CTAF Overview

- Core program of the Institute for Clinical and Economic Review (ICER)
- Goal: Help patients, clinicians, insurers, and policymakers understand and apply evidence to improve the quality and value of health care
- Deliberation and voting by CTAF Panel – independent clinicians, methodologists, and public representatives
- Supported by grants from the Blue Shield of California Foundation, the California HealthCare Foundation, and the Laura and John Arnold Foundation

Agenda

- Public Meeting Convened, Topic Overview | 9:00 am
- Presentation of the Evidence and Economic Modeling, Q&A | 9:05 – 9:50 am (Dr. Jeff Tice and Dr. Rick Chapman)
- Public Comments | 9:50 – 10:20 am
- CTAF Deliberation and Votes | 10:20 – 11:00 am
- Policy Roundtable Discussion | 11:00 am – 12:00 pm
- Reflections from CTAF Panel | 12:00 – 12:15 pm
- Lunch | 12:15 pm

> Download meeting materials: [http://tinyurl.com/ctaf-degludec](http://tinyurl.com/ctaf-degludec)

Evidence Review

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Division of General Internal Medicine
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Insulin Degludec (Tresiba®, Novo Nordisk) for the Treatment of Diabetes

February 12, 2016
Disclosures:
I have no conflicts of interest.

Key review team members:
Jeff Tice, MD
Dan Ollendorf, PhD
Jed Weissberg, MD
Shanshan Liu, MS, MPH
Elizabeth Russo, MD
Patricia Synnott, MS
Karin Travers, DSc

Topic in Context
- Diabetes Mellitus (DM): 29 million Americans
  - 95% type 2, 5% type 1
  - Insulin therapy: 6 million
- Intensive management
  - Pre-meal glucose 80-130 mg/dL; HbA1c ≤ 7.0%
  - Decreased retinopathy, nephropathy, neuropathy
  - Increase in hypoglycemic events and deaths from CVD
    - Severe hypoglycemia can lead to seizure, coma, and death

Definitions of Hypoglycemia
- Severe hypoglycemia: requires assistance of another person to administer carbohydrate, glucagon, or other resuscitation
- Confirmed hypoglycemia: blood glucose level <70 mg/dL
- Nocturnal hypoglycemia: hypoglycemia at night
- Clinically significant improvement: 10-20% reduction in severe events or a 30% reduction in all events

From ADA Workgroup on Hypoglycemia

Insulin Degludec (Tresiba)
- Long-acting insulin (U100 and U200 formulations)
  - Half-life approximately 25 hours: once daily to maintain a steady level
- FDA-approved in September 2015
  - To improve glucose control in Adults with type 1 or type 2 DM
- Other long acting insulins
  - Insulin detemir (Levemir)
  - Insulin glargine U100 (Lantus, Basaglar)
  - Insulin glargine U300 (Toujeo)
**Methods**
- Systematic review following PRISMA guidelines
- Target population (FDA indication):
  - Adults with type 1 or 2 diabetes
- Intervention:
  - Insulin degludec
- Comparator:
  - Any long-acting insulin
- Outcomes
  - Cardiovascular events, microvascular events, HbA1c, hypoglycemia, other adverse events

**Included Studies**
- 8 industry-sponsored Phase III RCTs comparing insulin degludec to another long-acting insulin
  - 3 basal-bolus therapy type 1 DM
  - 4 basal-only therapy type 2 DM
  - 1 basal-bolus therapy type 2 DM
- All open-label “non-inferiority” trials
  - Treat to target AM fasting glucose 70-90 mg/dL
  - Long-acting insulin administration
    - Insulin degludec in the evening
    - Insulin glargine at any time, but always the same time
  - Primary outcome: HbA1c upper bound of 95% CI < 0.4%
  - Secondary outcomes: overall, severe, and nocturnal hypoglycemia

**Between-group Differences in HbA1c**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Comparator</th>
<th>Change in HbA1c* (Degludec – Comparator)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type 1 DM</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heller 2012</td>
<td>Glargine U100</td>
<td>-0.01% (-0.14 to 0.12)</td>
</tr>
<tr>
<td>Davies 2014</td>
<td>Detemir</td>
<td>-0.09% (-0.23 to 0.05)</td>
</tr>
<tr>
<td>Mathieu 2013</td>
<td>Glargine U100</td>
<td>0.17% (0.04 to 0.30)</td>
</tr>
<tr>
<td><strong>Type 2 DM Basal-only</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zinman 2012</td>
<td>Glargine U100</td>
<td>0.09% (-0.04 to 0.22)</td>
</tr>
<tr>
<td>Gough 2013</td>
<td>Glargine U100</td>
<td>0.04% (-0.11 to 0.19)</td>
</tr>
<tr>
<td>Onishi 2013</td>
<td>Glargine U100</td>
<td>0.11% (-0.03 to 0.24)</td>
</tr>
<tr>
<td>Meneghini 2013</td>
<td>Glargine U100</td>
<td>0.2 (NR)</td>
</tr>
<tr>
<td><strong>Type 2 DM Basal-bolus</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Garber 2012</td>
<td>Glargine U100</td>
<td>0.08% (-0.05 to 0.21)</td>
</tr>
</tbody>
</table>

* A negative number indicates a greater reduction in HbA1c with insulin degludec

**Meta-analysis for Hypoglycemia**

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Total Hypoglycemia Rate Ratio (95% CI)</th>
<th>Nocturnal Hypoglycemia Rate Ratio (95% CI)</th>
<th>Severe Hypoglycemia Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type 1 DM</strong></td>
<td>1.10 (0.96, 1.26)</td>
<td>0.83 (0.69, 1.00)</td>
<td>1.12 (0.68, 1.86)</td>
</tr>
<tr>
<td><strong>Type 2 DM Basal-only</strong></td>
<td>0.83 (0.70, 0.98)*</td>
<td>0.64 (0.48-0.86)*</td>
<td>0.14 (0.03, 0.70) †</td>
</tr>
<tr>
<td><strong>Type 2 DM Basal-bolus</strong></td>
<td>0.82 (0.69, 0.99)*</td>
<td>0.75 (0.58, 0.99)*</td>
<td>&gt;1.0</td>
</tr>
</tbody>
</table>

* p<0.05
† Likely an error. It is identical to an outlier from one trial only. The meta-analysis does not report that the other trials were excluded.
Major Adverse Cardiovascular Events (MACE)
- Higher MACE rates for patients treated with insulin degludec were a concern of the FDA when it initially declined to approve the drug in 2012
  - 70/5794 versus 21/3461
  - RR 1.67, 95% CI 1.01 to 2.75
- Interim data from an ongoing trial were submitted to FDA prior to its decision to approve degludec in 2015
  - These data have not been made public

Effectiveness: Controversies and Uncertainties
- Primary uncertainty: lack of peer-reviewed data on MACE
- Major benefit of insulin degludec is lower rates of nocturnal hypoglycemia, but the clinical impact of these events is controversial
- Non-inferiority goal was met, but the change in HbA1c consistently greater with glargine U100
- Variation in timing of glargine U100 administration may impact nocturnal hypoglycemia

Effectiveness: Summary
- Moderate certainty of small comparative net health benefit in comparison to insulin glargine/detemir in patients with type 2 DM on basal-only or basal-bolus insulin regimens
  - Based on “non-inferior” glycemic control and consistent findings of reduced nocturnal hypoglycemia
- Greater uncertainty in patients with type 1 DM, as no consistent and statistically significant reductions in hypoglycemia observed
- Residual concerns about potentially higher rates of MACE in all subpopulations
- Comparative clinical effectiveness of insulin degludec judged “promising but inconclusive” using the ICER Evidence Rating Matrix

Public Comments Received
- HbA1c reduction nominally greater with comparator insulin than with insulin degludec
- The definition of confirmed hypoglycemia (<56 mg/dL) is not standard
- The timing of insulin administration was always in the evening for insulin degludec, but was variable for insulin glargine
- The target AM glucose level was unusually tight
- Differentiate between glargine U100 (Lantus), which was the comparator and glargine U300 (Toujeo)
Research Question
- What is the cost-effectiveness of insulin degludec vs. insulin glargine U100 in:
  - Patients with type 1 DM
  - Patients with type 2 DM on basal-only regimens
  - Patients with type 2 DM on basal-bolus regimens

Methods
- Used UKPDS Outcomes Model v.2
  - Added hypoglycemia sub-model
- Population: Adults ages 18 years and older with type 1 DM or type 2 DM, considered as separate populations
  - UKPDS evaluated patients with type 2 DM only
  - Type 1 DM cohort modeled by setting age & other patient characteristics consistent with those reported in type 1 DM insulin degludec trials
- Payer perspective: direct health care costs only
- Lifetime horizon

Disclosures:
I have no conflicts of interest.

Key modeling team members:
Dan Ollendorf, PhD

Incremental Costs Per Outcomes Achieved
Rick Chapman, PhD, MS
Director of Health Economics
Institute for Clinical and Economic Review
Key Assumptions

- Non-inferiority trials, so no comparisons of glycemic control & extrapolation to downstream micro-/macro-vascular complications
- Primary effect: avoided mild/moderate hypoglycemic events in type 2 DM
  - Short-term reduction in health-related quality of life for each event (different for daytime, nocturnal, severe)
  - Cost for each severe event (no cost assumed for mild/moderate events)
- Note: No significant differences in hypoglycemia for type 1 DM patients

Results: Base Case

<table>
<thead>
<tr>
<th>Type 2 DM Basal-only</th>
<th>Type 2 DM Basal-bolus</th>
</tr>
</thead>
<tbody>
<tr>
<td>QALY</td>
<td>Total Costs</td>
</tr>
<tr>
<td>Insulin glargine U100</td>
<td>11.779  $109,609</td>
</tr>
<tr>
<td>Insulin degludec</td>
<td>11.813  $121,631</td>
</tr>
<tr>
<td>Increment (insulin degludec – insulin glargine U100)</td>
<td>0.034 $12,022  0.237 $39,498</td>
</tr>
<tr>
<td>Cost/QALY</td>
<td>$353,020</td>
</tr>
</tbody>
</table>

Note: Cost/QALY could not be calculated for type 1 DM because there were no QALY differences under our base case assumption of no difference in hypoglycemia between insulin degludec and insulin glargine U100.
Results: One-way Sensitivity Analyses (Type 2 DM Basal-Only)

Base case = $353,020/QALY

*Hypoglycemia disutilities varied from -0.02357 to -0.00076 for daytime mild/moderate hypoglycemia, -0.038426 to -0.00124 for nocturnal mild/moderate hypoglycemia, and -0.020 to -0.005 for severe hypoglycemia.

Results: One-way Sensitivity Analyses (Type 2 DM Basal-Bolus)

Base case = $166,644/QALY

*Hypoglycemia disutilities varied from -0.02357 to -0.00076 for daytime mild/moderate hypoglycemia, -0.038426 to -0.00124 for nocturnal mild/moderate hypoglycemia, and -0.020 to -0.005 for severe hypoglycemia.

Results: Threshold Analysis for Annual Cost of Insulin Degludec

<table>
<thead>
<tr>
<th>ICER</th>
<th>Type 1 DM</th>
<th>Type 2 DM Basal-only</th>
<th>Type 2 DM Basal-bolus</th>
<th>Total (Weighted Average)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$50,000/QALY</td>
<td>$2,688*</td>
<td>$4,801</td>
<td>$12,878</td>
<td>$6,850</td>
</tr>
<tr>
<td>$100,000/QALY</td>
<td>$2,688*</td>
<td>$4,914</td>
<td>$13,683</td>
<td>$7,006</td>
</tr>
<tr>
<td>$150,000/QALY</td>
<td>$2,688*</td>
<td>$5,025</td>
<td>$14,498</td>
<td>$7,154</td>
</tr>
<tr>
<td>List Price Annual Cost</td>
<td>$2,873</td>
<td>$5,486</td>
<td>$14,765</td>
<td>$7,800</td>
</tr>
</tbody>
</table>

*Insulin glargine U100 cost as reference price; thresholds could not be calculated, as no clinical differences were assumed for the base-case.

Results: Scenario Analysis

Using point estimates for hypoglycemia events, HbA1c, and weight change regardless of statistical significance

<table>
<thead>
<tr>
<th></th>
<th>Type 1 DM</th>
<th>Type 2 DM Basal-only</th>
<th>Type 2 DM Basal-bolus</th>
</tr>
</thead>
<tbody>
<tr>
<td>QALY</td>
<td>Total Costs</td>
<td>QALY</td>
<td>Total Costs</td>
</tr>
<tr>
<td>Insulin glargine U100</td>
<td>12.769</td>
<td>$104,785</td>
<td>11.779</td>
</tr>
<tr>
<td>Insulin degludec</td>
<td>12.632</td>
<td>$111,248</td>
<td>11.793</td>
</tr>
<tr>
<td>Increment (insulin degludec – insulin glargine U100)</td>
<td>-0.136</td>
<td>$6,463</td>
<td>0.014</td>
</tr>
<tr>
<td>Cost/QALY</td>
<td>Dominated*</td>
<td>$807,942</td>
<td>$182,298</td>
</tr>
</tbody>
</table>

*Insulin degludec provides fewer QALYs at higher cost than insulin glargine U100
Key Model Limitations

- Given non-inferiority nature of the trials, results were sensitive to relative rates of hypoglycemia events, as well as disutility associated with these events
- Limited long-term data on effects of insulin degludec
  - Assumed that effects observed in short-term efficacy trials will continue over lifetime and will remain constant over time
- Need for research examining:
  - Micro- and macro-vascular complications
  - Long-term impact of severe and non-severe hypoglycemic episodes

Public Comments Received

- Primary analysis does not consider numeric differences in clinical results
- U.S.-specific cost and disutility measures should be used instead of international pooled estimates
- Analysis uses wholesale acquisition cost, which does not factor in negotiated discounts
- UKPDS OM2 model is not appropriate for patients with type 1 DM
- Model considers costs for severe hypoglycemia only
- Hypoglycemia costs and utilities appeared “front-loaded,” and did not seem to be discounted appropriately

Conclusions

- Use of insulin degludec appears to confer small net health benefits in comparison to insulin glargine in patients with type 1 or type 2 DM, limited to episodes of nocturnal hypoglycemia
- 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 current list price

Potential Budgetary Impact

Rick Chapman, PhD, MS
Director of Health Economics
Institute for Clinical and Economic Review
Budget Impact: Methods

- Estimated entire candidate populations for treatment:
  - Patients with type 1 DM on basal-bolus regimens = 0.55 million
  - Patients with type 2 DM on basal-only regimens = 3.5 million
  - Patients with type 2 DM on basal-bolus regimens = 1.55 million
  - TOTAL = 5.6 million
- Assumed uptake: 10% by year 5
- Year 5 treated estimates:
  - Patients with type 1 DM on basal-bolus regimens = 55,000
  - Patients with type 2 DM on basal-only regimens = 350,000
  - Patients with type 2 DM on basal-bolus regimens = 155,000
  - TOTAL = 560,000

Annual Budget Impact Threshold: Methods

- Based on calculations involving:
  - Target for overall health care cost growth (GDP+1%)
  - Number of new drug approvals annually
  - Contribution of drug spending to overall health care spending
- Serves as “policy trigger” for discussion of managing cost of new interventions
- 2015-2016 threshold is $904 million for each new drug

Budget Impact: Results at 5 Years

<table>
<thead>
<tr>
<th>Insulin Degludec</th>
<th>Eligible Population (millions)</th>
<th>Number Treated (thousands)</th>
<th>Weighted BI per Patient ($)</th>
<th>Average BI per year (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 DM</td>
<td>0.55</td>
<td>54.9</td>
<td>$538</td>
<td>$5.9</td>
</tr>
<tr>
<td>Type 2 DM Basal-only</td>
<td>3.50</td>
<td>350.1</td>
<td>$2,365</td>
<td>$165.6</td>
</tr>
<tr>
<td>Type 2 DM Basal-bolus</td>
<td>1.55</td>
<td>155.2</td>
<td>$7,950</td>
<td>$246.8</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>5.60</strong></td>
<td><strong>560.3</strong></td>
<td><strong>$3,733</strong></td>
<td><strong>$418.3</strong></td>
</tr>
</tbody>
</table>

Public Comments Received

- Budget impact analysis uses “arbitrary” thresholds, does not consider value to patients
- Economic analysis of an intervention deemed “inconclusive” is inappropriate.
Public Comments

Comparative Clinical Effectiveness Example Question
For patients with "condition X," is the evidence "adequate" to demonstrate that the net health benefits of "intervention A" is greater than that of "comparator B"?

Yes
No

Care Value Example Question
Given the available evidence, what is the care value of "intervention A" vs. "comparator B"?

A. Low
B. Intermediate
C. High
Health System Value Example Question
Given the available evidence, what is the provisional health system value of “intervention A” vs. “comparator B”?
A. Low
B. Intermediate
C. High

Practice Question
What is the best Valentine’s Day gift?
A. Diamonds
B. Flowers
C. Chocolates
D. Dinner
E. Tickets to a play
F. All of the above

Type 1 DM: Clinical Effectiveness
Q1. For patients with type 1 diabetes mellitus (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?
Yes
No

Type 1 DM: Care Value
Q2. Given the available evidence for patients with type 1 DM, what is the care value of treatment with insulin degludec vs. treatment with insulin glargine U100?
A. Low
B. Intermediate
C. High
Type 1 DM: Provisional Health System Value

Q3. Given the available evidence for patients with type 1 DM, what is the provisional health system value of treatment with insulin degludec vs. treatment with insulin glargine U100?

A. Low
B. Intermediate
C. High

Type 2 DM Basal-only: Clinical Effectiveness

Q4. For patients with type 2 DM 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?

Yes
No

Type 2 DM Basal-only: Care Value

Q5. Given the available evidence for patients with type 2 DM who are on basal-only insulin regimens, what is the care value of treatment with insulin degludec vs. treatment with insulin glargine U100?

A. Low
B. Intermediate
C. High

Type 2 DM Basal-only: Provisional Health System Value

Q6. Given the available evidence for patients with type 2 DM who are on basal-only insulin regimens, what is the provisional health system value of treatment with insulin degludec vs. treatment with insulin glargine U100?

A. Low
B. Intermediate
C. High
Type 2 DM Basal-bolus: Clinical Effectiveness

Q7. 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?

Yes
No

Type 2 DM Basal-bolus: Care Value

Q8. Given the available evidence for patients with type 2 DM who are on basal-bolus insulin regimens, what is the care value of treatment with insulin degludec vs. treatment with insulin glargine U100?

A. Low
B. Intermediate
C. High

Policy Roundtable Participants

- Neal Kohatsu, MD, MPH, Medical Director, California Department of Health Care Services
- Elizabeth Murphy, MD, DPhil, Chief, Endocrinology and Metabolism Division and Director of Diabetes Center for High Risk Populations, San Francisco General Hospital; Professor of Clinical Medicine, UCSF
- Manuel Quinones, MD, Internal Medicine and Diabetology, Healthcare Partners - Anaheim
- Tony Van Goor, MD, MMM, CPE, FACP, Senior Director, Medical Affairs, Medical Director for Policy and Technology Assessment, Blue Shield of California
Reflections from CTAF Panel

Summary and Closing Remarks

Lunch (12:15 – 12:40)