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Drug Effectiveness Review Project Summary Report – Long-acting Insulins

Date of Review: November 2015

Current Status of PDL Class:
See **Appendix 1.**

DERP Research Questions:

1. What is the comparative efficacy and effectiveness of long-acting insulins for children and adults with Type 1 or Type 2 diabetes mellitus (T1DM, T2DM)?
2. What is the comparative tolerability and frequency of adverse events with long-acting insulins for children and adults with T1DM or T2DM?
3. Are there subgroups of patients based on demographics (age, racial groups, gender), comorbidities (drug-disease interactions [eg, obesity]), or other medications (drug-drug interactions) for which long-acting insulins differ in efficacy/effectiveness or frequency of adverse events?

Conclusions:

- There is insufficient comparative evidence that evaluates long-term health outcomes (ie, macrovascular outcomes, microvascular outcomes, mortality or cancer) between insulin detemir and glargine products.
- There is insufficient comparative evidence between insulin detemir and glargine products in children.
- There is insufficient comparative evidence between insulin glargine pens and vials.
- In adults with T1DM or T2DM, there is no difference between insulin detemir and glargine in absolute reduction of hemoglobin A1c (HbA1c) or proportion with HbA1c of 7.0% or less between 12 to 52 weeks based on low quality evidence.
- In adults with T1DM or T2DM, there is no difference between insulin glargine U100 and U300 in absolute reduction in HbA1c or proportion with HbA1c of 7.0% or less between 4 to 6 months based on low to moderate quality evidence.
- There is insufficient evidence to determine if there are differences in nocturnal hypoglycemia rates between insulin detemir and glargine in adults with T1DM; however, there does not appear to be any differences in nocturnal hypoglycemia rates between these insulins in adults with T2DM based on low quality evidence.
- There is low quality evidence that there are no differences in rates of severe hypoglycemia or serious adverse events between insulin determir and glargine in adults enrolled in studies up to 1 year in length; however, there may be increased risk of drug discontinuation with insulin detemir due to adverse events (pooled RR 2.1; 95% CI, 1.4 to 3.3).
- In adults with T1DM or T2DM, glargine concentration (U100 vs. U300) did not affect rates of severe hypoglycemia or serious adverse events based on low quality evidence in studies up to 6 months in length. However, there is moderate quality evidence that rates of nocturnal hypoglycemia may be less with U300 in adults with T2DM, but not T1DM, over 6 months (38% vs. 51%; pooled RR 0.75; 95% CI, 0.67 to 0.84; I^2=0%).
- Rates of severe hypoglycemia may be lower with insulin glargine administered in a pen than via a vial, based on low quality evidence from observational studies in adults with T2DM that were observed over 12 months (RR 0.72; 95% CI, 0.65 to 0.79).

Author: Andrew Gibler, PharmD Date: November 2015

- There is insufficient evidence for differences in long-acting insulin products in specific subgroups based on demographics. One small, observational study observed neonates born to mothers on insulin detemir were at higher risk for being large for gestational age versus neonates born to mothers who took insulin glargine. However, the study was not able to adjust for potential confounding.

Recommendations:

- Make insulin glargine U300 non-preferred and subject to current PA criteria for insulin pens (**appendix 3**). Further research is needed to confirm place-in-therapy with other long-acting insulin products.
- Maintain at least one preferred long-acting insulin product on the PDL. No changes made to the PDL at this time.
- Review insulin degludec (Tresiba®) and insulin degludec/aspart (Ryzodeg® 70/30) as separate new drug evaluations at a later time.

Previous Conclusions and Recommendations:

- There is low quality evidence of no significant differences in change in HbA1C or overall and severe hypoglycemia between insulin detemir and insulin glargine and high quality evidence that insulin detemir is associated with less weight gain and low quality evidence of more injection site reactions compared to insulin glargine. With no clinically relevant difference in efficacy or safety of the two long acting agents, evaluate comparative costs.
- There is no significant new comparative evidence on the efficacy and safety of other agents on the PDL.
- Bring back full review of inhaled human recombinant insulin (Afrezza®) once available.
- Continue to include at least one agent from each subgroup (short-acting, rapid-acting, etc.) as preferred on the PDL and evaluate comparative costs in executive session.

Methods:

The September 2015 Drug Class Review on long-acting insulins by the Drug Effectiveness Review Project (DERP) at the Pacific Northwest Evidence-based Practice Center at the Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class.

The final original report is available to Oregon Pharmacy and Therapeutics Committee members upon request. An executive summary report is publically available on the DURM website.

The purpose of the DERP reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. OHSU does not recommend or endorse any guideline or recommendation developed by users of these reports.

See **Appendix 2** for **Highlights of Prescribing Information** from the manufacturer for new drug approval included in this review, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Summary Findings:
Eligible studies for inclusion into the systematic review were studies of adults or children with T1DM or T2DM that compared one long-acting insulin with another or compared the same insulin in a different formulation or device. Outcomes of interest were macrovascular disease (ie, cardiovascular events, cardiovascular-related mortality, stroke, extremity amputation, etc.), microvascular disease (diabetic neuropathy, nephropathy, or retinopathy), all-cause mortality, glycemic control (fasting, A1c, goal A1c), and harms (nocturnal hypoglycemia, severe hypoglycemia, withdrawals due to adverse events, serious adverse events, or malignancy). Studies had to be other systematic reviews or randomized controlled trials with head-to-head comparisons; however, for harms data, comparative observational studies were considered.

A total of 771 records were identified and screened for inclusion in the review. The DERP received dossiers from 3 pharmaceutical manufacturers: Eli Lilly (Basaglar; Peglispro), Novo Nordisk (Levemir®; Insulin Degludec), and Sanofi (Lantus®; Toujeo®, Insulin Glargine U300). Twenty-five studies (13 fair-quality head-to-head trials and 1 good-quality systematic review) of adults with T1DM or T2DM were included. There were no studies in children, and no studies reported long-term effectiveness outcome (eg, macro- or microvascular events). The insulin products included in the review are in table 1.

Table 1. FDA-approved Long-acting Insulin Products.

Drug	Trade Name	Formulation	FDA Approval
Insulin glargine	Lantus® (U100) Toujeo® (U300)	Pen or vial	4/20/2000; 2/25/2015
Insulin detemir	Levemir® (U100)	Pen or vial	6/16/2005

Key Question 1. What is the comparative efficacy and effectiveness of long-acting insulins for children and adults with diabetes mellitus?

T1DM OR T2DM

- There was no evidence directly comparing long-term health outcomes (eg, macro- or microvascular events) between included insulins or devices.

INSULIN DETERMIR vs. INSULIN GLARGINE

- T1DM: There was low-strength evidence, based on 2 fair-quality open-label trials (N=763), that there was no difference between insulin detemir and insulin glargine in glycemic control measured by achieving HbA1c goals or mean plasma glucose levels at 26 or 52 weeks.
- T2DM: There was low-strength evidence based on a good quality systematic review of 4 trials and 2 more recent fair quality trials (total N=2,750) that there was no difference between insulin detemir and insulin glargine in glycemic control measured by achieving HbA1c goals and the reduction in HbA1c at 12 to 52 weeks. There was statistical heterogeneity in these findings, with inconsistency in individual study results such that future studies are needed to strengthen the conclusion.

INSULIN GLARGINE U300 vs. INSULIN GLARGINE U100

- T1DM: Two fair-quality trials including a total of 602 patients provided low-strength evidence that glycemic control measured by hemoglobin A1C did not differ between patients given insulin glargine U300 and insulin glargine U100 for 4 to 6 months.
- T2DM: Three fair-quality Phase 3 trials in a total of 2,474 patients provided moderate-strength evidence that glycemic control measured by hemoglobin A1C did not differ between patients treated for 6 months with insulin glargine U300 and insulin glargine U100. Two of these Phase 3 trials have

completed 6-month treatment extension periods. Glycemic control was improved with insulin glargine U300 in 1 of the trials, but did not differ between insulin glargine concentrations in the other.

INSULIN GLARGINE PEN vs. INSULIN GLARGINE VIAL

- T1DM or T2DM: No evidence comparing insulin glargine delivered via pen versus vial met inclusion criteria.

Key Question 2. What is the comparative tolerability and frequency of adverse events with long-acting insulins for children and adults with diabetes mellitus?

INSULIN DETERMIR vs. INSULIN GLARGINE

- T1DM: Low-strength evidence from 2 fair-quality randomized controlled trials (RCTs) and 2 observational studies suggested no difference in the risk of severe hypoglycemic events between insulin detemir and insulin glargine. Evidence on nocturnal hypoglycemia was insufficient due to sparse reporting (only 2 studies) and inconsistent findings. Future studies are needed to inform evidence on both outcomes. Low-strength evidence from 2 fair-quality RCTs suggested no differences in withdrawals due to adverse events or serious adverse events thought to be related to study insulin.
- T2DM: Low-strength evidence based on 1 systematic review (of 4 RCTs), 1 additional RCT, and 4 observational studies suggested that there was no difference in the incidence of either severe or nocturnal hypoglycemia between insulin detemir and insulin glargine. Low-strength evidence from a systematic review of 4 RCTs and 2 additional RCTs suggested no difference in serious adverse events. Analysis of all trials indicates that withdrawals due to adverse events occurred significantly more frequently for patients assigned to insulin detemir compared with insulin glargine over 12 to 52 weeks (RR 2.1; 95% CI, 1.4 to 3.3; I2=0%).

OTHER HARMS

- Evidence was inadequate to evaluate the comparative risk for cancer in either population.

INSULIN GLARGINE U300 vs. INSULIN GLARGINE U100

- T1DM: Two fair-quality trials in 608 patients showed no difference between insulin glargine U300 and insulin glargine U100 in severe hypoglycemia, withdrawals due to adverse events, serious adverse events (all low strength of evidence for no difference), or nocturnal hypoglycemia (moderate-strength) after 4 to 6 months' treatment.
- T2DM: Three fair-quality trials in 2,488 patients provided moderate- strength evidence that rates of nocturnal hypoglycemia were lower with insulin glargine U300 than with insulin glargine U100 (38% vs. 51%; EPC pooled RR 0.75; 95% CI, 0.67 to 0.84; I^2=0%). The 3 trials did not show differences between insulin glargine concentrations in rates of severe hypoglycemia, withdrawals due to adverse events, or serious adverse events (all low strength of evidence for no difference).

INSULIN GLARGINE PEN vs. INSULIN GLARGINE VIAL

- T1DM: No RCTs or observational studies comparing insulin glargine delivered via pen versus vial in patients with met inclusion criteria.
- T2DM: Seven observational studies in 24,564 patients provided low-strength evidence that rates of severe hypoglycemia were lower with insulin glargine via pen than with insulin glargine via vial and syringe (EPC pooled RR 0.72; 95% CI, 0.65 to 0.79; I^2=0%).

Key Question 3. Are there subgroups of patients based on demographics (age, racial groups, gender), comorbidities (drug-disease interactions [e.g., obesity]), or other medications (drug-drug interactions) for which long-acting insulins differ in efficacy/effectiveness or frequency of adverse events?

INSULIN DETERMIR vs. INSULIN GLARGINE

- T1DM: Two small, fair-quality observational studies (N=203) found inconsistent results with respect to perinatal mortality, neonatal birth weight outcomes, insulin dose, and neonatal hypoglycemia in neonates of women using insulin detemir or insulin glargine throughout pregnancy. Given these differences in findings, concerns over methodology, and the small size of the studies, the results are not sufficient to draw conclusions, and more study is needed.
- T2DM: No comparative evidence found.

INSULIN GLARGINE U300 vs. INSULIN GLARGINE U100

- Included studies did not report outcomes by subgroup.

INSULIN GLARGINE PEN vs. INSULIN GLARGINE VIAL

- Included studies did not report outcomes by subgroup.

Therefore, the strength of evidence for all outcomes across key questions and comparisons was primarily low, with few exceptions. In adults with T1DM, differences in efficacy or harms were not found between insulin detemir and insulin glargine, or insulin glargine U300 and insulin glargine U100. In patients with T2DM, no differences were found in efficacy outcomes. The few differences found in harms were that insulin glargine may result in fewer patients who discontinue due to adverse events than insulin detemir; in addition, nocturnal hypoglycemia may occur in fewer patients with insulin glargine U300 than with insulin glargine U100; lastly, insulin glargine given via pen may result in lower incidence of severe hypoglycemia than when given by vial and syringe. There was inadequate evidence to assess comparative effects on long-term health outcomes, in subgroups, or risk of cancer. Current evidence in pregnant women with T1DM suggests more research is needed to determine comparative effects of long-acting insulins on the neonate.

Appendix 1: Current Status of PDL Class.

Insulins (long-acting insulins bolded)

ROUTE	FORMULATION	BRAND	GENERIC	PDL	PA
SUB-Q	**VIAL**	**LANTUS**	**INSULIN GLARGINE,HUM.REC.ANLOG**	**Y**	Y
SUB-Q	**INSULN PEN**	**LANTUS SOLOSTAR**	**INSULIN GLARGINE,HUM.REC.ANLOG**	**Y**	Y
SUB-Q	**INSULN PEN**	**LEVEMIR FLEXTOUCH**	**INSULIN DETEMIR**	**Y**	Y
SUB-Q	CARTRIDGE	NOVOLOG	INSULIN ASPART	Y	Y
SUB-Q	INSULN PEN	HUMULIN 70/30 KWIKPEN	INSULIN NPH HUM/REG INSULIN HM	Y	Y
SUB-Q	INSULN PEN	NOVOLOG FLEXPEN	INSULIN ASPART	Y	Y
SUB-Q	INSULN PEN	NOVOLOG MIX 70-30 FLEXPEN	INSULIN ASPART PROTAM & ASPART	Y	Y
SUB-Q	VIAL	HUMALOG	INSULIN LISPRO	Y	
SUB-Q	VIAL	HUMALOG MIX 50-50	INSULIN NPL/INSULIN LISPRO	Y	
SUB-Q	VIAL	HUMALOG MIX 75-25	INSULIN NPL/INSULIN LISPRO	Y	
SUB-Q	VIAL	HUMULIN 70-30	INSULIN NPH HUM/REG INSULIN HM	Y	
SUB-Q	VIAL	HUMULIN N	INSULIN NPH HUMAN ISOPHANE	Y	
SUB-Q	VIAL	HUMULIN R U-500	INSULIN REGULAR, HUMAN	Y	
SUB-Q	VIAL	NOVOLIN 70-30	INSULIN NPH HUM/REG INSULIN HM	Y	
SUB-Q	VIAL	NOVOLIN N	INSULIN NPH HUMAN ISOPHANE	Y	
SUB-Q	VIAL	NOVOLOG	INSULIN ASPART	Y	
SUB-Q	VIAL	NOVOLOG MIX 70-30	INSULIN ASPART PROTAM & ASPART	Y	
INJECTION	VIAL	HUMULIN R	INSULIN REGULAR, HUMAN	Y	
INJECTION	VIAL	NOVOLIN R	INSULIN REGULAR, HUMAN	Y	
SUB-Q	**INSULN PEN**	**TOUJEO SOLOSTAR**	**INSULIN GLARGINE,HUM.REC.ANLOG**	**N**	Y
SUB-Q	**VIAL**	**LEVEMIR**	**INSULIN DETEMIR**	**N**	
INHALATION	CART W/DEV	AFREZZA	INSULIN REGULAR, HUMAN	N	
SUB-Q	CARTRIDGE	HUMALOG	INSULIN LISPRO	N	Y
SUB-Q	INSULN PEN	APIDRA SOLOSTAR	INSULIN GLULISINE	N	Y
SUB-Q	INSULN PEN	HUMALOG KWIKPEN	INSULIN LISPRO	N	Y
SUB-Q	INSULN PEN	HUMALOG MIX 50-50 KWIKPEN	INSULIN NPL/INSULIN LISPRO	N	Y
SUB-Q	INSULN PEN	HUMALOG MIX 75-25 KWIKPEN	INSULIN NPL/INSULIN LISPRO	N	Y
SUB-Q	INSULN PEN	HUMULIN N KWIKPEN	INSULIN NPH HUMAN ISOPHANE	N	Y
SUB-Q	VIAL	APIDRA	INSULIN GLULISINE	N	

Appendix 2: Highlights of Prescribing Information.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TOUJEO safely and effectively. See full prescribing information for TOUJEO.

TOUJEO (insulin glargine injection) U-300, for subcutaneous use
Initial U.S. Approval: 2015

----------INDICATIONS AND USAGE----------

TOUJEO is a long- acting human insulin analog indicated to improve glycemic control in adults with diabetes mellitus (1)

Limitations of Use:

Not recommended for treating diabetic ketoacidosis. (1)

----------DOSAGE AND ADMINISTRATION----------

- Individualize dose based on type of diabetes, metabolic needs, blood glucose monitoring results and glycemic control goal. (2.1, 2.2, 2.3)
- Administer subcutaneously once daily at any time during the day, at the same time every day. (2.1)
- Rotate injection sites to reduce the risk of lipodystrophy. (2.1)
- Do not dilute or mix with any other insulin or solution. (2.1)
- Closely monitor glucose when changing to TOUJEO and during initial weeks thereafter. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 300 units/mL insulin glargine in 1.5 mL SoloStar® disposable prefilled pen (3)

----------CONTRAINDICATIONS----------

- During episodes of hypoglycemia (4)
- Hypersensitivity to TOUJEO or one of its excipients (4)

----------WARNINGS AND PRECAUTIONS----------

- *Never share* a TOUJEO SoloStar® disposable prefilled pen between patients, even if the needle is changed (5.1)
- *Hyper- or hypoglycemia with changes in insulin regimen:* Carry out under close medical supervision. (5.2)
- *Hypoglycemia*: May be life-threatening. Increase frequency of glucose monitoring with changes to: insulin dosage, co-administered glucose lowering medications, meal pattern, physical activity; and in patients with renal impairment or hepatic impairment or hypoglycemia unawareness. (5.3, 6.1)
- *Medication Errors:* Accidental mix-ups between insulin products can occur. Instruct patients to check insulin labels before injection. (5.4)
- *Hypersensitivity reactions:* Severe, life-threatening, generalized allergy, including anaphylaxis, can occur. Discontinue TOUJEO, monitor and treat if indicated (5.5, 6.1)
- *Hypokalemia:* May be life-threatening. Monitor potassium levels in patients at risk of hypokalemia and treat if indicated (5.6).
- *Fluid retention and heart failure with concomitant use of Thiazolidinediones (TZDs)*: Observe for signs and symptoms of heart failure; consider dosage reduction or discontinuation if heart failure occurs (5.7)

----------ADVERSE REACTIONS----------

Adverse reactions commonly associated with TOUJEO (≥5%) are:

- Hypoglycemia, allergic reactions, injection site reaction, lipodystrophy, pruritus, rash, edema and weight gain. (6.1, 6.2)

To report SUSPECTED ADVERSE REACTIONS, contact sanofi-aventis at 1-800-633-1610 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

- *Drugs that affect glucose metabolism:* Adjustment of insulin dosage may be needed; closely monitor blood glucose. (7.1, 7.2, 7.3)
- *Anti-Adrenergic Drugs (e.g., beta-blockers, clonidine, guanethidine, and reserpine):* Signs and symptoms of hypoglycemia may be reduced or absent (7.3, 7.4)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Use during pregnancy only if the potential benefit justifies the potential risk to the fetus (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: February 2015

Insulins

Goal:

- Restrict certain insulin products to specified patients populations to ensure appropriate and safe use.

Length of Authorization:

Up to 12 months

Requires PA:

- Non-preferred insulins
- All pre-filled insulin pens, cartridges and syringes

Covered Alternatives:

Preferred alternatives listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is this an OHP covered diagnosis?	Yes: Go to #3	No: Pass to RPh. Deny; not funded by the OHP
3. Is the request for an Insulin Pen or Cartridge?	Yes: Go to #4	No: Go to #5
4. Is the insulin being administered by the patient or a non-professional caregiver AND any of the following criteria apply: • The patient has physical dexterity problems/vision impairment • The patient is unable to comprehend basic administration instructions • The patient has a history of dosing errors with use of vials • The patient is on 40 units or less of insulin per day • The patient is a child less than 18 years of age	Yes: Go to #5	No: Pass to RPh; deny for medical appropriateness

Approval Criteria		
5. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require a copay • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics (P&T) Committee	Yes: Inform prescriber of covered alternatives in class. Approve insulin pens/cartridges for up to 12 months (other preferred products do not require PA)	No: Approve for up to 12 months

P&T / DUR Review: *11/15 (AG); 9/10*
Implementation: *1/1/11*