



CALIFORNIA TECHNOLOGY ASSESSMENT FORUMSM

**Insulin Degludec (Tresiba[®], Novo Nordisk A/S) for
the Treatment of Diabetes:
Effectiveness, Value, and Value-Based Price Benchmarks**

Summary of Public Comments Received on Initial Draft Report and ICER Response

The Institute for Clinical and Economic Review (ICER) values the opportunity to receive and respond to public comment on its work products by interested stakeholders. There were three sets of stakeholder comments submitted in response to the initial draft CTAF report on insulin degludec (Tresiba[®], Novo Nordisk A/S) for the treatment of diabetes that was posted on December 21, 2015. Below is a summary of the major comments received, organized by major report component, as well as responses from the ICER team and its research collaborators, including any major changes made to the report.

Evidence Review

- Stakeholders suggested that we clearly label the comparator of interest in the clinical trials of focus as insulin glargine U100 (Lantus[®]) to avoid confusion with the newer U300 formulation (Toujeo[®]). We have added additional descriptors to the report to address this concern, and describe the U300 formulation only for the purposes of context-setting and in our discussion of market uptake assumptions for insulin degludec.
- We also received comments that our evidence review did not fully address concerns with trial design and findings. Specifically, reductions in HbA1c were nominally (but not statistically significantly) lower for insulin degludec than for insulin glargine U100. In addition, dosing of insulin degludec was done in the evening, but timing of insulin glargine U100 dosing was at the discretion of the treating physician, which could have had an impact on hypoglycemia findings. The trial also used a threshold for hypoglycemia (<56 mg/dL) that is lower than the standard definition promulgated in American Diabetes Association (ADA) guidelines (<70 mg/dL).¹ We have added discussion of these concerns to our synthesis of the evidence, but do not feel that these additions warrant changing our level of certainty and evidence rating of “promising *but* inconclusive.”
- Stakeholders disagreed with our assertion that there is a <10% chance of net harm with insulin degludec, citing the FDA’s initial concerns regarding major adverse cardiovascular events (MACE), and the fact that the final results of a large cardiovascular trial of insulin degludec (DEVOTE) are not yet public. However, given that interim results of this trial were provided to the FDA and the drug was then approved, we feel that substantial evidence of net harm arising from MACE events is unlikely, and have therefore made no changes in the revised draft report.



Comparative Value

- We were criticized for not considering numeric differences in clinical results as part of our primary analysis (rather than in sensitivity analyses). We note that insulin degludec was equally or less effective and costlier in the type 1 diabetes population in both sets of analyses, and that cost-effectiveness was above commonly-accepted thresholds for the type 2 subpopulations regardless of the approach employed.
- Stakeholders also commented that U.S.-specific estimates for the models should always be preferred, citing examples of multi-country estimates for disutility of hypoglycemia and Canadian costs for managing hypoglycemia. We note that the author of the multi-country disutility concluded the hypoglycemia effects are “comparable and independent of healthcare system differences”² and so preferred to use estimates from the larger sample. While we did find U.S. sources for costs of managing hypoglycemia, they were highly variable, and in fact bracketed our estimate. In addition, this concern had essentially no impact on model findings, given that the incidence of severe hypoglycemia (the only type of event assumed to generate costs) did not differ between treatment groups in any diabetes subpopulation. We have made no changes in the revised draft report.
- Several stakeholders mentioned our use of wholesale acquisition costs to estimate drug costs, suggesting that all payers receive some form of discount. We agree, but note that levels of discount are rarely made public, and a major purpose in producing our value-based price benchmarks is to identify levels of discounting that might better align drug costs with benefits provided to patients.
- Our use of the UKPDS model in a type 1 population was called into question. We agree that this is a limitation of our approach, but unlike in type 2 diabetes, there are no publicly-available externally-validated type 1 models. In addition, given the lack of clinical data to distinguish insulin degludec from insulin glargine U100 in type 1 patients, the focus of attention is narrowed to differences in cost.
- Stakeholders also questioned our assumption that only severe episodes of hypoglycemia generate costs. Interestingly, the source named as an example identified patients based on health encounters for hypoglycemia,³ which generally matches the definition of a severe event (i.e., hypoglycemia requiring third-party intervention). No changes have been made in the revised draft report.
- Concern was also raised regarding an apparent “front-loading” of the costs and utilities of hypoglycemia from our submodel without appropriate discounting applied. Cost and utility effects were discounted along the pattern of life expectancy generated by the UKPDS model, and so were not “front-loaded”. We have clarified this description in the report, and have also clarified our description of the disutilities as short-term (i.e., a “transient” effect per event).



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- Multiple comments were made on our methods for calculating budget impact, including an apparent lack of consideration of value to patients, and its use of “arbitrary” thresholds. We have received similar comments from multiple constituencies and have responded to them in kind. Please see <http://www.icer-review.org/wp-content/uploads/2014/01/National-Pharmaceutical-Council-comments-on-ICER-Value-Framework-Assessment-with-ICER-responses-Final1.pdf> for further details.

Other Comments

- We received comments suggesting that an economic analysis of an intervention that our evidence review has deemed “inconclusive” is inappropriate. We disagree; regardless of the state of the evidence, the intervention is FDA-approved and available for use. Decision-makers will naturally have questions regarding not only the clinical data but also the potential economic impacts at both the patient and health-system levels.
- Finally, stakeholder comments called into question our decision to announce the major findings of our initial draft report via press release, suggesting that news organizations will not focus on the draft status of the report or subsequent revisions that will be made. We note that, while we do direct readers of the press release to our major conclusions, releases are always made at the same time the report is posted publicly, and interested readers can easily obtain further detail. Other organizations often release findings from major clinical studies in advance of their publication or public availability.

References:

1. American Diabetes Association. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association workgroup on hypoglycemia. *Diabetes Care* 2005;28:1245-1249.
2. Evans M, Khunti K, Mamdani M, et al. Health-related quality of life associated with daytime and nocturnal hypoglycemic events: a time trade-off survey in five countries. *Health Qual Life Outcomes* 2013;11:90. doi: 10.1186/1477-7525-11-90.
3. Zhao Y, Campbell CR, Fonseca V, Shi L. Impact of hypoglycemia associated with antihyperglycemic medications on vascular risks in veterans with Type 2 diabetes. *Diabetes Care* 2012;35:1126-1132.