

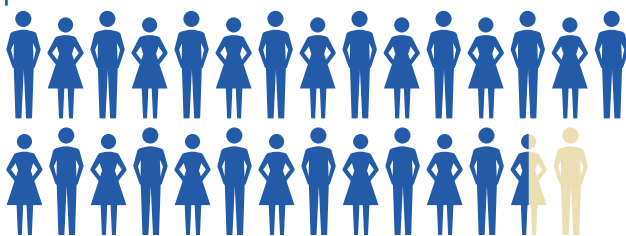
For Treating Diabetes

Does this new drug meet an important need?

The Burden of Diabetes

Number of people in the U.S. with diabetes mellitus (DM): 29.1 million

95% have type 2 diabetes



Number of adults newly diagnosed with diabetes each year: 1.7 million

Annual direct medical cost to treat diabetes in 2012:

\$176 billion

Source: CDC, 2014

The Therapeutic Role of Insulin Degludec

Insulin degludec (Tresiba®, Novo Nordisk A/S) is a long-acting insulin analog intended to meet the basal insulin needs of patients with type 1 or type 2 DM. Insulin degludec allows for once-daily flexible dosing to maintain steady insulin levels, and comes in two formulations: a less concentrated formulation, U100, and a more concentrated formulation, U200. U200 is intended for use by patients with type 2 DM and higher insulin needs.

Insulin degludec offers a new treatment option in addition to other available long-acting insulins, including insulin glargine U100 (Lantus®, Sanofi) and insulin detemir (Levemir®, Novo Nordisk A/S).

Annual Costs of Insulin Degludec*

■ Costs for insulin glargine U100 ■ Costs for insulin degludec

Patients with Type 1 DM

\$2,688

\$2,873

Patients with Type 2 DM on basal insulin regimen

\$4,686

\$5,486

Patients with Type 2 DM on basal-bolus regimen

\$12,063

\$14,765

* The weighted average list price per unit of insulin degludec is \$7,800. Annual costs were based on average patient weight and insulin degludec needs in each of the populations.

How strong is the evidence that insulin degludec works?

Insulin Degludec vs. Insulin Glargine U100

Blood glucose control: Hemoglobin A1c (HbA1c) reduction:

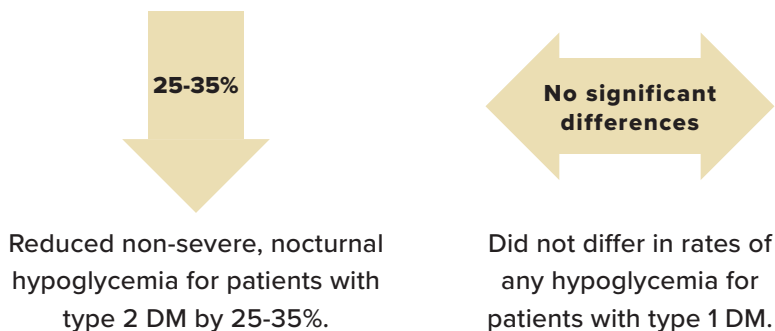
Insulin degludec has been studied in eight major clinical trials, all of which were designed to determine whether it was “non-inferior” to other long-acting insulins (especially insulin glargine U100) in its ability to control blood glucose levels. The studies consistently found that insulin degludec met this non-inferiority standard. However, in six of seven studies insulin degludec was marginally less effective than insulin glargine U100 at lowering HbA1c levels.

Hypoglycemia:

One of the most important side effects of insulin treatment is hypoglycemia, when blood sugar drops too low, resulting in symptoms such as dizziness, sweating, palpitations, and, rarely, shock or even death.

Weaknesses in study design and outcome measurement limit the ability to judge whether insulin degludec leads to lower rates of severe hypoglycemia in patients with type 2 DM.

Compared to insulin glargine U100, insulin degludec:



Patient quality of life:

Evidence on the effects on quality of life was limited and not consistently reported.

How strong is the evidence that insulin degludec works? (continued)

Sources of Uncertainty

Major adverse cardiovascular events. Data on major adverse cardiovascular events (MACE) with insulin degludec is limited. Higher MACE rates for patients treated with insulin degludec were highlighted as a concern by the FDA when it initially declined to approve the drug in 2012. A double-blind randomized trial comparing insulin degludec to insulin glargine U100 that focuses on MACE events is scheduled to be completed in 2016. Interim data from this trial were submitted to the FDA prior to its decision to approve insulin degludec in 2015, but to preserve the integrity of the ongoing study, these data have not been made public.

Hypoglycemia. There are several concerns about the reliability of hypoglycemia results from the degludec trials:

- Trials defined hypoglycemia as blood glucose less than 56 mg/dL, whereas the American Diabetes Association recommends a threshold of less than 70 mg/dL. The lower threshold may have decreased the number of events observed in trials, but more of the detected events would be considered clinically relevant in practice.
- The trials were open label, which could have affected the reporting and adjudication of hypoglycemic events.
- The target fasting glucose level was lower than that typically used for tight glycemic control, which may have increased the incidence of hypoglycemia, though this should not cause differences between the two treatment groups.
- Patients most at risk for hypoglycemic events were excluded from the trials. The results of the trials should not be generalized to this subgroup.
- Because the major differentiating factor in favor of insulin degludec appears to be lower rates of nocturnal hypoglycemia, the lack of data on the clinical impact of these types of events is of concern.

ICER's Evidence Rating

In summary, we find that the evidence provides only moderate certainty of a small comparative net health benefit for insulin degludec versus insulin glargine U100 in patients with type 2 DM. This small comparative net health benefit is due to equivalent blood glucose control with consistent findings of reduced nocturnal hypoglycemia. We find the current evidence does not suggest comparative benefits for patients with type 1 DM. Even for patients with type 2 DM, residual uncertainty regarding the measurement of hypoglycemia outcomes and the risk for higher rates of major adverse cardiovascular events lead us to judge the current body of evidence on the overall comparative clinical effectiveness of insulin degludec to be “promising but inconclusive” in the framework of the [ICER Evidence Rating Matrix](#).

Given its cost, what is the drug’s value to patients and the health care system?

Long-Term Cost-Effectiveness*

Type 2 DM basal-only regimen:

\$353,020/QALY

Type 2 DM basal-bolus regimen:

\$166,644/QALY

Computer modelling of long-term clinical benefits and costs estimated the gain in quality of life from a reduction in episodes of hypoglycemia. Even considering some possible reduction in emergency room and hospital costs with less hypoglycemia, overall costs were increased.

The incremental cost-effectiveness ratio was measured by calculating the cost per additional quality-adjusted life year (QALY). The cost per QALY was \$353,020 for patients with type 2 DM using a basal-only insulin regimen, and \$166,644 for patients using a basal-bolus regimen. The cost per QALY range that represents “reasonable” value in the US is \$50,000–\$150,000 so **insulin degludec does not represent good value for money in the long-term.**

*Cost-effectiveness ratios could not be calculated for patients with type 1 DM, as clinical trials did not demonstrate significant differences in hypoglycemia

Potential Short-Term Budget Impact

\$418.3 million per year

When considering all three patient groups that might use insulin degludec, approximately 5.6 million individuals in the US would be eligible for treatment. If insurers were not to apply strict coverage criteria, we estimate that approximately 10 percent of all eligible patients, or 560,000 individuals, would be prescribed the drug over the first five years after FDA approval.

Under these assumptions the potential budget impact over five years is \$2.09 billion, with an average annual budget impact of approximately \$418.3 million.

This figure does not exceed ICER’s annual threshold of \$904 million for the potential budget impact at which a drug would overly strain affordability of the health care system so **insulin degludec does not pose a substantial threat to health system affordability in the short term.**

ICER’s Value-Based Price Benchmark

\$7,006–\$7,154 per year

- This price range reflects an 8–10% discount from the weighted average cost per year across all three patient populations of \$7,800.
- No additional price reduction would be necessary to avoid a substantial threat to health system affordability.

ICER’s value-based price benchmark is comprised of two components: a range associated with the prices needed to achieve long-term cost-effectiveness between \$100,000–\$150,000 per QALY; and, if necessary, a lower price at which short-term potential budget impact does not threaten overall health system affordability.

Public Deliberation and Evidence Votes

California Technology Assessment Forum (CTAF) Panel Votes

The California Technology Assessment Forum (CTAF) deliberated on key questions raised by ICER's report on insulin degludec at a public meeting on February 12, 2016. The results of the vote are presented below.

CTAF Panel Votes

For patients with type 1 DM, is the evidence adequate to demonstrate that the net health benefit of treatment with insulin degludec is greater than that of treatment with insulin glargine U100?

CTAF Panel Vote:	0 Yes (0%)	16 No (100%)
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For patients with type 2 DM who are on basal-only insulin regimens, is the evidence adequate to demonstrate that the net health benefit of treatment with insulin degludec is greater than that of treatment with insulin glargine U100?

CTAF Panel Vote:	1 Yes (6%)	15 No (94%)
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For patients with type 2 DM who are on basal-bolus insulin regimens, is the evidence adequate to demonstrate that the net health benefit of treatment with insulin degludec is greater than that of treatment with insulin glargine U100?

CTAF Panel Vote:**	2 Yes (13%)	14 No (88%)
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* Care value and provisional health system value votes were not taken due to the "no" votes on sufficiency of clinical evidence.

** Percentages exceed 100 percent due to rounding.

Key Policy Implications and Recommendations

Payers

- Given the CTAF Panel's judgment that current evidence is inadequate to demonstrate that insulin degludec is superior to insulin glargine U100, payers should consider using the full range of utilization management tools to regulate the uptake of insulin degludec.

Providers

- Providers should consider the potential benefit of full-day coverage with insulin degludec for patients who have financial or other constraints on their ability to adhere to insulin-based treatment regimens.

Patients

- Patients should discuss the relative effectiveness of available insulins with their providers and be aware that newly approved insulins may not have evidence to clearly demonstrate their superiority to other insulins already on the market. They should also consider effectiveness before switching to a new medication. This is especially important for patients of limited financial means to determine whether the cost impact of switching insulins is worth any health benefit the new insulin would provide.
- Although newer long-acting insulins may allow for flexible dosing schedules, clinicians still recommend that patients aim to keep insulin administration time as consistent as possible as a best practice.

Manufacturers

- In order to provide the evidence needed by patients, clinicians, and payers, manufacturers should ensure that future trials be double-blinded and powered to detect meaningful clinical differences in objective outcomes such as severe hypoglycemia and HbA1c, as opposed to surrogate and/or non-standardized subjective outcomes.
- Although the FDA specifies that non-inferiority trial design is adequate for approval, manufacturers should seek other trial designs when competing therapies are available in the marketplace, as non-inferiority studies do not provide sufficient information to patients, payers, or clinicians in their determinations of treatment to use or reimburse.
- Future developmental trials for diabetes drugs should use widely-accepted thresholds for hypoglycemia (plasma glucose <70 mg/dL) as opposed to the lower thresholds used in the clinical trials for insulin degludec (<56 mg/dL) to ensure that trial evidence is applicable to real-world practice.
- Future developmental trials should be conducted among patients with severe or frequent hypoglycemia, a clinically important group that was excluded from the non-inferiority trials of insulin degludec.
- Further study is required to better understand the long-term effects of hypoglycemia, including non-severe events.
- Further research is needed to determine insulin degludec's effectiveness relative to other insulins, particularly for patients with type 1 DM.

Conclusion

In Summary

- Based on currently-available evidence and the non-inferiority design of major clinical trials, use of insulin degludec appears to confer small net health benefits in comparison to insulin glargine U100 in patients with type 1 or type 2 DM. Benefits are limited to episodes of nocturnal hypoglycemia.
 - At the current wholesale acquisition cost, the estimated cost-effectiveness of insulin degludec exceeds commonly-cited thresholds. However, achieving levels of value more closely aligned with patient benefit would require relatively modest discounts (8-10%) from the current list price.
 - Across all subpopulations, the potential budget impact of insulin degludec is not estimated to exceed ICER's short-term (five-year) threshold linked to national health care cost growth targets.
- Note that these conclusions are independent of the voting results of the CTAF Panel. The CTAF Panel concluded that when the evidence was considered in its totality, the evidence was insufficient to conclude a true benefit despite the small net health benefit found in ICER's report.

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).