Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Update: Diabetes, Insulins

Date of Review: September 2019

Date of Last Review: November 2018
Dates of Literature Search: 06/01/2017 – 05/27/2019

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

Purpose for Class Update:
The purpose of this update is to review new evidence on the efficacy and safety of insulin products published since the last review.

Research Questions:
1. In patients with diabetes mellitus (DM), is there any new comparative evidence for insulin therapies based on surrogate efficacy outcomes (e.g., hemoglobin A1c [HbA1c]) and long-term clinically meaningful effectiveness outcomes (e.g., microvascular outcomes, macrovascular outcomes and mortality)?
2. In patients with DM, is there any new comparative evidence for non-insulin diabetes treatments based on harms outcomes (e.g., severe hypoglycemia, heart failure, diabetic ketoacidosis, etc.)?
3. Are there subpopulations of patients with DM for which specific therapies may be more effective or associated with less harm?

Conclusions:
- New high-quality evidence comes from three systematic reviews, five randomized controlled trials and one guideline. Four guidelines are available for clinical context. New evidence supports current policy of no clinically significant differences in glucose lowering between long-acting insulin products or between the short-acting insulin products.

Efficacy
- A high quality systematic review and meta-analysis found glucose lowering to be similar in patients with diabetes for insulin degludec, detemir and glargine, based on moderate to high strength of evidence.[1]
- World Health Organization (WHO) guidelines on second- and third-line therapies for non-pregnant adult patients with diabetes support current preferred drug list (PDL) recommendations for insulins.[2]
- Limited evidence suggests no difference in glucose lowering between glargine products in the elderly population, based on a study in patients 65 years and older which found glargine U100 to be noninferior to glargine U300 for the outcome of change in HbA1c from baseline at 26 weeks (least squares mean difference [LSMD] 0.02; 95% confidence interval [CI], -0.092 to 0.129).[3]

Author: Kathy Sentena, PharmD

Safety
- There is moderate quality evidence that there is no difference between adjudicated cardiovascular (CV) events in patients with type 2 diabetes mellitus (T2DM) at high risk of a cardiovascular (CV) events treated with insulin degludec compared to insulin glargine over 1.8 years (hazard ratio [HR] 0.91; 95% CI, 0.78 to 1.06; P<0.001 for noninferiority).[4]
- Moderate strength of evidence found less hypoglycemia in patients treated with insulin degludec compared to insulin glargine. The difference of nocturnal hypoglycemia was less in patients with type 1 diabetes mellitus (T1DM) (relative risk [RR] 0.68; 95% CI, 0.56 to 0.81; p<0.05) and T2DM (RR 0.71; 95% CI, 0.63 to 0.79; p<0.05).[1] Severe hypoglycemia was also less with insulin degludec compared to insulin glargine in patients with T2DM.[1]

New Formulations
- A new fast-acting insulin aspart (FIASP®) was approved based on noninferiority findings compared to insulin aspart. The major difference is that FIASP can be given up to 20 minutes after the meal has started.[5]
- A new fast-acting follow-on to insulin lispro, Admelog®, was approved based on noninferiority findings.[6]

Recommendations:
- No changes to the preferred drug list (PDL) are recommended based on the review of clinical efficacy.
- After evaluation of costs in executive session, designate insulin detemir vials, insulin glulisine pens and vials, insulin regular, human U-500 pens, insulin lispro protamine/lispro 75-25 and 50-50 pens as preferred. Remove prior authorization requirement for insulin glulisine, insulin regular, human U-500, and insulin lispro protamine/lispro pens.

Summary of Prior Reviews and Current Policy
- A 2018 Drug Effectiveness Review Project report of long-acting insulins found moderate to high quality evidence that there were no clinically significant differences between the insulins for a majority of comparisons.
- Moderate to high quality evidence found no differences in HbA1c lowering between the long-acting insulin products. The DERP review found a reduced risk of hypoglycemia with insulin degludec compared to insulin glargine in patients with T1DM and T2DM.
- A review of Basaglar® demonstrated noninferiority to insulin glargine.
- No policy changes were made after reviewing evidence for the long-acting insulins in 2018. A 2017 review of insulin products resulted in removal of the PA requirement for insulin glargine (Lantus®) pens and insulin aspart (Novolog®). The requirement that patients must use 40 units or less per day of insulin to be candidates for an insulin pen was also removed to allow patients who use large amounts of insulin access to concentrated insulin products.
- Current preferred products are insulin aspart (cartridge, pen, vial, 70-30 mix), insulin detemir pen, insulin glargine (pen, vial), insulin lispro (vial, 50-50 mix, 75-25 mix), NPH (vial), regular insulin (vial) and NPH/R insulin (vial and pen) (**Appendix 1**).
- Short and long-acting insulins account for a substantial number of claims and costs to the OHP system. Approximately 86% of insulin utilization is for preferred products.

Background:
More than 29 million people in the United States are thought to be living with diabetes.[7] In Oregon, it is estimated that 287,000 adults have diabetes, in which 38,000 are thought to be OHP members. There are over 7,000 patients in the Oregon Medicaid fee-for-service population alone that have T2DM and almost 1,000 have T1DM.[8] Caring for patients with diabetes enrolled in OHP accounted for $106 million in direct medical claims for diabetes and diabetes-related complications in 2012. The overall cost to the state is estimated at $3 billion a year.[8]

Insulin is used to mimic endogenous insulin release in patients with T1DM and is often necessary to obtain glucose targets in patients with T2DM. Adjustments in insulin doses are made to obtain target fasting and prandial glucose levels while minimizing the risk of hypoglycemia. Insulins are categorized by onset and duration of action. Most T1DM patients use multiple daily injections of basal and prandial insulins. Patients with T2DM who require insulin therapy are usually initiated on a basal insulin product. Basal insulins include NPH and recombinant analog formulations glargine, detemir, and degludec. Prandial insulins include formulations of regular insulin, and recombinant analogs lispro, aspart and glulisine. Evidence suggests no clinical differences in A1C lowering between the different basal insulins products in patients with T1DM or T2DM.[9] Hemoglobin A1C lowering has been shown to be similar between the different prandial insulins. Common insulin adverse reactions are hypoglycemia, injection site reactions, and weight gain. Basal insulin analogs and rapid-acting insulin analogs may have a reduced risk of hypoglycemia.[10] However, recent retrospective observational data from 25,489 patients found no clinically or statistically significant differences in hypoglycemia-related emergency department visits or hospital admissions between basal insulin analogs and NPH insulin (between group difference of 3.1 events per 1000 person-years (95% CI, -1.5 to 7.7; p=0.07).[11]

Clinically meaningful outcomes in patients with diabetes include microvascular (i.e., retinopathy, nephropathy, neuropathy) and macrovascular complications (i.e., stroke, myocardial infarction), mortality, and severe hypoglycemia. Because hyperglycemia is associated with increased microvascular complications and possibly macrovascular outcomes, A1C changes are often used as a surrogate marker to assess comparative efficacy of different antidiabetic therapies.[12] The Diabetes Control and Complication Trial (DCCT), which was a large prospective trial in patients with T1DM, provided evidence that intensive insulin therapy led to improved glucose control and reductions in microvascular outcomes.[13] A study in T2DM patients reiterated the DCCT findings, that maintenance of glucose lowering targets minimized microvascular complications in this population.[14] Due to the increased risk of CV disease in patients with diabetes, the effect of insulin on CV outcomes is of high importance. Evidence has shown that intensive glucose control produced a trend towards less risk of CV events in patients with T1DM.[13] In patients with T2DM intensive glucose control reduced CV outcomes based on the United Kingdom Prospective Diabetes Study (UKPDS) study; however, this was not shown in subsequent studies (Action to Control Cardiovascular Risk in Diabetes [ACCORD], The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation [ADVANCE] and Veterans Affairs Diabetes Trial [VADT]).[12] There is a paucity of evidence on the risk or benefit of insulin use on CV outcomes in patients with diabetes from randomized controlled trials (RCTs) specifically designed to assess CV events. One study compared insulin glargine to standard of care and n-3 fatty acids or placebo in patients with CV risk factors plus impaired fasting glucose, impaired glucose tolerance, or T2DM. The study found similar rates of CV outcomes (nonfatal MI, nonfatal stroke, or death from CV causes) in both groups: 2.94 and 2.85 per 100 person-years in patients with a median follow-up of 6.2 years (HR 1.02; 95% CI, 0.94 to 1.11).[15] Cardiovascular effects were also similar between insulin degludec and insulin glargine in patients with T2DM at high risk for CV events, 8.5% versus 9.3% (HR 0.91; 95% CI, 0.78 to 1.06; P<0.001 for noninferiority).[4]

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

Cochrane – Short-acting Insulin Analogues versus Regular Human Insulin
In 2018, Cochrane evaluated the short-acting insulins (insulin lispro, insulin aspart, insulin glulisine, or biosimilars) compared to regular insulin in adult, non-pregnant persons with T2DM.[16] Ten trials (n=2751) were included that were at least 24 weeks long (mean 41 weeks). All trials were open-label and five were non-inferiority trials. Patients were a mean age of 57 years, the average duration of diabetes was 13 years, baseline HbA1c was 8.1% and 45% were female.[16]

Mortality was described in 6 trials. Moderate quality evidence found no difference in deaths between regular insulin and insulin analogs, 0.2% and 0.4% (odds ratio [OR] 1.66; 95% CI, 0.41 to 6.64; P=0.48).[16] The mean difference in A1c was -0.3% lower with insulin analogs (95% CI, -0.15 to 0.09; p=0.43), which was not clinically or statistically significant.[16] The number of severe hypoglycemic events was low and similar between regular insulin and insulin analogs; however, evidence was limited. Evidence for all other outcomes were found to be of very low or low quality.

Limitations to the evidence include a high risk of detection and performance bias, due to the studies being an open-label design. Overall, there was no substantial difference between regular insulin and insulin analogs.

Cochrane – Treatments for Women with Gestational Diabetes Mellitus
A 2018 Cochrane systematic review and meta-analysis analyzed the efficacy and safety of therapies for women with gestational diabetes.[17] The review only included previous Cochrane Systematic Reviews and excluded women with pre-existing diabetes. Fourteen reviews were included, 10 of which were considered high-quality and had at low risk of bias.[17] Oral antidiabetic therapies included: glibenclamide (glyburide), metformin and acarbose. Included insulin therapies were insulin lispro, regular insulin and NPH insulin. Absolute risk reduction was not reported.

Moderate quality evidence found lifestyle interventions effectively reduced the infant outcome, large-for-gestational age, compared to usual care (RR 0.60; 95% CI, 0.50 to 0.71); however, lifestyle intervention versus usual care also increased the risk of induction of labor (RR 1.20; 95% CI, 0.99 to 1.46; moderate quality evidence).[17] Exercise versus control (no exercise) had no impact on assisting women in returning to their pre-pregnancy weight. The use of insulin versus oral therapy was found to possibly increase the risk of induction of labor (RR 1.3; 95% CI, 0.96 to 1.75) based on moderate quality of evidence.[17] Additionally, moderate quality of evidence found the use of insulin in pregnant women possibly increases the risk of hypertensive disorders in pregnancy (RR 1.89; 95% CI, 1.14 to 3.12).[17] The authors concluded that even though there is possible increase risk of induction of labor and hypertensive disorders, the overall body of evidence is insufficient to provide strong conclusions. Evidence was inconclusive for other outcomes (e.g., childhood adiposity, caesarean section, pre-eclampsia, perinatal mortality).

Holmes, et al – Comparative Effectiveness and Harms of Long-acting Insulins for Type 1 and Type 2 Diabetes
A good quality meta-analysis compared the efficacy and harms of long-acting insulins.[1] The review was commissioned by the Drug Effectiveness Review Project (DERP) and was conducted in accordance with the high-quality methodology utilized for the DERP reviews. The following interventions were included in the review: follow-on insulin glargine (Semglee), follow-on insulin glargine (Lusduna [approved but not available due to pending lawsuit] Nexvue [not available]), follow-on insulin glargine (U100) (Basaglar and Abasaglar), insulin degludec (U100 & U200) (Tresiba), insulin degludec/insulin aspart (Ryzodeg 70/30), insulin glargine U300 (Toujeo), insulin detemir (Levemir), and insulin glargine U100 (Lantus). Seventy studies, lasting 16 weeks to 2 years, met the criteria for inclusion;

76% of fair quality, 12% good quality and 12% poor quality.[1] Outcomes of interest were: HbA1c, hypoglycemia (severe, nocturnal), withdrawals due to adverse events, cancer and cardiovascular events.

For a majority of comparisons there was low or insufficient evidence (**Table 1**).[1] Comparisons with moderate to high strength of evidence for selected outcomes are presented in **Table 2**. No statistical or clinical differences were found between insulin degludec, detemir, and glargine for the outcome of glucose lowering. Less hypoglycemia was found with insulin degludec compared to insulin glargine in patients with T1DM and T2DM. Patients taking insulin detemir experienced less weight gain (difference of approximately 1 kg) than patients taking insulin degludec or glargine; however, differences are unlikely to be clinically significant.

Table 1. Long-acting Insulin Comparisons with Low or Insufficient Evidence for All Outcomes Studied[1]

Insulin degludec/insulin aspart 70/30 vs. insulin detemir/insulin aspart	Insulin degludec/insulin aspart vs. insulin detemir/insulin aspart
Insulin degludec U200 vs. insulin degludec 100	Insulin degludec/insulin aspart 70/30 vs. insulin degludec/insulin aspart
Basaglar vs. insulin glargine	Insulin glargine pen vs. insulin glargine vial

Table 2. Long-acting Insulin Comparisons with Moderate to High Strength of Evidence[1]

Comparison	Outcome	Results*	Strength of Evidence
Adults with T1DM			
Insulin degludec + insulin aspart vs. Insulin glargine + insulin aspart	HbA1c	MD 0.07% (95% CI, -0.05 to 0.19) (4 RCTs; p>0.05) *No difference between treatments*	Moderate
	Nocturnal hypoglycemia	RR 0.68 (95% CI, 0.56 to 0.81; p<0.05) (4 RCTs) *Less nocturnal hypoglycemia with degludec compared to glargine*	Moderate
Insulin glargine U300 vs. insulin glargine U100	Nocturnal hypoglycemia	RR 0.91 (95% CI, 0.80 to 1.05; p<0.05) (RCTs 4) *No difference between treatments*	Moderate
Adults with T2DM			
Insulin degludec + insulin aspart vs. Insulin glargine + insulin aspart	Patients achieving an HbA1c <7%	RR 0.97 (95% CI, 0.91 to 1.03; p>0.05) (7 RCTs) *No difference between treatments*	High
	Severe hypoglycemia	RR 0.72 (95% CI, 0.54 to 0.96; p<0.05) (9 RCTs) *Less severe hypoglycemia with degludec compared to glargine*	Moderate
	Nocturnal hypoglycemia	RR 0.71 (95% CI, 0.63 to 0.79; p<0.05) (10 RCTs)	Moderate

		Less nocturnal hypoglycemia with degludec compared to glargine	
	Major CV events	RR 0.92 (95% CI, 0.80 to 1.06; p>0.05) (4 RCTs) *No difference in CV events*	Moderate
Insulin degludec/insulin aspart 70/30 vs. insulin glargine (U100)	Patients achieving an HbA1c <7%	Insulin degludec/aspart: 43% Insulin glargine: 41% RR 1.04 (95% CI, 0.90 to 1.21; p>0.05) (2 RCTs) *No difference between treatments*	Moderate
Insulin detemir vs. insulin glargine	Withdrawals due to adverse events	RR 2.1 (95% CI, 1.4 to 3.3; p>0.05) (4 RCTs) *More withdrawals due to adverse events with detemir compared to glargine*	Moderate
Insulin glargine U300 vs. insulin glargine U100	Patients achieving an HbA1c <7%	Insulin glargine U300: 35% Insulin glargine U100: 35% RR 1.0 (95% CI, 0.92 to 1.1; p>0.05) (4 RCTs) *No difference between treatments*	Moderate
	Nocturnal hypoglycemia	Insulin glargine U300: 37% Insulin glargine U100: 50% RR 0.78 (95% CI, 0.59 to 1.03; p>0.05) (3 RCTs) *No difference between treatments*	Moderate

Key: * Absolute risk reductions included if reported

Abbreviations: CI = confidence interval; CV = cardiovascular events; HbA1c = hemoglobin A1c; MD = mean difference; RCT = randomized controlled trial; RR = rate ratio; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus

After review, seven systematic reviews were excluded due to poor quality (e.g, indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:

World Health Organizations – Guidelines on Second-and Third-line Diabetic Medicines and Type of Insulins

A 2018 WHO publication provided recommendations on the management of non-pregnant patients with diabetes.[2] The focus of the guideline is to provide recommendations for primary care providers in low resource settings. The guideline methodology was evaluated and found to be of high quality. This review will focus on recommendations for the use of insulin and will not cover oral therapies. Treatment recommendations are presented in **Table 3**.[2] The recommendation for human insulin is based on the lack of high quality evidence demonstrating that insulin analogues are more effective compared to human insulin. The

recommendation for long-acting insulin analogues is considered weak because there is insufficient high-quality comparative evidence for diabetes complications and mortality demonstrating superior efficacy of the long-acting insulin analogues over intermediate-acting human insulin.

Table 3. WHO Recommendations for Insulin Use as a second- or third-line Treatment in Patients with Diabetes[2]

Recommendation	Strength of Recommendation and Quality of Evidence
• Introduce human insulin treatment to patients with T2DM who do not achieve glycemic goals with metformin and/or sulfonylurea	Strong recommendation; very low quality evidence
• Use human insulin (regular or NPH insulin) in adult patients with T1DM or T2DM who require insulin to manage glucose levels	Strong recommendation; very low quality evidence
• Consider using long-acting insulin analogues in adults with T1DM or T2DM who experience frequent severe hypoglycemia with human insulin	Weak recommendation; low or very low quality evidence
Abbreviations: NPH = neutral protamine Hagedorn; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus	

Additional Guidelines for Clinical Context:

The American Diabetes Association (ADA) published their annual Standards of Medical Care in Diabetes for 2019 in January.[18] Due to lack of details on guideline methodology and a significant portion of the professional practice committee members having conflicts of interest with industry, the standards will not be reviewed in detail or relied upon for policy making decisions.

A second guidance on the cardiovascular management of non-pregnant adults with diabetes was published by the ADA in April of 2018.[19] However, details are not included due to the same limitations cited above for the Standards of Medical Care in Diabetes.

The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) published a T2DM management algorithm in 2018.[10] Similar to the ADA recommendations, this management algorithm was authored by a majority of authors with industry affiliations and the methods for guideline development were not disclosed. Due to these limitations, the algorithm will not be presented.

The International Diabetes Federation (IDF) published clinical practice recommendations for managing type 2 diabetes in primary care.[20] Recommendations were based on worldwide diabetes treatment guidelines. Guidelines were graded by the Agree II instrument with scores ranging from 36-97%, indicating that low to high quality sources were considered in making recommendations. Therefore, the IDF recommendations will not be included in detail.

New Formulations or Indications:
FIASP – a new formulation of insulin aspart (FIASP®) was approved in 2017, indicated to improve glucose control in adults with diabetes.[5] The new formulation has a faster onset of action compared to insulin aspart, allowing for dosing at meal time or within 20 minutes of starting the meal. Trials found FIASP to be non-inferior to insulin aspart in patients with T1DM and T2DM.[5]

Admelog – A new fast-acting follow-on to insulin lispro was approved in 2017. Admelog® is approved for use in adults and pediatric patients 3 years and older with T1DM and T2DM to improve glycemic control. In clinical trials, Admelog® was found to be noninferior to insulin lispro.[6]

Label Changes:
Xultophy – the combination product, insulin degludec and liraglutide (Xultophy®), had the label updated in February 2019 to remove the requirement for previous therapy with either insulin or liraglutide.[21] Previous indications required a failure to one of these treatments.

Soliqua – removal of the requirement to fail monotherapy with insulin or lixisenatide before using the combination product, insulin glargine and lixisenatide (Soliqua™), was changed in the prescribing information in February of 2019.[22]

New FDA Safety Alerts:

Table 4. Description of new FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Insulin human[23]	Afrezza	4/2018	Warnings and precautions	Lung cancer (2 cases in 2,750 patient-years of exposure) and 2 additional cases after clinical trial completion
Insulin degludec and liraglutide[21]	Xultophy	2/2019	Warnings and precautions	An increased incidence of acute events of the gallbladder was found in a recent trial, 3.1% for liraglutide and 1.9% for placebo

Randomized Controlled Trials:
A total of 226 citations were manually reviewed from the initial literature search. After further review, 221 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining five trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 5. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Klonoff, et al[24] DB, NI, TTT, RCT, Phase 3	Fast-acting insulin aspart (FA) CSQI Vs. Insulin aspart (A) CSQI 16 weeks	Patients with T1DM treated with CSQI (n=417)	Change from baseline HbA1c at 16 weeks	FA: -0.1% A: -0.1% ETD 0.09% (95% CI, 0.01 to 0.17; P<0.001) *Fast-acting aspart was non-inferior to aspart*
Marso, et al[4]	Insulin degludec once daily Vs. Insulin glargine U100 once daily	Patients with T2DM and at high risk of cardiovascular events	Time to adjudicated major CV event (death	D: 325 (8.5%) G: 356 (9.3%) HR 0.91 (95% CI, 0.78 to 1.06; P<0.001 for noninferiority)

			from CV causes, nonfatal MI, or nonfatal stroke)	*Insulin degludec was noninferior to insulin glargine for the risk of CV events*
DB, TTT, ED, RCT	1.8 years	(n=7637)		
Ritzel, et al[3] MC, OL, RCT, Phase 3b	Insulin glargine 300 u/mL (G300) Vs. Insulin glargine 100 u/mL (G100) 26 weeks	Patients 65 years and older (mean age 71 years) with T2DM (n=1014)	Change in baseline HbA1c at week 26	G300: -0.89% G100: -0.91% LSMD 0.02 (95% CI, -0.092 to 0.129) *Insulin glargine 300u/mL was non-inferior to insulin glargine 100 u/mL*
Rosenstock, et al[25] MC, OL, AC, PG, NI	Insulin glargine 300 u/mL (G300) Vs. Insulin degludec 100 u/mL (D100) 24 weeks	Insulin-naïve adult patients with uncontrolled T2DM (HbA1c of ≥7.5% or up to 10.5% on oral medication) (n=929)	Change in baseline HbA1c at 24 weeks	G300: -1.7% D100: -1.6% LSMD -0.5 (95% CI, -0.15 to 0.05; P<0.0001 for noninferiority) *Insulin glargine 300 u/mL was non-inferior to insulin degludec 100 u/mL*
Wysham, et al[26] (SWITCH-2) DB, MC, TTT, RCT, CO, Phase 3a	Insulin degludec (D) Vs. Insulin glargine (G) 16 week titration period and 16 week maintenance period	Adult patients with T2DM and at least 1 hypoglycemia risk factor and prior history of basal insulin use (with or without oral antidiabetic agents) (n=721)	Rate of overall symptomatic hypoglycemia rates[+] during maintenance period	D: 185.6/100 patient years G: 265.4/100 patient years RR 0.70 (95% CI, 0.61 to 0.80: P<0.001)

Key: * In combination with insulin degludec, + severe or blood glucose confirmed <56 mg/dL

Abbreviations: AC = active-controlled; CO = cross over; CSQI = continuous subcutaneous infusion; CV = cardiovascular; DB = double-blind; ED = event-driven; ETD = estimated treatment difference; HbA1c = hemoglobin A1c; LSMD = least square mean difference; MC = multi-center; MI = myocardial infarction; NI = non-inferiority; OL = open-label; PG = parallel group; RCT = randomized clinical trial; RR = rate-ratio; TTT = treat to target; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; u=units

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL
insulin aspart	NOVOLOG	CARTRIDGE	SQ	Y
insulin aspart	NOVOLOG FLEXPEN	INSULN PEN	SQ	Y
insulin aspart	NOVOLOG	VIAL	SQ	Y
insulin aspart prot/insuln asp	NOVOLOG MIX 70-30 FLEXPEN	INSULN PEN	SQ	Y
insulin aspart prot/insuln asp	NOVOLOG MIX 70-30	VIAL	SQ	Y
insulin detemir	LEVEMIR FLEXTOUCH	INSULN PEN	SQ	Y
insulin glargine,hum.rec.anlog	LANTUS SOLOSTAR	INSULN PEN	SQ	Y
insulin glargine,hum.rec.anlog	LANTUS	VIAL	SQ	Y
insulin lispro	HUMALOG	VIAL	SQ	Y
insulin lispro	INSULIN LISPRO	VIAL	SQ	Y
insulin lispro protamin/lispro	HUMALOG MIX 50-50	VIAL	SQ	Y
insulin lispro protamin/lispro	HUMALOG MIX 75-25	VIAL	SQ	Y
insulin NPH hum/reg insulin hm	HUMULIN 70/30 KWIKPEN	INSULN PEN	SQ	Y
insulin NPH hum/reg insulin hm	NOVOLIN 70-30 FLEXPEN	INSULN PEN	SQ	Y
insulin NPH hum/reg insulin hm	HUMULIN 70-30	VIAL	SQ	Y
insulin NPH hum/reg insulin hm	NOVOLIN 70-30	VIAL	SQ	Y
insulin NPH human isophane	HUMULIN N	VIAL	SQ	Y
insulin NPH human isophane	NOVOLIN N	VIAL	SQ	Y
insulin regular, human	HUMULIN R	VIAL	IJ	Y
insulin regular, human	NOVOLIN R	VIAL	IJ	Y
insulin regular, human	HUMULIN R U-500	VIAL	SQ	Y
insulin aspart (niacinamide)	FIASP FLEXTOUCH	INSULN PEN	SQ	N
insulin aspart (niacinamide)	FIASP	VIAL	SQ	N
insulin degludec	TRESIBA FLEXTOUCH U-100	INSULN PEN	SQ	N
insulin degludec	TRESIBA FLEXTOUCH U-200	INSULN PEN	SQ	N
insulin degludec	TRESIBA	VIAL	SQ	N
insulin degludec/liraglutide	XULTOPHY 100-3.6	INSULN PEN	SQ	N
insulin detemir	LEVEMIR	VIAL	SQ	N
insulin glargine,hum.rec.anlog	BASAGLAR KWIKPEN U-100	INSULN PEN	SQ	N
insulin glargine,hum.rec.anlog	TOUJEO MAX SOLOSTAR	INSULN PEN	SQ	N
insulin glargine,hum.rec.anlog	TOUJEO SOLOSTAR	INSULN PEN	SQ	N
insulin glargine/lixisenatide	SOLIQUA 100-33	INSULN PEN	SQ	N
insulin glulisine	APIDRA SOLOSTAR	INSULN PEN	SQ	N
insulin glulisine	APIDRA	VIAL	SQ	N
insulin lispro	HUMALOG	CARTRIDGE	SQ	N
insulin lispro	HUMALOG JUNIOR KWIKPEN	INS PEN HF	SQ	N
insulin lispro	ADMELOG SOLOSTAR	INSULN PEN	SQ	N

insulin lispro	HUMALOG KWIKPEN U-100	INSULN PEN	SQ	N
insulin lispro	HUMALOG KWIKPEN U-200	INSULN PEN	SQ	N
insulin lispro	INSULIN LISPRO KWIKPEN U-100	INSULN PEN	SQ	N
insulin lispro	ADMELOG	VIAL	SQ	N
insulin lispro protamin/lispro	HUMALOG MIX 50-50 KWIKPEN	INSULN PEN	SQ	N
insulin lispro protamin/lispro	HUMALOG MIX 75-25 KWIKPEN	INSULN PEN	SQ	N
insulin NPH human isophane	HUMULIN N KWIKPEN	INSULN PEN	SQ	N
insulin regular, human	AFREZZA	CART INHAL	IH	N
insulin regular, human	HUMULIN R U-500 KWIKPEN	INSULN PEN	SQ	N

Appendix 2: Abstracts of Comparative Clinical Trials

A randomized, multicentre trial evaluating the efficacy and safety of fast-acting insulin aspart in continuous subcutaneous insulin infusion in adults with type 1 diabetes (onset 5).

Klonoff DC, Evans ML, Lane W, Kempe HP, Renard E, DeVries JH, Graungaard T, Hyseni A, Gondolf T, Battelino T

AIM: To evaluate the efficacy and safety of fast-acting insulin aspart (faster aspart) vs insulin aspart (IAsp) used in continuous subcutaneous insulin infusion (CSII) in participants with type 1 diabetes (T1D).

MATERIALS AND METHODS: This was a double-blind, treat-to-target, randomized, 16-week trial investigating CSII treatment with faster aspart (n = 236) or IAsp (n = 236). All available information, regardless of treatment discontinuation, was used for the evaluation of effect.

RESULTS: Faster aspart was non-inferior to IAsp regarding the change from baseline in glycated haemoglobin (HbA1c; primary endpoint). The mean HbA1c changed from 58.4 mmol/mol (7.5%) at baseline to 57.8 mmol/mol (7.4%) with faster aspart and to 56.8 mmol/mol (7.4%) with IAsp after 16 weeks' treatment, with an estimated treatment difference (ETD) of 1.0 mmol/mol (95% confidence interval [CI] 0.14; 1.87) or 0.09% (95% CI 0.01; 0.17; P < 0.001) for non-inferiority (0.4% margin; P < 0.02 for statistical significance in favour of IAsp). Faster aspart was superior to IAsp in change from baseline in 1-hour postprandial glucose (PPG) increment after a meal test (ETD -0.91 mmol/L [95% CI -1.43; -0.39] or -16.4 mg/dL [95% CI -25.7; -7.0]; P = 0.001), with statistically significant reductions also at 30 minutes and 2 hours. The improvement in PPG was reflected in the change from baseline in 1-hour interstitial glucose increment after all meals (ETD -0.21 mmol/L [95% CI -0.31; -0.11] or -3.77 mg/dL [95% CI -5.53; -2.01]). There was no statistically significant difference in the overall rate of severe or blood glucose-confirmed hypoglycaemia (estimated rate ratio 1.00 [95% CI 0.85; 1.16]). A numerical imbalance in severe hypoglycaemic episodes between faster aspart and IAsp was seen in the treatment (21 vs 7) and 4-week run-in periods (4 vs 0).

CONCLUSIONS: Faster aspart provides an effective and safe option for CSII treatment in T1D.

Efficacy and Safety of Degludec versus Glargine in Type 2 Diabetes.

Marso SP, McGuire DK, Zinman B, Poulter NR, Emerson SS, Pieber TR, Pratley RE, Haahr PM, Lange M, Brown-Frandsen K, Moses A, Skibsted S, Kvist K, Buse JB

BACKGROUND: Degludec is an ultralong-acting, once-daily basal insulin that is approved for use in adults, adolescents, and children with diabetes. Previous open-label studies have shown lower day-to-day variability in the glucose-lowering effect and lower rates of hypoglycemia among patients who received degludec than among those who received basal insulin glargine. However, data are lacking on the cardiovascular safety of degludec.

METHODS: We randomly assigned 7637 patients with type 2 diabetes to receive either insulin degludec (3818 patients) or insulin glargine U100 (3819 patients) once daily between dinner and bedtime in a double-blind, treat-to-target, event-driven cardiovascular outcomes trial. The primary composite outcome in the

time-to-event analysis was the first occurrence of an adjudicated major cardiovascular event (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) with a prespecified noninferiority margin of 1.3. Adjudicated severe hypoglycemia, as defined by the American Diabetes Association, was the prespecified, multiplicity-adjusted secondary outcome.

RESULTS: Of the patients who underwent randomization, 6509 (85.2%) had established cardiovascular disease, chronic kidney disease, or both. At baseline, the mean age was 65.0 years, the mean duration of diabetes was 16.4 years, and the mean (±SD) glycated hemoglobin level was 8.4±1.7%; 83.9% of the patients were receiving insulin. The primary outcome occurred in 325 patients (8.5%) in the degludec group and in 356 (9.3%) in the glargine group (hazard ratio, 0.91; 95% confidence interval, 0.78 to 1.06; P<0.001 for noninferiority). At 24 months, the mean glycated hemoglobin level was 7.5±1.2% in each group, whereas the mean fasting plasma glucose level was significantly lower in the degludec group than in the glargine group (128±56 vs. 136±57 mg per deciliter, P<0.001). Prespecified adjudicated severe hypoglycemia occurred in 187 patients (4.9%) in the degludec group and in 252 (6.6%) in the glargine group, for an absolute difference of 1.7 percentage points (rate ratio, 0.60; P<0.001 for superiority; odds ratio, 0.73; P<0.001 for superiority). Rates of adverse events did not differ between the two groups.

CONCLUSIONS: Among patients with type 2 diabetes at high risk for cardiovascular events, degludec was noninferior to glargine with respect to the incidence of major cardiovascular events. (Funded by Novo Nordisk and others; DEVOTE ClinicalTrials.gov number, NCT01959529 .).

A Randomized Controlled Trial Comparing Efficacy and Safety of Insulin Glargine 300 Units/mL Versus 100 Units/mL in Older People With Type 2 Diabetes: Results From the SENIOR Study.

Ritzel R, Harris SB, Baron H, Florez H, Roussel R, Espinasse M, Muehlen-Bartmer I, Zhang N, Bertolini M, Brulle-Wohlhueter C, Munshi M, Bolli GB

OBJECTIVE: SENIOR compared the efficacy and safety of insulin glargine 300 units/mL (Gla-300) with glargine 100 units/mL (Gla-100) in older people (≥65 years old) with type 2 diabetes.

RESEARCH DESIGN AND METHODS: SENIOR was an open-label, two-arm, parallel-group, multicenter phase 3b trial designed to enroll ~20% of participants aged ≥75 years. Participants were randomized 1:1 to Gla-300 or Gla-100, titrated to a fasting self-monitored plasma glucose of 5.0-7.2 mmol/L (90-130 mg/dL).

RESULTS: In total, 1,014 participants were randomized (mean age: 71 years). Comparable reductions in HbA$_{1c}$ were observed from baseline to week 26 for Gla-300 (-0.89%) and Gla-100 (-0.91%) in the overall population (least squares mean difference: 0.02% [95% CI -0.092 to 0.129]) and for participants aged ≥75 years (-0.11% [-0.330 to 0.106]). Incidence and rates of confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycemia events were low and similar between both treatment groups, with lower rates of documented symptomatic hypoglycemia with Gla-300. The lower risk of hypoglycemia with Gla-300 versus Gla-100 was more apparent in the subgroup aged ≥75 years versus the overall population. Significantly lower annualized rates of documented symptomatic (≤3.9 mmol/L [≤70 mg/dL]) hypoglycemia were observed (Gla-300: 1.12; Gla-100: 2.71; rate ratio: 0.45 [95% CI 0.25-0.83]).

CONCLUSIONS: Efficacy and safety of Gla-300 was demonstrated in older people (≥65 years of age) with type 2 diabetes, with comparable reductions in HbA$_{1c}$ and similarly low or lower risk of documented symptomatic hypoglycemia versus Gla-100. A significant benefit in hypoglycemia reduction was seen in participants aged ≥75 years.

More Similarities Than Differences Testing Insulin Glargine 300 Units/mL Versus Insulin Degludec 100 Units/mL in Insulin-Naive Type 2 Diabetes: The Randomized Head-to-Head BRIGHT Trial.

Rosenstock J, Cheng A, Ritzel R, Bosnyak Z, Devisme C, Cali AMG, Sieber J, Stella P, Wang X, Frías JP, Roussel R, Bolli GB

OBJECTIVE: To compare insulin glargine 300 units/mL (Gla-300) versus insulin degludec 100 units/mL (IDeg-100) in this first head-to-head randomized controlled trial.

RESEARCH DESIGN AND METHODS: BRIGHT (NCT02738151) was a multicenter, open-label, active-controlled, two-arm, parallel-group, 24-week, noninferiority study in insulin-naive patients with uncontrolled type 2 diabetes. Participants were randomized 1:1 to evening dosing with Gla-300 (N = 466) or IDeg-100 (N = 463), titrated to fasting self-monitored plasma glucose of 80-100 mg/dL. The primary end point was HbA$_{1c}$ change from baseline to week 24. Safety end points included incidence and event rates of hypoglycemia.

RESULTS: At week 24, HbA$_{1c}$ improved similarly from baseline values of 8.7% (72 mmol/mol) in the Gla-300 group and 8.6% (70 mmol/mol) in the IDeg-100 group to 7.0% (53 mmol/mol)-least squares mean difference -0.05% (95% CI -0.15 to 0.05) (-0.6 mmol/mol [-1.7 to 0.6])-demonstrating noninferiority of Gla-300 versus IDeg-100 (P < 0.0001). Hypoglycemia incidence and event rates over 24 weeks were comparable with both insulins, whereas during the active titration period (0-12 weeks) the incidence and rate of anytime (24-h) confirmed hypoglycemia (≤70 and <54 mg/dL) were lower with Gla-300. Both insulins were properly titrated and exhibited no specific safety concerns.

CONCLUSIONS: Gla-300 and IDeg-100 provided similar glycemic control improvements with relatively low hypoglycemia risk. Hypoglycemia incidence and rates were comparable with both insulins during the full study period but lower in favor of Gla-300 during the titration period. The choice between these longer-acting basal insulins may be determined by factors such as access and cost, alongside clinical considerations.

Effect of Insulin Degludec vs Insulin Glargine U100 on Hypoglycemia in Patients With Type 2 Diabetes: The SWITCH 2 Randomized Clinical Trial.

Wysham C, Bhargava A, Chaykin L, de la Rosa R, Handelsman Y, Troelsen LN, Kvist K, Norwood P

IMPORTANCE: Hypoglycemia, a serious risk for insulin-treated patients with type 2 diabetes, negatively affects glycemic control.

OBJECTIVE: To test whether treatment with basal insulin degludec is associated with a lower rate of hypoglycemia compared with insulin glargine U100 in patients with type 2 diabetes.

DESIGN, SETTING, AND PARTICIPANTS: Randomized, double-blind, treat-to-target crossover trial including two 32-week treatment periods, each with a 16-week titration period and a 16-week maintenance period. The trial was conducted at 152 US centers between January 2014 and December 2015 in 721 adults with type 2 diabetes and at least 1 hypoglycemia risk factor who were previously treated with basal insulin with or without oral antidiabetic drugs.

INTERVENTIONS: Patients were randomized 1:1 to receive once-daily insulin degludec followed by insulin glargine U100 (n = 361) or to receive insulin glargine U100 followed by insulin degludec (n = 360) and randomized 1:1 to morning or evening dosing within each treatment sequence.

MAIN OUTCOMES AND MEASURES: The primary end point was the rate of overall symptomatic hypoglycemic episodes (severe or blood glucose confirmed [<56 mg/dL]) during the maintenance period. Secondary end points were the rate of nocturnal symptomatic hypoglycemic episodes (severe or blood glucose confirmed, occurring between 12:01 am and 5:59 am) and the proportion of patients with severe hypoglycemia during the maintenance period.

RESULTS: Of the 721 patients randomized (mean [SD] age, 61.4 [10.5] years; 53.1% male), 580 (80.4%) completed the trial. During the maintenance period, the rates of overall symptomatic hypoglycemia for insulin degludec vs insulin glargine U100 were 185.6 vs 265.4 episodes per 100 patient-years of exposure (PYE) (rate ratio = 0.70 [95% CI, 0.61-0.80]; P < .001; difference, -23.66 episodes/100 PYE [95% CI, -33.98 to -13.33]), and the proportions of patients with hypoglycemic episodes were 22.5% vs 31.6% (difference, -9.1% [95% CI, -13.1% to -5.0%]). The rates of nocturnal symptomatic hypoglycemia with insulin degludec vs insulin glargine U100 were 55.2 vs 93.6 episodes/100 PYE (rate ratio = 0.58 [95% CI, 0.46-0.74]; P < .001; difference, -7.41 episodes/100 PYE [95% CI, -11.98 to -2.85]), and the proportions of patients with hypoglycemic episodes were 9.7% vs 14.7% (difference, -5.1% [95% CI, -8.1% to -2.0%]). The proportions of patients experiencing severe hypoglycemia during the maintenance period were 1.6% (95% CI, 0.6%-2.7%) for insulin degludec vs 2.4% (95% CI, 1.1%-3.7%) for insulin glargine U100 (McNemar P = .35; risk difference, -0.8% [95% CI, -2.2% to 0.5%]). Statistically significant reductions in overall and nocturnal symptomatic hypoglycemia for insulin degludec vs insulin glargine U100 were also seen for the full treatment period.

CONCLUSIONS AND RELEVANCE: Among patients with type 2 diabetes treated with insulin and with at least 1 hypoglycemia risk factor, 32 weeks' treatment with insulin degludec vs insulin glargine U100 resulted in a reduced rate of overall symptomatic hypoglycemia.

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R)** 1946 to May Week 5 2019
Search Strategy:

#	Searches	Results
1	inulin glargine.mp.	0
2	insulin determir.mp.	2
3	insulin aspart.mp. or Insulin Aspart/	902
4	insulin NPH.mp. or Insulin, Isophane/	1067
5	insulin lispro.mp. or Insulin Lispro/	1047
6	insulin regular.mp. or Insulin/	179973
7	insulin degludec.mp.	322
8	insulin glulisine.mp.	205
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	180887
10	limit 9 to (english language and humans and yr="2017 -Current")	5553
11	limit 10 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	233

Appendix 4: Key Inclusion Criteria

Population	Patients with type 1 and type 2 diabetes
Intervention	Insulins
Comparator	Other active treatments or placebo
Outcomes	Mortality, micro and macrovascular complications, glucose lowering, hypoglycemia
Timing	New onset or established diabetes
Setting	Outpatient

Insulins

Goal:

Provide evidence-based and cost-effective insulin options to patients with diabetes mellitus.

- **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 glulisine (Apidra SoloSTAR®), insulin regular, human (Humulin R U-500 Kwikpen®) insulin lispro protamine-lispro (Humalog® Mix 75-25 Kwikpen), insulin lispro protamine-lispro (Humalog® Mix 50-50 Kwikpen) insulin aspart (Novolog Flexpen®), insulin detemir (Levemir® Flextouch), insulin glargine (Lantus SoloSTAR®)

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. Will the prescriber consider a change to a preferred product? Message: Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee	**Yes:** Inform prescriber of covered alternatives	**No:** Go to #4
4. Is the request for an insulin pen or cartridge?	**Yes:** Go to #5	**No:** Approve for up to 12 months

Approval Criteria		
5. Has the patient tried and failed or have contraindications to any of the preferred pens or cartridges listed above?	**Yes:** Go to #6	**No:** Pass to RPh; deny and recommend a trial of one of the preferred insulin products

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: Approve for up to 12 months	**No:** Pass to RPh; deny for medical appropriateness