Public Comments Received on "Insulin Degludec (Tresiba®, Novo Nordisk) for the Treatment of Diabetes by January 12, 2016

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To: California Technology Assessment Forum (CTAF), by email to ctaf@icer-review.org

From: Richard KP Sun, MD, MPH, Sacramento, CA (as an individual, not as a representative of any organization)

Date: December 30, 2015

Subject: **Recommendations Concerning "Insulin Degludec (Tresiba®, Novo Nordisk A/S) for the Treatment of Diabetes: Effectiveness, Value, and Value-Based Price Benchmarks | Draft Report | December 21, 2015"** (accessed December 27, 2015 at http://ctaf.org/sites/default/files/u148/Diabetes_Draft_Report_122115.pdf)

Thanks to CTAF for another splendid draft report. The recommendations below are separated into "Content" ("C") versus "Formatting and Other Relatively Minor Issues" ("F"). Please note that since the CTAF mepolizumab and insulin degludec draft reports released the same day share many features, many of the recommendations concerning the two reports are similar or identical.

CONTENT

Recommendation C1: In the title, make the part after the colon "Effectiveness, Value, and Related Considerations."

The discussion of value-based price benchmarks is only a small part of the report and can be subsumed under the rubric of "Value." The report contains information that cannot be classified as either "Effectiveness" or "Value" (see Recommendations C4 and F4 below).

Recommendation C2: Shorten the executive summary.

Although there is no universally-accepted standard, many Web pages at .edu domains suggest that the length of such a summary not exceed 10% of the length of a full report.[1] In a separate email please find edits to bring the executive summary of the 73-page insulin degludec full report (prior to any changes recommended below) down to about 7 pages.

Recommendation C3: Add relevant references and accompanying text.

The PICOTS framework on page 1 needs a reference. Somewhere in the document there should be a description of combination insulin degludec and liraglutide, with a reference and with an explanation of why studies on the combination were excluded.

Recommendation C4: Combine "3. Summary of Coverage Policies" and "Appendix C. Public and Representative Private Insurer Coverage Policies" to become an Appendix after "Comparative Value Supplemental Information."

Material on coverage policies was absent from CTAF reports before "Supplemental Screening Tests Following Negative Mammography in Women with Dense Breast Tissue" of late 2013. Such material does not directly pertain to the two pillars of current reports, which are "Effectiveness" and "Value" (Recommendation C1 above). Based on documents at the CTAF Web site, information on coverage policies is used only in the Policy Roundtable (after CTAF votes on effectiveness and value are counted) and in Action Guides. Other parts of the draft document (e.g., the Executive Summary) do not refer to the coverage policies section. Unlike

published scientific literature, coverage policies change frequently. The CTAF Panel excludes "current employees of any California state health agency [or] private insurer,"[2] which is inconsistent with discussion of coverage policies in a background document for the CTAF Panel. Technology assessments and related documents produced by organizations such as AHRQ and USPSTF do not consider coverage policies by insurers.

Recommendation C5: Delete Appendix Table A1, "PRISMA 2009 Checklist," and the reference to Appendix Table A1 under "4. Comparative Clinical Effectiveness."

The PRISMA list is readily available on the Web, pertains more to reporting of methods rather than the preferred methods themselves, is not specific to CTAF, and contains steps other than "Search Strategies and Results" (the title of Appendix A).

Recommendation C6: Under "6. Comparative Value," re-do the tornado diagram.

On page 34 the dollar figures at the left and right ends of the bars are not very helpful since the X axis is labeled in dollars. Instead, it would be useful to know the minimum and maximum values of the independent variables (e.g., "Cost of insulin degludec") associated with the minimum and maximum dollar figures. Compare with the bracketed numbers on the left side of Figure 4 in the mepolizumab report.

Recommendation C7: Under "6.4 Potential Budget Impact," revise Figure 6 ("Combined Cost-effectiveness and Potential Budget Impact") and the accompanying text.

On pages 39-40, the "As can be seen in Figure 6..." text confuses the reader. The word "national" should be used to indicate that the "annual budget impact" is not California-specific. The title of Figure 6 does not describe the data well. The $904M threshold should be indicated as a colored horizontal bar. It is unreasonable to show budget impact for uptake that is over two times the best estimate (i.e., uptake that is >20%). Please see the separate email displaying specific recommended edits to the text and figure.

Recommendation C8: Request that the CTAF Panel and Advisory Board formally vote to adopt or reject the methodologies underlying "6.4 Potential Budget Impact" and "6.5 Draft Value-based Benchmark Prices," especially the concept of "Potential Budget Impact Threshold."

Beyond the brief explanation in section 6.4, "Potential Budget Impact," I cannot find detailed information on how the total national $904 million "Potential Budget Impact Threshold" was decided upon.[3] At CTAF, the concept appears to have been introduced with the CardioMEMS and Entresto draft paper of September 2015.[4] Although there do not seem to be any public comments on the "Potential Budget Impact Threshold" on the CTAF site, public comments for the New England CEPAC's draft paper on PCSK9 inhibitors earlier this year expressed concerns with the concept[5] that in my opinion were incompletely addressed[6].

While the threshold is appealing because it takes into consideration both the utilization of a drug and its per-unit cost, it is problematic because it does not account for variation across health plans. Let us consider hypothetical drugs X and Y. Drug X costs $100 per patient per year and will be used by 5M Americans, for a total national expenditure of $500M. Drug Y costs $1M per patient per year and will be used by 500 Americans, for a total national expenditure of $500M. Neither drug will exceed the national "Potential Budget Impact Threshold"; however, the impact

of Drug Y on a single health plan can be considerable, making it worthy of "policy actions to manage affordability."

CTAF might want to add a separate "Individual Cost Impact Threshold" of $12,502 per patient per year, which is double the 2015 average annual premium for employer-based health coverage for a single person.[7] At current list prices, insulin degludec for an individual patient will not exceed $12,502 per year, making it a low-priority subject for potential policy actions.

More broadly, the methodologies underlying "6.4 Potential Budget Impact" and "6.5 Draft Value-based Benchmark Prices" appear unique to the Institute for Clinical and Economic Review and to my knowledge have not been published in a peer-reviewed scientific journal. (In contrast, the methods used for sections 4.1-4.3 on Comparative Clinical Effectiveness and for sections 6.1-6.3 on Comparative Value are widespread in the academic literature.) It is therefore important that CTAF formally accept the 6.4/6.5 methodology prior to issuing reports using the methodology. Currently, there is nothing on the CTAF Web site suggesting that the CTAF Panel and Advisory Board have thoroughly contemplated the pros and cons of the approaches embodied in 6.4 and 6.5.

FORMATTING AND OTHER RELATIVELY MINOR ISSUES

Recommendation F1: Create a file naming convention that includes the specific service being studied and the term "CTAF." Such a convention would help people who download a file to find it later on their computers. A file name such as "Insulin_Degludec_Draft_Report_CTAF122115" would have been better.

Recommendation F2: Place a unique identifier in the footer of each page with the date, the nature of the document (eg, draft vs final), the term "CTAF," and the specific service being studied. One possibility would be to place in the footer the improved file name per Recommendation F1.

Recommendation F3: In four places (starting with "3. Summary of Coverage Policies"), correct the punctuation/capitalization of "CVS Caremark" to "CVS/caremark."[8]

Recommendation F4: Move section 5, "Other Benefits or Disadvantages," to an Appendix. This information is not pertinent to either "Effectiveness" or "Value" (see Recommendation C1 above).

Recommendation F5: In Appendix D on "Previous Systematic Reviews and Technology Assessments," improve the reference numbering and format. It is confusing to have the systematic reviews of insulin degludec numbered 1-11 on pages 63-64 but the superscripts on page 64 refer to the References starting on page 43. Reference 2 should not be in all caps. In reference 8, "Basal" should not be capitalized but "begin" should be all caps.

Recommendation F6: In Appendix E, change the title to "Ongoing Registered Clinical Trials" and add ClinicalTrials.gov as a source. "Ongoing Studies" is too general a title if the list includes only clinical trials registered at ClinicalTrials.gov.

Recommendation F7: Improve the tables in Appendix F (e.g., by increasing font size and by adding horizontal bars). Due to space limitations here, for details please see the attachment to the separate email.

REFERENCES

1. For example, see http://libguides.usc.edu/writingguide/executivesummary , https://www.uakron.edu/cba/docs/communications/WritingExecutiveSummaries.pdf , http://classes.engr.oregonstate.edu/mime/fall2011/ie497/Handouts/executive_summary.pdf , https://www.umuc.edu/writingcenter/writingresources/exec_summaries.cfm , http://writing.colostate.edu/guides/guide.cfm?guideid=76 , http://public.wsu.edu/~campbelld/engl402/execsum.htm , http://facpub.stjohns.edu/~flanagap/3305/readings/executive_summary.doc , and https://www.isenberg.umass.edu/sites/default/files/Documents/Executive_Summaries.pdf . Indeed, some Web pages at .edu domains, such as http://www.muskingum.edu/dept/polisci/downloads/WritinganExecutiveSummary.pdf and http://www.newhaven.edu/772778.pdf , advise capping an executive summary at 5% of the number of pages in a full report.
2. http://ctaf.org/about-ctaf/news/2012/panel-application-process
3. The documents linked to http://www.icer-review.org/impact-and-%20outcomes/value-assessment-project/ contain some background information, but there does not appear to be a full white paper about the threshold.
4. http://ctaf.org/sites/default/files/u148/CHF_Draft_Report_091115.pdf
5. At http://cepac.icer-review.org/wp-content/uploads/2015/04/Public-Comments-PCSK9.pdf , one sees criticisms such as "The ICER warning threshold for a drug's budget impact is not a meaningful method for assessing health system value" (PDF page 9); "ICER's model applies the same $900 million threshold for all new medicines regardless of the size of the population being treated by the medicine, and is not linked to the clinical importance or effect size of the particular medicine" (page 10); "The approach outlined by ICER sets a budget threshold of $904 million in total annual costs for a new drug. Applying this threshold to past innovations, such as statins and anti-retrovirals, would have limited access to these drugs at the time they were introduced to the market" (page 19).
6. At http://cepac.icer-review.org/wp-content/uploads/2015/04/PCSK9_-PublicComment_ResponseSummary_100815.pdf , the only response was "The annual budget threshold of $904 million was also criticized as an arbitrary 'cap' that is exclusively focused on drug cost and not on the net clinical benefit to patients. As described in the report, this threshold is intended to serve as a policy trigger to stimulate efforts to address utilization, pricing, and payment mechanisms to improve overall health system value."
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8. e.g., see "CVS Caremark Announces Corporate Name Change to CVS Health to Reflect Broader Health Care Commitment" at https://www.cvshealth.com/content/cvs-caremark-announces-corporate-name-change-cvs-health-reflect-broader-health-care and current web site at https://www.caremark.com .

Sanofi appreciates the opportunity to provide feedback to the ICER draft report, titled "Insulin degludec for the treatment of diabetes." Our comments center upon the following four domains:

- ***Specification of comparison treatments.*** The ICER review compares data from degludec (Tresiba®) and insulin glargine U100 (Lantus®) only. However, the draft report also makes references to Toujeo® (insulin glargine U300), a new basal insulin formulation of glargine 300 units/mL that has a more constant pharmacokinetic profile with a prolonged duration of action when compared with Lantus®. In the absence of head-to-head clinical trials, comparison of clinical or cost-effectiveness of degludec relative to glargine U300 (Toujeo®) should be excluded.
- ***Comparative clinical effectiveness***. In a number of clinical trials, a numerical improvement in HbA1c lowering was observed with Lantus vs. degludec: this finding should be reflected in the review. Furthermore, evidence for the claim that a nocturnal hypoglycemia difference exists between degludec and Lantus® is limited and largely driven by trial design. As acknowledged in the degludec (Tresiba®) U.S. prescribing information, *"…comparing rates of hypoglycemia in clinical trials for Tresiba® with the incidence of hypoglycemia for other products may be misleading."*[1]
- ***Cost-effectiveness***. The cost-effectiveness analysis should explicitly incorporate the differential risk of major adverse cardiovascular events (MACE), as well as observed numeric improvements in HbA1c.
- ***Budget impact framework***. Imposing a uniform threshold for all new products can stifle innovation for high-value treatments that affect diseases with the highest prevalence. Further, basing this threshold on GDP growth is arbitrary and not supported by standard economic analysis.

These limitations raise concerns about the report's conclusions. Below, we outline these issues and provide our recommendations in more detail.

Specification of Comparison Treatments

ICER should specify that its report compares degludec against insulin glargine U100 (Lantus®), not against insulin glargine U300 (Toujeo®). Clinical trials used in ICER's comparative clinical effectiveness and cost-effectiveness analysis compare degludec and Lantus®; none of the evidence cited in the report compares degludec against Toujeo.

Recommendation:

1. Remove the comparative effectiveness references to Toujeo in the final version of the report. In addition, the draft voting questions for deliberation at the February 12, 2016 meeting should be revised to specify ICER has compared degludec with *Lantus®* and not with *glargine* (which refers to both Lantus® (glargine U100) and Toujeo® (glargine U300)).

Comparative Clinical Effectiveness

Evidence does not support the conclusion that degludec has a *"moderate certainty of a small comparative net health benefit vs. Lantus®."* A review of the degludec non-inferiority trials found that "*mean reductions from baseline in HbA1c were numerically (but not statistically) smaller with degludec…compared with [Lantus®]*."[2] Moreover, several clinical trials enrolling both patients with T1DM and T2DM demonstrated a statistically superior HbA1c lowering with Lantus® vs. degludec.[2] Thus, asserting that degludec and Lantus® are equivalent in this domain obfuscates important differences suggested by the clinical trials.

Study design, rather than actual treatment benefit, may be partially responsible for the purported nocturnal hypoglycemia advantage of degludec. Nocturnal hypoglycemia in patients with T2DM is the only outcome where ICER identifies a clinically meaningful difference between degludec and Lantus. However, the observed difference may be attributed to dosing time and nocturnal time parameters used in the clinical trials. Also, the report wording should be more precise when using "incidence" vs "event rates" while describing the hypoglycemic outcomes.

Specifically, in the degludec-Lantus® trials used to measure nocturnal hypoglycemia differences, degludec was administered in the evening, whereas Lantus® was administered "according to label" at an unspecified time each day.[3-9] To our knowledge, there are no head-to-head clinical trials where degludec and Lantus® were administered at the same time every day, precluding a reliable comparison of nocturnal hypoglycemic events. Further, the FDA statistical reviewers concluded that hypoglycemia descriptive data in the degludec trials shows "*a lack of consistency across trials, across hypoglycemia definitions, across time periods considered and across comparators and do not suggest an advantage of degludec over comparators for the risk of hypoglycemia*."[10]

Finally, as the FDA has noted, the advantage of degludec in nocturnal hypoglycemic events measured between 00:01AM and 5:59AM disappeared when this period was extended to 00:01AM-7:59 AM.[11] This sensitivity casts doubt on whether a true clinical difference for this outcome exists.[2]

The glycemic threshold to define hypoglycemia and the fasting glucose targets differ from the ones endorsed by leading diabetes medical associations. The degludec clinical trials defined confirmed hypoglycemia as <56 mg/dL plus hypoglycemic symptoms; however, the American Diabetes Association (ADA) uses a definition of <70 mg/dL plus symptoms.[12] The trials also applied unusually tight titration targets (FPG 70 to <90 mg/dL), which are lower than standard clinical conditions. These important differences limit how applicable the results are to real-world practice.

Recommendations:

2. Revise the glycemic control analysis to integrate the actual HbA1c levels reduction of degludec relative to Lantus.
3. Acknowledge that significant uncertainty remains as to whether an advantage exists in nocturnal hypoglycemia for degludec and revise the conclusion on this issue.

Cost-Effectiveness

Sanofi supports ICER's decision to use a lifetime horizon for modeling the cost-effectiveness of degludec. Diabetes is a chronic illness, so adopting a lifetime horizon allows for the realization of full clinical benefits of diabetes interventions on glucose control and the prevention of diabetes-related complications.

A large cardiovascular outcome trial is ongoing to evaluate the cardiovascular safety of degludec. ICER assumes an identical risk of major adverse cardiovascular events **(**MACE) between degludec and Lantus. ICER acknowledges the paucity of data regarding MACE, although it should justify the report estimate that there is <10% probability of an increased rate of MACE from degludec (p. ES6). Furthermore, because MACE are associated with significant costs and reduced quality of life,[13-14] excluding this probability from the report results in overstating the cost-effectiveness of degludec.

ICER's models do not take into account observed numeric improvements of Lantus® in HbA1c levels, relative to degludec. Trial results suggest that Lantus® has an advantage over degludec in lowering HbA1c levels.[2] ICER's base-case methodology assumes HbA1c differences (as well as all other differences, such as T1DM nocturnal hypoglycemia) are zero. In its scenario analysis, however, ICER uses the clinical trial point estimates of the differences, in place of the zeros (appendix table G3). These approaches should be reversed so that the point estimates are used in the baseline model. Cost-effectiveness analyses should incorporate point estimates for population differences, whether or not those differences are statistically significant.[15-18] This is consistent with best practices in the statistical analysis of clinical outcomes.[19]

ICER should use U.S.-specific cost and disutility measures whenever possible. A critical component of ICER's model is an estimate of the relative disutility of nocturnal versus daytime hypoglycemia, obtained from Evans et al. (2013).[20] ICER's analysis uses Evans et al.'s *pooled* estimate (63% greater disutility), which was based on a survey across five countries. ICER should use the *U.S.-specific* estimate (40% greater disutility) instead.

ICER's modeling should account for the fact that incremental disutility of hypoglycemic events decreases as additional events occur. The model assumes that increasing the number of events decreases utility in a linear fashion. Analyzing data from the same study that provided ICER's estimate of the relative disutility of nocturnal hypoglycemia,[20] Lauridsen et al. (2014) found that the disutility of additional hypoglycemic events decreases as the number of events increases.[21] Using a linear model overestimates the total QALY effect of multiple hypoglycemic events.

Drug pricing based on wholesale acquisition cost (WAC) understates cost effectiveness. It is well known that private sector discounts between manufacturers, payers and patients create deviations from the WAC. ICER should incorporate sensitivity analyses that use varying estimates of realistic discounts offered to plans and co-pay assistance offered to patients or clearly state that discounts are not considered and this may bias study results.

Key components of the analysis are not adequately described to enable external validation. For example, the sources for Table 6 are noted as "from insulin degludec clinical trials," but in many cases it is unclear whether ICER has used an individual trial or an estimate derived from meta-analysis. Further, the baseline diabetes and complication disutilities were cited as coming from UKPDS 82 (Hayes et al. 2013),[22] which does not discuss utilities. The basal-bolus insulin dosing used in the report is based on the total insulin dose for both components and not the basal component. The costs are based on the basal plus bolus dosages. If the choice was to include the bolus component in the cost-effectiveness analysis, this should be stated.

Recommendations:

4. Both degludec's potential increased risk of MACE and more realistic pricing assumptions (e.g., product discounts, co-pay assistance) should be incorporated into sensitivity analyses.
5. U.S.-specific cost and disutility measures should be used, as opposed to using international estimates.
6. The marginal disutility of additional non-severe hypoglycemic events should be modeled to decrease as the aggregate number of events increases, consistent with prior research.
7. More detailed descriptions of data sources and assumptions should be provided to enable third-party validation.

Budget Impact

ICER's budget impact framework ignores the value of a product to a population. ICER's budget impact framework applies an identical threshold for each new molecular entity, which does not incorporate the value to patients or their caretakers for a disease with high prevalence. Applying this structure to products at the time they are introduced may severely curtail patient access to innovative products.[23,24]

ICER's budget impact threshold subjects new products to restrictions unrelated to their value to society. The threshold is partially determined by GDP growth and by the number of new drugs introduced during the same period. These factors are unrelated to value and should be excluded. This framework conflicts with standard economic analysis in which spending is deemed beneficial if it generates larger benefits than the costs incurred.

Recommendation:

8. The budget impact analysis should be revised to follow the good practice guidelines provided by ISPOR.[25]

Conclusion

We appreciate ICER's consideration of our comments and recommendations.

Sincerely,

Ed Greissing

Vice President, US Corporate Affairs, Sanofi US

References

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Dear Dr. Tice et al.,

Thank you for providing the opportunity to comment on ICER's draft assessment of insulin degludec. We believe that the available data do not support the analysis as performed, and question not only how it was done but whether it should have been done at all.

On page 20 of the draft, the analysis concludes that the available evidence on clinical effectiveness is "promising but inconclusive." If the evidence is inconclusive, then the results of any subsequent economic analysis must also be considered inconclusive. Results from the DEVOTE trial will be available later this year. These results will undoubtedly provide a stronger basis for an economic analysis than the currently available data. We suggest that ICER revisit the analysis when these data are released.

In the case of the diabetes type 1 population, the case for refraining from conducting an economic analysis is even stronger. As the authors have pointed out on page ES7, degludec was equally effective and more expensive, i.e., "dominated". In this situation, a CE framework is not suitable and not necessary. The price benchmark analysis could still be carried out, without the CE analysis using the UKPDS OM2 and as the authors have done by setting the price to be the same as that of the comparator.

Moreover, the UKPDS OM2 is not suitable for type 1 diabetes population. Simply changing the baseline characteristics to match those of the type 2 diabetes population is not enough. The disease progression and pathology is different and therefor the risk equations used for type 1 and type 2 diabetes are likely to be different. Unless ICER made a large number of undescribed alterations to the base model, the model should only be used for the population for which it was designed. Please reconsider whether the model has been correctly applied, and if the necessary changes have been made, please document them.

There appears to be a pasting error in Table 6. Patient weight in the Type 1 and Type 2-Basal populations are the same. This represents a contrast from comparable data in Table 5. While patient weights in the two tables are broadly comparable for other patient groups, patients in the Type 2 Basal Only group are significantly heavier in Table 5. Please ensure that the tables are correct and that the correct patient weights were input into the subsequent analyses.

The economic analysis makes a number of assumptions that do not accurately reflect the business environment or standard medical practice. These assumptions severely limit the usefulness of the economic model. For example:

- The model assumes that there will be no payer or provider efforts to restrain utilization. As payers and providers are certain to attach prerequisites, step edits and other restrictions to utilization, this is clearly a false assumption.
- Estimated uptake rates are entirely speculative. If any market research data is available for this population, we strongly suggest incorporating it rather than simply pulling numbers from the air.
- The model assumes that only severe episodes of hypoglycemia generate costs. This assumption ignores long-term incremental effects of hypoglycemia such as cardiovascular events (See Zhao et al., 2012, for example) as well as the immediate costs generated by falls, motor vehicle accidents, etc. that can result from hypoglycemia.

Pr Proprietary

- Cost estimates are based on the reported wholesale price of the medications. These prices represent only the basis for negotiation, not the actual prices paid for them. Prices are thus inflated compared to prices actually paid. ICER should specifically acknowledge this fact.
- The analysis assumes that prices will remain stable throughout the period of the analysis. In reality, introduction of biosimilars and other competing products will drive prices down in the near future. The estimated budget impact is thus overstated.
- The analysis failed to take into account that both insulin degludec and its comparator will vary in price depending on the payer as well as over time. The analysis should include a sensitivity analysis in which the price of insulin glargine is varied.
- The economic model is based on the established UKPDS model. However, this model does not include effects of hypoglycemia, and does not include patients with Type 1 DM. While it is within the realm of standard practice in economic modeling to modify an existing model to meet the needs of an analysis, additions to the model should not be a black box. Best practices demand that the revised model be transparent, with all assumptions clearly stated. Because the ICER model does not achieve this standard, all results are rendered questionable. For its results to be considered credible, ICER must provide a transparent description of the model. For example:

    - It appears that CADTH's hypoglycemia submodel is not fully integrated into the UKPDS OM1 at patient level and hypo data has to be "front-loaded" at baseline and thus preventing proper discounting (CADTH 2010, page 6). If this is also the case with the submodel with the current study, it would contribute to a larger than expected QALY difference.
    - It is not stated whether the disutility is applied as transient, chronic, or both. If chronic disutility or both chronic and transient disutility is applied, it would contribute to a larger than expected QALY difference.

At no point in the document are the terms "hypoglycemic event" or "severe hypoglycemic event" defined, and no effort is made to determine whether they are defined the same way in the clinical studies and the economic analyses from which the costing data is derived. Unless the publications reporting incidence and those reporting costs are using the same definitions, the calculated costs and cost savings associated with treatment will be inaccurate. Please provide some assurance that the same definitions are being applied.

Similarly, costs of hypoglycemia are derived from a Canadian database that is probably outdated. Please provide some assurance that Canadian practices in treating severe hypoglycemic events from a decade ago are sufficiently similar to modern American methods that these costs are relevant.

The QALY difference (0.034) reported in Table 8 appears large compared to the reported inputs (Rate difference and disutilities) into the model. Please ensure a mistake has not been made. If the QALY difference is indeed overestimated, then the true incremental cost effectiveness ratio would be much higher.

The economic analysis is based on clinical evidence that ICER has described as "inconclusive." All of the factors described above serve to introduce still greater uncertainty into the economic analysis. The reported sensitivity analyses fail to capture this level of uncertainty. Additional one-way analyses as well as probabilistic sensitivity analyses should be conducted to quantify the severe lack of robustness in the data underlying any conclusion reached by ICER. In addition, ICER must fully acknowledge this lack of robustness, not only in the document but in any press releases that may be issued, so that decision-makers can be fully informed of the weakness of the foundation on which they are basing their conclusions.

We are unable to discover an explanation for line 8 of Table 10. The calculation of a budget threshold as double the average cost growth (itself a rather arbitrary figure) does not appear to have a basis in policy. We hope that when ICER releases its value assessment framework white paper later this month it includes a rationale for this calculation.

Finally, we note that ICER has once again announced the release of a draft analysis with a press release. We find this to be deeply problematic, as news organizations have reported the results of the draft analysis as factual, without noting that they are subject to revision in the final document. When the final document is released, it is unlikely that news organizations will report on any changes made from the draft. Medical decision-makers have made decisions based on the flawed draft, and are unlikely to alter these decisions based on subsequent revisions. As Fleischmann and Pons demonstrated decades ago, science should not be conducted via press release. To do so renders subsequent interactions political, rather than scientific interactions. We strongly urge that future press releases announce only that a draft has been issued for stakeholder comment, without discussing the content of the draft, and noting that the analysis is subject to revision following peer review.

Sincerely,

Richard Chapell
For the Merck Insulin Glargine Comment Team

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