up to 50% of the eligible patient population. However, at oral semaglutide's estimated net price, despite meeting common lifetime cost-effectiveness thresholds versus background therapy alone, only approximately 7% to 14% of eligible US patients could be treated in a given year before crossing ICER's potential budget impact threshold of \$819 million. As such, ICER is issuing an Access and Affordability alert. Currently, this alert is based on the assumed net price, and it should be noted that the findings are subject to change if and when the actual net price becomes available.

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 care system to absorb over the short term without displacing other needed services or contributing to rapid growth in health care insurance costs. Thus, if these issues are not appropriately planned for, there is a risk to sustainable access to high-value care for all patients.

Voting Results

The New England CEPAC deliberated on key questions raised by ICER's report at a public meeting on November 14, 2019. The results of the votes are presented below. More detail on the voting results is provided in the [full report](#).

CLINICAL EVIDENCE

- All panelists found adequate evidence to support a positive net health benefit of adding oral semaglutide to ongoing background therapy compared to ongoing background therapy alone.
- All panelists found adequate evidence that adding oral semaglutide to ongoing background therapy provides a superior net health benefit over adding sitagliptin to ongoing background therapy.
- A majority of panelists did not find sufficient evidence to show a superior net health benefit when adding oral semaglutide to ongoing background therapy compared to adding liraglutide to ongoing background therapy.
- A majority of panelists did not find enough evidence to distinguish the net health benefit between adding oral semaglutide to background therapy or adding empagliflozin to ongoing background therapy.

LONG-TERM VALUE FOR MONEY

- Half of the panelists found that oral semaglutide provides an intermediate long-term value for money compared to ongoing background therapy alone.
- Of the remaining panelists, a majority found that oral semaglutide provides a low long-term value for money compared to ongoing background therapy alone.

OTHER BENEFITS AND CONTEXTUAL CONSIDERATIONS

- A majority of panelists found that, for patients currently receiving ongoing background therapy, adding oral semaglutide offers reduced complexity that will significantly improve patient outcomes compared to adding liraglutide.
- A majority of participants found that adding oral semaglutide is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.

Policy Recommendations

For Payers

- Prior authorization criteria for antihyperglycemic products should be based on clinical evidence, specialty society guidelines, and input from clinical experts and patient groups.
- The process for submitting prior authorization material should be clear and efficient for providers.

For Providers

- As the treatment options for T2DM continue to evolve, primary care providers should make themselves aware of the 2019 ADA Guidelines on treatment of T2DM to ensure that all treating clinicians know how to identify the varying risks and benefits of different agents for particular subpopulations.

For Manufacturers and Clinical Researchers

- Manufacturers with new agents for diabetes mellitus should seize the opportunity to come to market with a lower list price to benefit patients.
- To provide high quality head-to-head evidence on the comparative effectiveness of emerging treatment options for patients with diabetes, manufacturers should look to the example set by the PIONEER trials of oral semaglutide.
- Given the high rate of gastrointestinal side effects with oral semaglutide, real world evidence on adherence should be studied and reported.
- It will be important to understand the relative benefits of GLP-1 RAs and SGLT-2i's on patient important outcomes such as cardiovascular events; these can likely best be assessed in head-to-head pragmatic clinical trials.
- Trials of combination therapies, particularly of GLP-1 RAs and SGLT-2i's, should be performed.

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-review.org).