Long-Acting Insulins for Type 1 and Type 2 Diabetes

Update 2 Final Report

Executive Summary

July 2018

This report is intended only for state employees in states participating in the Drug Effectiveness Review Project (DERP). Do not distribute outside your state Medicaid agency and public agency partners.
This report updates the comparative evidence on long-acting insulins (LAIs). The prior DERP report (Update 1) was published in May, 2017.

**Key Questions**
- What is the evidence on the comparative effectiveness and harms of long-acting insulins in adults and children with diabetes mellitus?
  - Drug vs. drug
  - Follow-on vs originator drug
  - Pen vs. vial
  - More concentrated (300 or 200 units/mL) vs. less concentrated (100 units/mL)
- Is there evidence on whether effectiveness or harms vary in subgroups of patients?

**Background**
Thirty million people in the U.S. have diabetes, 1.25 million with Type 1 diabetes. Long-term consequences include cardiovascular disease, renal disease, and blindness. Long-acting insulins (LAIs) mimic basal physiologic insulin secretion, with durations of action from 8 to greater than 42 hours (degludec > glargine > detemir).

The percent glycated hemoglobin (HbA1c) reflects mean blood glucose over previous 2 to 3 months, and is used to monitor control of diabetes. The American Diabetes Association suggests goal of HbA1c < 7%. Hypoglycemia may occur with insulin treatment, and is the most common adverse event reported. Severe hypoglycemia, requiring assistance from others or admission to the emergency department or hospital is associated with loss of consciousness, injury, seizures, and mortality. Nocturnal hypoglycemia is typically defined as blood glucose < 70 mg/dL at night, and is concerning due to the potential to miss warning signs of severe hypoglycemia. Differences in pharmacokinetic profiles of the LAIs are thought to lead to variation in risk for severe or nocturnal hypoglycemia.

Glargine was the first LAI approved, as Lantus®, in 2000. More recently, follow-on versions have been approved or are under by the US Food and Drug Administration (Basaglar®, Lusduna, Semglee).

**Inclusion Criteria for Systematic Review**
**Populations:** Adults or children with Type 1 or Type 2 diabetes mellitus.
**Drugs:** Listed in Table below.
**Comparators:** Head to head including fixed-dose combinations), one formulation/device vs. same insulin in another formulation/device (e.g. vial/syringe versus pen).

**Key Outcomes:**
Cardiovascular (CV) events (microvascular and macrovascular), mortality, glycemic control (HbA1c at 2-3 months), nocturnal and severe hypoglycemia and adverse event withdrawals

**SOE** = Strength of Evidence (low, moderate, high or insufficient)

### Table 1: Included Insulins

<table>
<thead>
<tr>
<th>Drug</th>
<th>Forms</th>
<th>Frequency</th>
</tr>
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<tbody>
<tr>
<td>Glargine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lantus®, U100</td>
<td>Vial</td>
<td>Once daily</td>
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<tr>
<td>Toujeo®, U300</td>
<td>Pen</td>
<td></td>
</tr>
<tr>
<td>F-O insulin Semglee</td>
<td>Pen</td>
<td></td>
</tr>
<tr>
<td>F-O insulin Lusduna</td>
<td>Vial or</td>
<td></td>
</tr>
<tr>
<td>Nexvue</td>
<td>pen</td>
<td></td>
</tr>
<tr>
<td>F-O insulin</td>
<td>Pen</td>
<td></td>
</tr>
<tr>
<td>Basaglar®</td>
<td>Pen</td>
<td></td>
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<tr>
<td>Detemir</td>
<td></td>
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</tr>
<tr>
<td>Levemir®, U100</td>
<td>Vial or pen</td>
<td>Once or twice daily</td>
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<tr>
<td>Degludec</td>
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<tr>
<td>Tresiba® U100, U200</td>
<td>Pen</td>
<td>Once daily</td>
</tr>
<tr>
<td>Ryzodeg® 70/30</td>
<td>Pen</td>
<td>Once or twice daily</td>
</tr>
<tr>
<td>Degludec/ aspart</td>
<td>Pen</td>
<td></td>
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</tbody>
</table>

F-O, Follow-on Insulin (patent infringement lawsuits have been filed against products with FDA approvals)

**Overview of Included Evidence**
For this update, we included 12 new studies (9 RCTs, 3 observational studies, and 8 extension studies or subgroup analyses). Cumulatively, there are 71 included studies of LAIs (Table 2). Trial sample sizes ranged from 615 to 7,637, and 6 were rated poor quality. The majority
of the RCTs were 8 to 12 weeks in duration, with 1 being 52 weeks. Most of the studies were funded by 1 of the included insulin’s manufacturers.

Outcomes reported in RCTs are primarily glycemic control and adverse events. One new trial (DEVOTE) was designed to measure CV outcomes with degludec versus glargine in patients with Type 2 diabetes. Observational studies provided evidence on other harms, such as cancer and neonatal exposure to LAIs.

**Findings**

**Degludec**

**Versus Detemir**

Type 1 DM: No significant difference in glycemic control (2 RCTs, SOE: Low). Evidence from a 52-week extension trial in adults did not change these findings.

**Versus Glargine**

Type 1 DM: No significant difference in glycemic control at 16 to 52 weeks (4 RCTs, SOE: Moderate). Incidence of nocturnal hypoglycemia was **significantly lower** with degludec than with glargine (4 RCTs, pooled rate ratio 0.68, 95% CI 0.56 to 0.81) (SOE: Moderate) (Figure 2).

**Type 2 DM**: No significant differences in glycemic control (9 RCTs, SOE: High), or adverse event withdrawals (9 RCTs, SOE: Low, 16 weeks - 2 years). Hypoglycemia **significantly less** with degludec (nocturnal: 9 RCTs, pooled rate ratio 0.71, 95% CI 0.63 to 0.79 and severe: 9 RCTs, 3.3% vs. 5.1% of patients, RR 0.72, 95% CI 0.54 to 0.96; SOE: Moderate) (Figure 3).

DEVOTE Trial: A CV outcomes trial randomized 7,637 patients at high risk for CV events. Event-driven trial continued until > 600 adjudicated major adverse CV events (CV death, nonfatal MI, or nonfatal stroke) occurred. The FDA mandated the trial due to concerns over CV harms (based on a meta-analysis of earlier trials). Combined with other RCT evidence, there is no significant difference in CV events (4 RCTs), deaths (8 RCTs), and cancer (6 RCTs).
**Detemir**

**Versus Glargine**

*Type 1 DM:* No significant differences in glycemic control, severe hypoglycemic events or withdrawal due to adverse events at 26 or 52 weeks (2 RCTs, SOE: Low).

*Type 2 DM:* No significant differences in glycemic control (6 RCTs, 12 - 52 weeks), severe or nocturnal hypoglycemia (6 RCTs, 6 cohort studies; SOE: Low). Adverse event withdrawals significantly greater with detemir (6 RCTs, pooled RR 2.1; 95% CI, 1.4 to 3.3; SOE: Moderate). Evidence does not support a difference in risk of any cancer (4 studies) or breast cancer (3 studies; SOE: Low).

**Glargine**

**Follow-On Glargine vs. Glargine**

*Type 1 and 2 DM:* No significant difference in glycemic control (1 RCT each, SOE: Low).

**Glargine U300 vs. Glargine U100**

*Type 1 DM:* No significant differences in glycemic control, severe hypoglycemia, adverse event withdrawals (4 RCTs, N=871, 2, 6 and 12 months; SOE: Low) or nocturnal hypoglycemia (2-12 months, SOE: Moderate).

*Type 2 DM:* No significant differences in glycemic control, severe hypoglycemia or adverse event withdrawals (4 RCTs, 6-12 months; SOE: Moderate, Low). Nocturnal hypoglycemia significantly less frequent with U300 (3 RCTs, pooled RR 0.74, 95% CI 0.66 to 0.82) at 2 to 6 months, not different at 12 months (SOE: Moderate).

**Glargine U100 Pen vs. Glargine U100 Vial**

*Type 2 DM:* Severe hypoglycemia significantly less frequent with pen than vial /syringe (pooled RR 0.72; 95% CI, 0.65 to 0.79, 7 cohort studies,) (SOE: Moderate).

**FDCP: Degludec/Aspart 70/30 Comparisons**

*Versus Degludec (Type 2):* Evidence was insufficient.

*Versus Detemir (Type 1):* Low-strength evidence (2 RCTs, 1 children, 1 adults) of no difference in glycemic control; 12-month extension in adults confirms these findings. Other outcomes had insufficient evidence.

*Versus Glargine (Type 2):* Moderate-strength evidence (2 RCTs) of no difference in glycemic control. Conflicting findings from 2 RCTs on risk of nocturnal hypoglycemia, possibly less frequent with FDCP but unclear. Other outcomes had insufficient evidence.

**Conclusions**

A total of 71 studies were included (90 publications), with 12 new studies this update and 5 new extension studies (12-months) of RCTs. Across the comparisons, there were no significant differences in glycemic control. Differences in adverse events were found in a few comparisons: degludec has lower risk of hypoglycemia than glargine (nocturnal hypoglycemia in Type 1 patients, and both nocturnal and severe hypoglycemia in Type 2 patients), adverse event withdrawals were greater with detemir than glargine in Type 2 patients, glargine U300 had lower risk of nocturnal hypoglycemia than U100 in the short-term (only), and glargine given via pen injector was associated with lower risk of severe hypoglycemia than via vial and syringe (observational evidence). Evidence on other harms (e.g. cancer, neonatal effects) or the
comparative harms of fixed-dose combination degludec/aspart 70/30 was insufficient to draw conclusions.

**DERP Systematic Review Methods**

We followed systematic review methodology and procedures developed specifically for the Drug Effectiveness Review Project (DERP) and that are in accordance with current guidance for systematic reviews; for example, using dual review for study inclusion, quality assessments, and data abstraction. We searched MEDLINE and the Cochrane randomized trial database through March 2018. We requested dossiers of study information from manufacturers of included drugs, but received none. We created evidence tables, strength of evidence tables, and updated meta-analyses found in systematic reviews with newer trial data, using random effects models in Stata. Additional details on our methods can be found in Appendix A of the full report.

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