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OHSU Drug Effectiveness Review Project Summary Report – Long-Acting Insulins

Date of Review: November 2018

Date of Last Review: September 2017
Literature Search: 08/17/18

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

Research Questions:
1. Is there any new comparative evidence for long-acting insulins based on surrogate efficacy outcomes (e.g., hemoglobin A1c [HbA1c]) or long-term clinically meaningful effectiveness outcomes (e.g., microvascular outcomes, macrovascular outcomes and mortality)?
2. Is there any new comparative evidence for long-acting insulins based on harms outcomes (e.g., severe hypoglycemia, nocturnal hypoglycemia)?
3. Are there subpopulations of patients which specific long-acting insulins may be more effective or associated with less harm?

Conclusions:
- A significant amount of evidence identified by the Drug Effectiveness Review Project (DERP) report was of low or insufficient quality, and therefore, not included per evidence inclusion criteria.[1]
- Overall evidence of moderate to high quality found no clinically significant differences between long-acting insulins for a majority of comparisons.

Clinical Efficacy
- Moderate to high quality evidence found no differences in HbA1c lowering between the long-acting insulin products.[1]

Harms
- Moderate quality evidence found no difference between insulin degludec and insulin glargine in major adverse cardiovascular events (rate ratio [RR] 0.92; 95% confidence interval [CI], 0.80 to 1.06; absolute risk reduction [ARR] not provided).[1]
- Based on moderate quality of evidence, nocturnal hypoglycemia risk was lower for insulin degludec compared to insulin glargine in patients with type 1 diabetes mellitus (T1DM), RR 0.68 (95% CI, 0.56 to 0.81).[1]
- The incidence of severe hypoglycemia events was lower with insulin degludec compared to insulin glargine in patients with type 2 diabetes mellitus (T2DM) (3.3% vs. 5.1%) and also for nocturnal hypoglycemia RR 0.84 (95% CI, 0.71 to 1.0; ARR not provided) (moderate quality of evidence).[1]

Recommendations:
- No changes to the preferred drug list (PDL) are recommended for the long-acting insulin based on review of efficacy and safety data provided by DERP.
- After evaluation of comparative drug costs in executive session, no PDL changes were recommended.

Summary of Prior Reviews and Current Policy

- Previous reviews have not identified clinically significant differences in efficacy or harms between the long-acting insulins. There is insufficient evidence on health outcomes (i.e., mortality) as well as cardiovascular comparisons to delineate preferred treatment options. The Oregon Health Plan (OHP) Fee-for-Service (FFS) policy includes the preferred long-acting insulins: detemir pens (requires prior authorization [PA]) and Lantus pens and vials are available without a PA (Basaglar pens and vials still require PA). A PA is required for non-preferred long-acting insulin pens and cartridges. For approval, the PA criteria requires that patients (or non-professional caregiver) have dexterity issues/vision impairment, comprehension difficulties, history of dosing errors, or is a child less than 18 years old. Policy was changed in September 2017 which removed maximum insulin utilization restrictions to allow access to concentrated insulin products if appropriate (PA dependent). There is 79% preferred drug utilization of insulin glargine followed by 8% utilization of the non-preferred insulin glargine formulation, Basaglar, which accounts for a majority of the class expenditures.

Methods:

The July 2018 drug class report 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 original report is available to Oregon Pharmacy and Therapeutics Committee members upon request. An executive summary report is publically available in the agenda packet and 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. DERP 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.

Summary Findings:

In July 2018 DERP reported on the evidence for use of long-acting insulins in adult and children with T1DM and T2DM.[1] Twelve new studies were added to the most recent update with seventy-one studies included overall. Studies ranged from 16 weeks to 2 years and 74% were graded as fair quality by DERP. Insulins included in the review are the following: three follow-on insulin glargine products (Semglee [not available in the United States], Lusduna Nexvue [tentatively approved by the FDA but not yet available], and Basaglar), insulin degludec (Tresiba), insulin degludec/insulin aspart (Ryzodeg 70/30), insulin glargine (Toujeo), insulin detemir (Levemir) and insulin glargine U100.[1] Placebo-controlled trials and pooled analyses combining selected studies without reproducible methods were excluded. Differences in concomitant antidiabetic therapy and/or dosing schedules of insulins resulted in the inability to pool results and/or produced evidence which lacked precision preventing strong conclusions for many of the analyses. Evidence on outcomes of moderate to high quality with applicable external validity to the Oregon Medicaid population are included in **Table 1**.

Table 1. Insulin Comparisons: Outcomes with Evidence of Moderate to High Quality[1]

Comparison	Outcome	Result	Strength of Evidence†
Type 1 DM			
Insulin degludec+ **Vs.**	HbA1c	Insulin degludec: 6.92% Insulin glargine: 6.78%	Moderate

Insulin glargine+		WMD 0.07% (95% CI, -0.05 to 0.19%) *No difference between treatments*	
	Nocturnal Hypoglycemia	RR 0.68 (95% CI, 0.56 to 0.81) ARRs not provided *Favored insulin degludec*	Moderate
Insulin glargine U300 **Vs.** **Insulin glargine U100**	Nocturnal hypoglycemia	RR 0.91 (95% CI, 0.80 to 1.05) ARRs not provided *No difference between treatments*	Moderate
Type 2 DM			
Once daily insulin degludec* **Vs.** **Once daily insulin glargine**	Percent of patients obtaining an HbA1c of ≤7%	RR 0.97 (95% CI, 0.91 to 1.03) ARRs not provided *No difference between treatments*	High
	Severe hypoglycemia episodes	Insulin degludec: 3.3% Insulin glargine: 5.1% RR 0.72 (95% 0.54 to 0.96) *Favored insulin degludec*	Moderate
	Nocturnal hypoglycemia episodes	RR 0.84 (95% CI, 0.71 to 1.0) ARRs not provided *Favored insulin degludec*	Moderate
	Major adverse cardiovascular events	RR 0.92 (95% CI, 0.80 to 1.06) ARRs not provided *No difference between treatments*	Moderate
FDCP Insulin Degludec/Aspart **Vs.** **Insulin glargine alone**	Patients with HbA1c <7%	Degludec/Aspart: 43% Glargine: 41% RR 1.04 (95% CI, 0.90 to 1.21) *No difference between treatments*	Moderate
Insulin glargine U300 **Vs.** **Insulin glargine U100**	Patients with HbA1c <7%	Insulin glargine U300: 35% Insulin glargine U100: 35% RR 1.0 (95% CI, 0.92 to 1.1) *No difference between treatments*	Moderate

	Nocturnal hypoglycemia	Insulin glargine U300: 37% Insulin glargine U100: 50% RR 0.74 (95% CI, 0.66 to 0.82) *Favored insulin glargine U300*	Moderate
Abbreviations: ARR – absolute risk reduction, CI – confidence interval, DM – diabetes mellitus, ETD – estimated treatment difference, FDCP – fixed dose combination product, HbA1c – hemoglobin A1c, RR – rate ratio; WMD – weighted mean difference **Key: † Evidence grades provided by DERP, * included fixed and flexible dosing, + in combination with bolus insulin aspart**			

Subgroup analysis

Severe hypoglycemia rates were lower in patients treated with insulin degludec, versus insulin glargine, in women who were not Hispanic or Latino, had history of cardiovascular (CV) disease, and were residing in the United States (US).

References

1. McDonagh M, Holmes R, Hsu F, et al. Long-acting insulins. Update 2 Final Report, prepared by the Pacific Northwest Evidence-based Practice Center for the Drug Effectiveness Review Project. Oregon Health and Science University, Portland, Oregon, July 2018.

Appendix 1: Current Preferred Drug List

Generic	Brand	FormDesc	PDL
insulin detemir	LEVEMIR FLEXTOUCH	INSULN PEN	Y
insulin glargine,hum.rec.anlog	LANTUS SOLOSTAR	INSULN PEN	Y
insulin glargine,hum.rec.anlog	LANTUS	VIAL	Y
insulin degludec	TRESIBA FLEXTOUCH U-100	INSULN PEN	N
insulin degludec	TRESIBA FLEXTOUCH U-200	INSULN PEN	N
insulin degludec/liraglutide	XULTOPHY 100-3.6	INSULN PEN	N
insulin detemir	LEVEMIR	VIAL	N
insulin glargine,hum.rec.anlog	BASAGLAR KWIKPEN U-100	INSULN PEN	N
insulin glargine,hum.rec.anlog	TOUJEO MAX SOLOSTAR	INSULN PEN	N
insulin glargine,hum.rec.anlog	TOUJEO SOLOSTAR	INSULN PEN	N
insulin glargine/lixisenatide	SOLIQUA 100-33	INSULN PEN	N

Appendix 2: Search History

Database(s): **Ovid MEDLINE(R)** 1946 to August Week 2 2018

Search Strategy:

#	Searches	Results
1	degludec.mp.	296
2	detemir.mp.	767
3	glargine.mp. or Insulin Glargine/	2151
4	1 or 2 or 3	2610
5	limit 4 to (english language and humans and yr="2017 -Current")	224
6	limit 5 to (clinical trial, phase iii or guideline or meta analysis or systematic reviews)	44

Appendix 3: Prior Authorization Criteria

Insulins

Goal:

- Restrict certain insulin products to specific patient populations to ensure appropriate use.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred insulin vials
- All pre-filled insulin pens, cartridges and syringes with the exception of insulin glargine (Lantus SoloSTAR®) or insulin aspart (Novolog Flexpen®)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is this an OHP-funded 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 #7
4. Is the request for either a short-acting or a long-acting insulin pen or cartridge?	**Yes:** Go to #5	**No:** Got to #6
5. Has the patient tried and failed or have contraindications to either: • Insulin aspart (Novolog®) if the request is for short-acting insulin OR • Insulin glargine (Lantus®) if the request is for long-acting insulin?	**Yes:** Go to #6	**No:** Pass to RPh: deny and recommend a trial of insulin glargine (Lantus Solostar®) or insulin aspart (Novolog Flexpen®)

Approval Criteria		
6. Will the insulin be administered by the patient or a non-professional caregiver **AND** do 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 a child less than 18 years of age?	**Yes:** Go to #7	**No:** Pass to RPh; deny for medical appropriateness
7. Will the provider consider a change to a preferred product? <u>Message:</u> • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee	**Yes:** Inform prescriber of covered alternatives	**No:** Approve for up to 12 months

P&T / DUR Review: *11/18 (KS), 9/17 (KS), 3/16; 11/15; 9/10*
Implementation: *11/1/17; 10/13/16; 1/1/11*