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Drug Class Literature Scan: Insulin Class

Date of Review: June 2024

Date of Last Review: February 2020
Literature Search: 1/1/20 – 11/20/23 (initial)
11/20/23--5/6/24 (second)

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

Plain Language Summary:

- This scan looks at new research for medicine called insulin. Insulin is produced by the pancreas and keeps the body's blood sugar in a healthy range. In people with diabetes, their body cannot make enough insulin or their body cannot use insulin as well as it should. When there is not enough insulin or cells stop responding to insulin, too much blood sugar stays in the blood stream. Over time, this can cause serious health issues such as heart disease, vision loss, and kidney disease. Insulin is a medicine that is used to treat almost all patients with type 1 diabetes mellitus, and some patients with type 2 diabetes mellitus or gestational diabetes to help the body use the glucose (sugar) in the blood.
- Some kinds of insulins work quickly but do not last long in the body and are given near mealtime. These are called bolus or prandial insulins. Other kinds work very slowly over a longer period of time, these are called basal insulins. Some patients may need both basal and bolus insulin.
- A high quality guideline from the Department of Veterans Affairs and Department of Defense does not make recommendations for any particular insulin over another in people with type 2 diabetes.
- A high-quality guideline from the American Diabetes Association recommends certain long acting insulins combined with rapid or ultrarapid insulins as the preferred choice for patients with type 1 diabetes who inject insulin multiple times a day. In patients who have type 2 diabetes, the choice of insulin is more individualized and often used in combination with other types of medicines.
- One of the side effects of taking insulin is hypoglycemia, which is very low blood sugar. Symptoms of low blood sugar include shakiness, sweating, headache, dizziness, or confusion. If someone has these symptoms, eating a high-sugar food or drinking juice helps get blood sugar into normal range. Some evidence shows that patients with type 1 or 2 diabetes using certain long-acting basal insulins may have fewer cases of hypoglycemia than patients taking an intermediate-acting insulin.
- Three new insulin products were recently approved. Two of them, SEMGLEE and REZVOGLAR, are interchangeable biosimilars with insulin glargine (LANTUS). This means they are very similar insulin glargine (LANTUS) and switching from one to the other is not expected to cause changes in blood glucose control. The third new insulin, insulin lispro-aabc (LYUMJEV) is not a biosimilar and starts working a little bit faster than insulin lispro (HUMALOG). It is not designated as interchangeable with HUMALOG.
- New government rules starting January 1, 2024 will affect the prices of many insulin medicines.
- Insulin detemir, a preferred product, will start to become difficult for pharmacies to order in January 2024 and become unavailable by the end of 2024.
- Drug Use Research and Management recommends that no changes be made to coverage of insulins based on new evidence, but that costs of preferred and non-preferred products and formulations should be reviewed.

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Conclusions:

- Three high quality systematic reviews, 2 guidelines, and 9 randomized controlled trials (RCTs) are included in this update.
- A Cochrane review comparing the efficacy and safety of basal insulin formulations found that patients with type 1 diabetes mellitus (T1DM) may have fewer episodes of hypoglycemia with insulin detemir than with neutral protamine Hagedorn (NPH) insulin (detemir 79/1000 vs. NPH 115/1000; relative risk [RR] 0.69, 95% confidence interval [CI] 0.52 to 0.92; moderate certainty evidence).[1] Hemoglobin A1c (HbA1c) and other outcomes of interest and comparisons found no difference or lack of evidence to assess differences between insulin detemir and NPH insulin.
- A Cochrane review comparing the efficacy and safety of basal insulin formulations in patients with type 2 diabetes mellitus (T2DM) showed less hypoglycemia with insulin glargine or insulin detemir when either product was compared to NPH insulin.[2] Evidence certainty varied for each type of hypoglycemia, but was generally better for insulin glargine (very low to moderate certainty, depending on hypoglycemia type) when compared to NPH insulin than detemir compared to NPH (very-low to low certainty, depending on hypoglycemia type).[2]
- A systematic review comparing daily doses of insulin degludec 100 unit/mL or 200 unit/mL and insulin glargine 300 unit/mL in outpatient adult patients with either type 1 or type 2 diabetes.[3] There was no difference between the interventions in HbA1C (mean difference 0.07%, 95% CI -0.06 to 0.19; p=0.29; very low-certainty evidence; 3 studies; n=2881).[3] Change in fasting plasma glucose found a significant reduction in favor of insulin degludec (mean difference 10.27 mg/dL, 95% CI 7.25 to 13.29; P<0.001, low certainty evidence; 3 studies; n=2881).[3] There was no difference found in anytime hypoglycemia, nocturnal hypoglycemia, or severe hypoglycemia and these outcomes were rated to have high RoB and low to very-low certainty of evidence.[3]
- The Canadian Agency for Drugs and Technologies in Health (CADTH) committee commissioned a network meta-analysis (NMA) to compare the safety and efficacy of different basal insulin formulations in patients with T1DM. For the primary outcome of hemoglobin A1c (HbA1c) with basal insulins, long-acting insulin had a greater HbA1c decrease compared to intermediate insulin (mean difference [MD] - 0.14%, 95% CI -0.22% to -0.06%, n=8327, 25 trials).[4] The reduction in fasting plasma glucose (FPG) (n=7685, 21 trials) was statistically significant for both long-acting insulin compared to intermediate insulin (MD -1.03, 95% CI -1.33 to -0.73) and ultra-long-acting insulin compared to intermediate-acting insulin (MD -1.45, 95% CI -2.12 to -0.79).[4]
- The Department of Veterans Affairs and Department of Defense updated the 2017 guidelines for the management of T2DM in 2023.[5] It is intended for use in adult patients with T2DM. There were no recommendations related to specific insulin formulations or preferences for one formulation or biosimilar over another.[5]
- The American Diabetes Association updated guidelines in 2023.[6] Patients with T1DM should receive a rapid acting insulin analogue to reduce hypoglycemia risk (Grade A: high-quality evidence).[6] The preferred regimen for most patients with T1DM is a long-acting insulin analogue combined with a rapid-acting or ultra-rapid acting analogue. Patients with T2DM should receive a more person-centered approach to guide the choice of pharmacologic agents considering the effects on cardiovascular and renal comorbidities, efficacy, hypoglycemia risk, impact on weight, cost and access, risk for side effects, and individual preferences (Grade E: expert consensus).[6]
- Nine recently published, comparative RCTs are summarized in **Appendix 2, Table 1**. No new evidence was identified that would result in changes to the preferred drug list (PDL).
- Three new insulin products have been approved to improve glycemic control in adults and pediatric patients with diabetes mellitus (DM).
    - Insulin glargine-yfgn (SEMGLEE) and insulin glargine-aglr (REZVOGLAR) are interchangeable biosimilars for LANTUS.
    - Insulin Lispro-aabc (LYUMJEV) has a faster onset than HUMALOG and is not interchangeable.

Recommendations:

- No changes to the PDL are recommended based on the clinical review of efficacy and safety.
- After review of costs in executive session, no changes were made to preferred drug list.

Summary of Prior Reviews and Current Policy

- Current PDL status available in **Appendix 1**. Non-preferred products are subject to prior authorization (PA).
- The insulin class was last reviewed in 2020 and 2019. Neither review found clinically significant differences in glucose lowering between long-acting insulin products or between short-acting insulin products.
- After executive session in 2020, the prior authorization (PA) for insulin detemir pens (LEVEMIR FLEXTOUCH) was removed. All forms of insulin lispro, except ADMELOG, were designated as preferred.
- The American Rescue Plan (ARP) Act of 2021 included a provision that eliminates the statutory cap on rebates paid to Medicaid by drug manufacturers. Beginning January 1st, 2024, rebates will no longer be capped at 100% of the quarterly average manufacturer price (AMP). This cap previously reduced the amount of rebates paid, particularly for drugs with significant price increases over time. This "AMP CAP" removal has the potential to significantly affect drug rebate amounts. Significant price fluctuations are anticipated in response to this provision, particularly in certain drug classes, including insulins, which have seen large prices increases over time.[7-9]
- Insulin detemir products will be phased out with injection pens being discontinued in April 2024 and vials to be discontinued by the end of 2024. Supply disruptions are anticipated to begin in mid-January 2024. LEVEMIR vials, LEVEMIR FLEXPEN, and LEVEMIR FLEXTOUCH pen are all preferred on the PDL.[10] Insulin glargine (LANTUS vials and LANTUS SOLOSTAR pens) are designated preferred on the PDL and available on the market as an alternative long-acting basal insulin.

Methods:

A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, 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:

<u>(Ultra-) Long-Acting Insulin Analogues For People With Type 1 Diabetes Mellitus[1]</u>

A 2021 Cochrane review evaluated the long-term effects of the use of long-acting or ultra-long-acting insulin analogues compared to each other or NPH insulin in people with T1DM.[1] The review included 24 published and 2 unpublished RCTs of 24 to 104 week duration and including 8784 participants.[1] Eight of the 26 studies included, and 21% of all participants were children.[1] The literature search included materials published through August 24, 2020.[1] The outcomes of interest were all-cause mortality, health-related quality of life (QoL), severe hypoglycemia, non-fatal myocardial infarction/stroke, severe nocturnal hypoglycemia, severe adverse events (SAEs), and hemoglobin A1c (HbA1c).[1] The studies included had the following comparisons:

- NPH insulin vs. insulin degludec- 0 studies
- NPH insulin vs. insulin detemir- 9 studies

- NPH insulin vs. insulin glargine- 9 studies
- Insulin detemir vs. insulin glargine- 2 studies
- Insulin degludec vs insulin detemir- 2 studies
- Insulin degludec vs insulin glargine- 4 studies

Patients treated with insulin detemir had fewer episodes of severe hypoglycemia than those treated with NPH insulin (detemir 79/1000 vs. NPH 115/1000; RR 0.69, 95% CI 0.52 to 0.92; moderate certainty evidence).[1] This result is limited by inconsistency. There were no clear differences for severe night-time hypoglycemia (moderate certainty evidence), health-related QoL (low certainty evidence), SAEs (moderate certainty evidence), or HbA1c levels (moderate certainty evidence).[1] There were no clear difference in heart attack (low certainty evidence), stroke (insufficient evidence), or death (moderate certainty evidence), however these were limited by low event rates and stroke was not reported.[1]

Patients treated with insulin glargine had no clear differences compared to those treated with NPH insulin for main outcomes.[1] Moderate certainty evidence supported the results of no difference for all-cause mortality, severe hypoglycemia, severe nocturnal hypoglycemia, SAEs, and HbA1c.[1] Low certainty evidence supported health related QoL and non-fatal myocardial infarction/stroke.[1] Mortality and non-fatal myocardial infarction/stroke were limited by low event rates, and no reported myocardial infarction.[1]

The comparisons between the long-acting or ultra-long-acting insulin analogues did not find clear differences in main outcomes, and these were supported by low and very low certainty evidence usually due to few studies including these comparisons and concerns for indirectness, overall risk of bias, and imprecision.[1] There were no clear differences between adults and children for all insulin comparisons.[1]

<u>(Ultra-) Long-Acting Insulin Analogues For Adults With Type 2 Diabetes Mellitus[2]</u>

A 2020 Cochrane review evaluated the long-term effects of the use of long-acting or ultra-long-acting insulin analogues compared to each other or NPH insulin in adults with type 2 diabetes included literature through November 5, 2019.[2] A total of 24 RCTs (n=3419 adults) were included with 16 comparing insulin glargine vs. NPH insulin and 8 insulin detemir to NPH insulin. No trials comparing ultra-long-acting insulin glargine U300 or insulin degludec with NPH insulin were identified. The RCT duration ranged between 24 weeks and 5 years though only 1 study was longer than 12 months, and all trials had unclear or high risk of bias for several risk of bias domains.[2]

Insulin glargine had a reduced risk of severe hypoglycemia when compared to NPH insulin (glargine 25/1000 vs NPH 37/1000; RR 0.68, 95% CI 0.46 to 1.01; P = 0.06; absolute risk reduction (ARR) –1.2%, 95% CI –2.0 to 0; 14 trials, 6164 participants; very low-certainty evidence).[2] The incidence of confirmed hypoglycemia (BG < 55 mg/dL) was lower with insulin glargine compared to NPH (glargine 159/1000 vs. NPH 180/1000; RR 0.88, 95% CI 0.81 to 0.96, 8 trials, 4388 participants, moderate certainty evidence), as was confirmed nocturnal hypoglycemia (BG < 75 mg/dL) (glargine 274/1000 vs. NPH 351/1000; RR 0.78, 95% CI 0.68 to 0.89, 8 trials, 4225 participants, very low certainty evidence) and confirmed nocturnal hypoglycemia (BG < 55 mg/dL) (glargine 85/1000 vs. NPH 115/1000; RR 0.74, 95% CI 0.64 to 0.85, 8 trials, 4759 participants, moderate certainty evidence).[2]

Insulin detemir was no different when compared to NPH insulin for severe hypoglycemia (detemir 8/1000 vs. NPH 17/1000; RR 0.45, 95% CI 0.17 to 1.20; P = 0.11; ARR –0.9%, 95% CI –1.4 to 0.4; 5 trials, 1804 participants; very low-certainty evidence).[2] Serious hypoglycemia was less common with detemir (detemir 2/1000 vs. NPH 11/1000; Peto OR 0.16, 95% CI 0.04 to 0.61; 5 trials, 1777 participants; low-certainty evidence).[2] Insulin detemir had lower rates when compared to NPH insulin of confirmed hypoglycemia (BG < 75 mg/dL) (detemir 410/1000 vs. NPH 562/1000; RR 0.73, 95% CI 0.61 to 0.86; 4 trials, 1718 participants; low-

certainty evidence), confirmed hypoglycemia (BG < 55 mg/dL) (detemir 237/1000 vs. NPH 493/1000; RR 0.48, 95% CI 0.32 to 0.71; 4 trials, 1718 participants; low-certainty evidence), confirmed nocturnal hypoglycemia (BG <75 mg/dL) (detemir 176/1000 vs. NPH 309/1000; RR 0.57, 95% CI 0.47 to 0.68; 4 trials, 1718 participants; low-certainty evidence), and confirmed nocturnal hypoglycemia (BG < 55 mg/dL) (detemir 13/1000 vs. NPH 40/1000; RR 0.32, 95% CI 0.16 to 0.63; 4 trials, 1718 participants; low-certainty evidence).[2]

Evidence was insufficient or lacking in almost all trials to evaluate death from any cause, diabetes-related complications, health-related QoL, and socioeconomic effects. The insulin analogues and NPH insulin showed no clear difference in weight gain.[2]

Comparative Efficacy and Safety of Ultra-Long-Acting, Long-Acting, Intermediate-Acting, and Biosimilar Insulins for Type 1 Diabetes Mellitus: a Systematic Review and Network Meta-Analysis[4]

A 2021 systematic review and NMA, commissioned by Health Canada and the CADTH and informed by the World Health Organization (WHO) insulin access initiative, evaluated RCTs, non-randomized controlled trials, quasi-randomized trials, quasi-experimental studies, and cohort studies for the primary efficacy outcomes of glycemic control (HbA1c, FPG). Sixty-five unique studies were included with 13 additional companion reports (n=14,200).[4] Sixty-four of the 65 studies were RCTs. Trial sample sized ranged from 8 to 749 individuals aged 23 to 54 years with duration of T1DM of 8 to 27 years.[4] The baseline average HbA1c was 7-10% and most studies were conducted in Europe and North America.[4] The risk of bias (RoB) assessment varied by included study, but unclear or high RoB was assigned to the categories of allocation concealment (75%), blinding of participants and personnel (78%), blinding of outcome assessment (44%), incomplete outcome data (28%), selective reporting (63%), and "other" bias (e.g., funding bias, 92%).[4]

For the NMA of primary HbA1c outcomes with basal insulins, long-acting insulin had a greater HbA1c decrease compared to intermediate insulin (MD - 0.14%, 95% CI -0.22% to -0.06%, n=8327, 25 trials).[4] Ultra-long-acting insulin was not statistically significant for differences in HbA1c compared to intermediate-acting insulin (MD -0.08%, 95% CI:- 0.25% to 0.10%) or long-acting insulin (MD 0.06%, 95% CI -0.10% to 0.22%).[4] The reduction in FPG (n=7685, 21 trials) was statistically significant for both long-acting insulin compared to intermediate insulin (MD -1.03, 95% CI -1.33 to -0.73) and ultra-long-acting insulin compared to intermediate-acting insulin (MD -1.45, 95% CI -2.12 to -0.79).[4] Long-acting insulin was statistically superior to intermediate-acting insulin in several secondary outcomes including weight gain, major or serious hypoglycemia, and nocturnal hypoglycemia.[4] Ultra-long-acting insulin was statistically superior to intermediate-acting insulin for the secondary outcome of nocturnal hypoglycemia.[4]

Efficacy and safety of insulin glargine 300 units/mL vs insulin degludec in patients with type 1 and type 2 diabetes: a systematic review and meta-analysis[3]

A 2024 systematic review included RCTs of outpatient adult patients with either type 1 or type 2 diabetes who were insulin naïve or insulin experienced.[3] Studies evaluated daily doses of insulin degludec 100 unit/mL or 200 unit/mL compared to insulin glargine 300 unit/mL for glycemic control or hypoglycemia outcomes.[3] Bias was assessed using the Cochrane risk-of-bias tool for randomized trials.[3] Four studies (n=2927) were included, all enrolling adults with 2 studies including patients with type 1 diabetes and 2 studies including patient with type 2 diabetes.[3] One was a crossover study design (n=46).[3] Studies had RoB for randomization, but unclear to high bias in most other domains.[3] There was no difference between the interventions in HbA1C (mean difference 0.07%, 95% CI -0.06 to 0.19; p=0.29; very low-certainty evidence; 3 studies; n=2881).[3] Change in fasting plasma glucose found a significant reduction in favor of insulin degludec (mean difference 10.27 mg/dL, 95% CI 7.25 to 13.29; P<0.001, low certainty evidence; 3 studies; n=2881).[3] There was no difference found in anytime hypoglycemia, nocturnal hypoglycemia, or severe hypoglycemia and these outcomes were rated to have high RoB and low to very-low certainty of evidence.[3]

After review of results from initial literature search, 307 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), outcome studied (e.g., non-clinical), or applicability to this literature scan. One additional systematic review was included from second literature search.

New Guidelines:
High Quality Guidelines:

VA/DoD Clinical Practice Guidelines for the Management of Type 2 Diabetes Mellitus[5]
The Department of Veterans Affairs and Department of Defense updated the 2017 guidelines for the management of T2DM in 2023.[5] It is intended for use in adult patients with T2DM who receive care at the VA or DoD health care delivery systems and not for pregnant or nursing persons or those with T1DM.

Recommendations relevant to the insulin class include:

- Recommendation 25 - In adults with T2DM, especially those 65 years and older, we suggest prioritizing drug classes other than insulin, sulfonylureas, or meglitinides to minimize the risk of hypoglycemia, if glycemic control can be achieved with other treatments. (Strength: Weak for; Category: Reviewed, New-added)[5]
- Recommendation 26 - In adults with T2DM who have concurrent cognitive impairment or risk of falls, there is insufficient evidence to recommend for or against specific treatment strategies for glucose lowering to reduce the risk of harms. (Strength: Neither for or against; Category: Reviewed, New-added)[5]

No recommendation related to specific insulin formulations or preferences for one formulation or biosimilar over another.

Standards of Care in Diabetes-2023[6,11]
The American Diabetes Association updates management standards for patients with diabetes mellitus on an annual basis.[6] Evidence recommendations are graded A (Clear evidence from well-conducted, generalizable RCTs that are adequately powered and supportive evidence from well-conducted RCTs that are adequately powered), B (supportive evidence from well-conducted cohort studies or case-control study), C (Supportive evidence from poorly controlled or uncontrolled studies or conflicting evidence with the weight of evidence supporting the recommendation, and E (Expert consensus or clinical experience).

Recommendations related to insulin therapy in T1DM include:

9.1 Most individuals with type 1 diabetes should be treated with multiple daily injections of prandial and basal insulin, or continuous subcutaneous insulin infusion. Grade A[6]
9.2 Most individuals with type 1 diabetes should use rapid-acting insulin analogs to reduce hypoglycemia risk. Grade A[6]
9.3 Individuals with type 1 diabetes should receive education on how to match mealtime insulin doses to carbohydrate intake, fat and protein content, and anticipated physical activity. Grade B[6]

The insulin regimen of choice for T1DM patients includes a long-acting insulin analogue combined with a rapid-insulin analogue or an ultra-rapid insulin analogue.[6] These types are preferred based on the priorities of flexibility and lower glycemic risk, though at the expense of higher cost.[6] Less preferred alternative regimens include NPH insulin combined with rapid-insulin analogue, an ultra-rapid insulin analogue, a short-acting (regular) insulin, or NPH twice daily with short-acting insulin or a pre-mix.[6]

Recommendations related to insulin therapy in T2DM include:

9.8 A person-centered approach should guide the choice of pharmacologic agents. Consider the effects on cardiovascular and renal comorbidities, efficacy, hypoglycemia risk, impact on weight, cost and access, risk for side effects, and individual preferences. Grade E[6]

9.11 If insulin is used, combination therapy with a glucagon-like peptide 1 receptor agonist is recommended for greater efficacy, durability of treatment effect, and weight and hypoglycemia benefit. Grade A[6]

Patients with T2DM would generally start on alternative oral and injectable pharmacotherapy before insulin. Insulin initiation may occur after insufficient response or contraindications/intolerance to alternative options. Therapy with a basal analogue or bedtime NPH dose would be first, and choice of basal insulin should be individualized for person-specific considerations, including cost.[6] Long-acting analogues (U-100 glargine or detemir) reduce the risk of symptomatic and nocturnal hypoglycemia compared to NPH, but these advantages are modest and may not persist.[6] Longer-acting basal analogues (U200 glargine and degludec) may have lower risk of hypoglycemia compared to U100 glargine when used in combination with oral agents.[6] Addition of prandial insulin may happen after maximization of other therapies. When added in addition to NPH, consider use of a pre-mixed version to decrease number of injections required.[6]

Additional Guidelines for Clinical Context:

Developing a Diabetes Mellitus Comprehensive Care Plan-2022 Update[12]

The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) published a diabetes (DM) care plan in 2022. This care plan included a conflict of interest mitigation strategy, but many task force members, including the chair and vice chair, had many industry affiliations. The methods for guideline development, specifically the detailed search strategy which used only a single search database (PubMed), were not included. Due to these limitations, the guidelines will not be presented.

After review from initial literature search, 11 guidelines were excluded due to poor quality or applicability to research questions.

New Formulations:[13]

- **Insulin Glargine (SEMGLEE)**-On June 11, 2020 SEMGLEE was approved by the FDA to improve glycemic control in adults and pediatric patients with T1DM and adults with T2DM as a biosimilar to LANTUS.
- **Insulin Glargine-yfgn (SEMGLEE)-**On July 28, 2021 SEMGLEE was approved by the FDA to improve glycemic control in adults and pediatric patients with DM as an *interchangeable* biosimilar to LANTUS.
- **Insulin Lispro-aabc (LYUMJEV)**-On June 15, 2020, LYUMJEV was approved by the FDA to improve glycemic control in adults with DM. The indication was expanded in October 2022 to include use in pediatric patients with DM and addition of continuous subcutaneous insulin infusion (U100 product) as a condition of use in the pediatric population. This product is formulated with treprostinil and citrate for faster absorption than insulin lispro (HUMALOG) and is not interchangeable. It is available as a U100 and U200 formulation and should not be mixed in the same syringe as other insulins.
- **Insulin Glargine-aglr (REZVOGLAR)**-On December 17, 2021, REZVOGLAR was approved by the FDA to improve glycemic control in adults and pediatric patients with T1DM and adults with T2DM as a biosimilar to LANTUS. In November 2022 this approval was expanded to improve glycemia control in adults and pediatric patients with DM as an *interchangeable* biosimilar to LANTUS.

New FDA Safety Alerts:

Table 1. Description of New FDA Safety Alerts[13]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Regular human insulin/ NPH insulin	HUMULIN 70/30	June 2022	Warnings and Precautions	New Subsection: Hypoglycemia due to medication errors Accidental mix-ups between insulin products have been reported. To avoid medication errors between HUMULIN 70/30 and other insulins, instruct patients to always check the insulin label before each injection.
NPH insulin	HUMULIN N	June 2022	Warnings and Precautions	New Subsection: Hypoglycemia due to medication errors Accidental mix-ups between insulin products have been reported. To avoid medication errors between HUMULIN N and other insulins, instruct patients to always check the insulin label before each injection.
Insulin detemir	LEVEMIR	July 2022	Warnings and Precautions	New Subsection: Hyperglycemia or hypoglycemia with changes in insulin regimen Changes in an insulin regimen (e.g., insulin strength, manufacturer, type, injection site or method of administration) may affect glycemic control and predispose to hypoglycemia or hyperglycemia. Repeated insulin injections into areas of lipodystrophy or localized cutaneous amyloidosis have been reported to result in hyperglycemia; and a sudden change in the injection site (to an unaffected area) has been reported to result in hypoglycemia.
Insulin Lispro-aabc	LYUMJEV	August 2021	Warnings and Precautions	New Subsection: Hyperglycemia and ketoacidosis due to insulin pump device malfunction Pump or infusion set malfunctions can lead to a rapid onset of hyperglycemia and ketoacidosis. Prompt identification and correction of the cause of hyperglycemia or ketosis is necessary. Interim therapy with subcutaneous injection of LYUMJEV may be required. Patients using continuous subcutaneous insulin infusion pump therapy must be trained to administer insulin by injection and have alternate insulin therapy available in case of pump failure.

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
insulin aspart	INSULIN ASPART PENFILL	SUBCUT	CARTRIDGE	Y
insulin aspart	NOVOLOG PENFILL	SUBCUT	CARTRIDGE	Y
insulin aspart	INSULIN ASPART FLEXPEN	SUBCUT	INSULN PEN	Y
insulin aspart	NOVOLOG FLEXPEN	SUBCUT	INSULN PEN	Y
insulin aspart	INSULIN ASPART	SUBCUT	VIAL	Y
insulin aspart	NOVOLOG	SUBCUT	VIAL	Y
insulin aspart prot/insuln asp	INSULIN ASPART PROT MIX 70-30	SUBCUT	INSULN PEN	Y
insulin aspart prot/insuln asp	NOVOLOG MIX 70-30 FLEXPEN	SUBCUT	INSULN PEN	Y
insulin aspart prot/insuln asp	INSULIN ASPART PROT MIX 70-30	SUBCUT	VIAL	Y
insulin aspart prot/insuln asp	NOVOLOG MIX 70-30	SUBCUT	VIAL	Y
*insulin detemir	LEVEMIR FLEXPEN	SUBCUT	INSULN PEN	Y
*insulin detemir	LEVEMIR FLEXTOUCH	SUBCUT	INSULN PEN	Y
*insulin detemir	LEVEMIR	SUBCUT	VIAL	Y
insulin glargine,hum.rec.anlog	LANTUS SOLOSTAR	SUBCUT	INSULN PEN	Y
insulin glargine,hum.rec.anlog	LANTUS	SUBCUT	VIAL	Y
insulin glulisine	APIDRA SOLOSTAR	SUBCUT	INSULN PEN	Y
insulin glulisine	APIDRA	SUBCUT	VIAL	Y
insulin lispro	HUMALOG	SUBCUT	CARTRIDGE	Y
insulin lispro	HUMALOG JUNIOR KWIKPEN	SUBCUT	INS PEN HF	Y
insulin lispro	INSULIN LISPRO JUNIOR KWIKPEN	SUBCUT	INS PEN HF	Y
insulin lispro	HUMALOG KWIKPEN U-100	SUBCUT	INSULN PEN	Y
insulin lispro	HUMALOG KWIKPEN U-200	SUBCUT	INSULN PEN	Y
insulin lispro	HUMALOG TEMPO PEN U-100	SUBCUT	INSULN PEN	Y
insulin lispro	INSULIN LISPRO KWIKPEN U-100	SUBCUT	INSULN PEN	Y
insulin lispro	HUMALOG	SUBCUT	VIAL	Y
insulin lispro	INSULIN LISPRO	SUBCUT	VIAL	Y
insulin lispro protamin/lispro	HUMALOG MIX 50-50 KWIKPEN	SUBCUT	INSULN PEN	Y
insulin lispro protamin/lispro	HUMALOG MIX 75-25 KWIKPEN	SUBCUT	INSULN PEN	Y
insulin lispro protamin/lispro	INSULIN LISPRO PROTAMINE MIX	SUBCUT	INSULN PEN	Y
insulin lispro protamin/lispro	HUMALOG MIX 50-50	SUBCUT	VIAL	Y
insulin lispro protamin/lispro	HUMALOG MIX 75-25	SUBCUT	VIAL	Y
insulin NPH hum/reg insulin hm	HUMULIN 70/30 KWIKPEN	SUBCUT	INSULN PEN	Y
insulin NPH hum/reg insulin hm	NOVOLIN 70-30 FLEXPEN	SUBCUT	INSULN PEN	Y
insulin NPH hum/reg insulin hm	HUMULIN 70-30	SUBCUT	VIAL	Y
insulin NPH hum/reg insulin hm	NOVOLIN 70-30	SUBCUT	VIAL	Y
insulin NPH human isophane	HUMULIN N	SUBCUT	VIAL	Y
insulin NPH human isophane	NOVOLIN N	SUBCUT	VIAL	Y

insulin regular, human	HUMULIN R U-500 KWIKPEN	SUBCUT	INSULN PEN	Y
insulin regular, human	HUMULIN R	INJECTION	VIAL	Y
insulin regular, human	NOVOLIN R	INJECTION	VIAL	Y
insulin regular, human	HUMULIN R U-500	SUBCUT	VIAL	Y
insulin aspart (niacinamide)	FIASP PENFILL	SUBCUT	CARTRIDGE	N
insulin aspart (niacinamide)	FIASP FLEXTOUCH	SUBCUT	INSULN PEN	N
insulin aspart (niacinamide)	FIASP	SUBCUT	VIAL	N
insulin aspart/B3/pump cart	FIASP PUMPCART	SUBCUT	CARTRIDGE	N
insulin degludec	INSULIN DEGLUDEC PEN (U-100)	SUBCUT	INSULN PEN	N
insulin degludec	INSULIN DEGLUDEC PEN (U-200)	SUBCUT	INSULN PEN	N
insulin degludec	TRESIBA FLEXTOUCH U-100	SUBCUT	INSULN PEN	N
insulin degludec	TRESIBA FLEXTOUCH U-200	SUBCUT	INSULN PEN	N
insulin degludec	INSULIN DEGLUDEC	SUBCUT	VIAL	N
insulin degludec	TRESIBA	SUBCUT	VIAL	N
insulin degludec/liraglutide	XULTOPHY 100-3.6	SUBCUT	INSULN PEN	N
insulin glargine,hum.rec.anlog	BASAGLAR KWIKPEN U-100	SUBCUT	INSULN PEN	N
insulin glargine,hum.rec.anlog	BASAGLAR TEMPO PEN U-100	SUBCUT	INSULN PEN	N
insulin glargine,hum.rec.anlog	INSULIN GLARGINE SOLOSTAR	SUBCUT	INSULN PEN	N
insulin glargine,hum.rec.anlog	TOUJEO MAX SOLOSTAR	SUBCUT	INSULN PEN	N
insulin glargine,hum.rec.anlog	TOUJEO SOLOSTAR	SUBCUT	INSULN PEN	N
insulin glargine,hum.rec.anlog	INSULIN GLARGINE	SUBCUT	VIAL	N
insulin glargine/lixisenatide	SOLIQUA 100-33	SUBCUT	INSULN PEN	N
insulin glargine-aglr	REZVOGLAR KWIKPEN	SUBCUT	INSULN PEN	N
insulin glargine-yfgn	INSULIN GLARGINE-YFGN	SUBCUT	INSULN PEN	N
insulin glargine-yfgn	SEMGLEE (YFGN) PEN	SUBCUT	INSULN PEN	N
insulin glargine-yfgn	INSULIN GLARGINE-YFGN	SUBCUT	VIAL	N
insulin glargine-yfgn	SEMGLEE (YFGN)	SUBCUT	VIAL	N
insulin lispro	ADMELOG SOLOSTAR	SUBCUT	INSULN PEN	N
insulin lispro	ADMELOG	SUBCUT	VIAL	N
insulin lispro-aabc	LYUMJEV KWIKPEN U-100	SUBCUT	INSULN PEN	N
insulin lispro-aabc	LYUMJEV KWIKPEN U-200	SUBCUT	INSULN PEN	N
insulin lispro-aabc	LYUMJEV TEMPO PEN U-100	SUBCUT	INSULN PEN	N
insulin lispro-aabc	LYUMJEV	SUBCUT	VIAL	N
insulin NPH human isophane	HUMULIN N KWIKPEN	SUBCUT	INSULN PEN	N
insulin NPH human isophane	NOVOLIN N FLEXPEN	SUBCUT	INSULN PEN	N
insulin regular, human	AFREZZA	INHALATION	CART INHAL	N
insulin regular, human	NOVOLIN R FLEXPEN	SUBCUT	INSULN PEN	N
insulin regular in 0.9 % NaCl	MYXREDLIN	INTRAVEN	PLAST. BAG	

***** Discontinuation from market by manufacturer anticipated in 2024 (Not related to safety or efficacy.)[10]

Appendix 2: New Comparative Clinical Trials

A total of 1027 citations were manually reviewed from the initial literature search. After further review, 1018 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining 9 trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Bartal et al.[14] RCT, OL	1. detemir (n=57) 2. NPH (n=51) 1:1 Randomization	Pregnant adults with T2D or overt T2D at $\leq$ 21 weeks gestation	Composite adverse neonatal complications including: Shoulder dystocia, LGA, NICU admission, respiratory distress in first 24 hours of life, neonatal hypoglycemia.	1. 58% 2. 70% 1 vs. 2 Adjusted RR 0.88 95% CrI 0.61 to 1.12	-6 study centers -Bayesian analysis -62% Hispanic, 26% African American -82% BMI >30 kg/m^2
CONCLUDE[15] RCT, OL	1. degludec U200 (n=805) 2. glargine U300 (n=804) 1:1 Randomization Duration up to 94 weeks	Adults with T2D on basal insulin ($\geq$ 18 y) Baseline HbA1c $\leq$ 9.5% BMI $\leq$ 45 kg/m^2	Symptomatic hypoglycemic events (Requiring 3rd party assistance or confirmed blood glucose <3.1 mmol/L)	1. 301 (40.6%) 2. 343 (46.3%) 1 vs. 2 RR 0.88 95% CI 0.73 to 1.09 NS	- approximately 9% attrition and 12.5% drug discontinuation in each arm -Industry funded
EDITION JUNIOR[16] Phase IIIb OL, RCT	1. GLA-300 (n=233) 2. GLA-100 (n=230) 1:1 Randomization	Children and Adolescents with T1DM (6 to <18 y) Baseline HbA1c $\geq$7.5 to $\leq$ 11.0%	HbA1C change from baseline to 26 weeks 1. -0.40% (0.06%) 2. -0.40% (0.06%)	1 vs. 2 LSM difference 0.004% 95% CI -0.17 to 0.18 for noninferiority	-Noninferiority design (margin 3.3 mmol/mol [0.3%]) -105 study centers, 24 countries -Industry funded
EXPECT[17] RCT, OL	1. degludec+IAsp (n=111) 2. detemir+IAsp (n=114)	Pregnant adults with T1DM ($\geq$ 18 y)	Last planned HbA1c before delivery	1. 6.2% 2. 6.3% 1 vs. 2 ETD -0.11%	-Noninferiority design (margin 0.4% for degludec vs. detemir) - 56 study centers, 14 countries -Industry funded

	1:1 Randomization			95% CI -0.31 to 0.08; p<0.0001 for noninferiority	
ONSET 9[18] Phase IIIb, RCT, DB	1. faster aspart (n=546) 2. IAsp (n=545) 1:1 Randomization	Adults with T2DM (≥ 18 y) T2D for ≥10 y Baseline HbA1c 7.0-10.0%	HbA1C change from baseline to 16 weeks	1 vs. 2 ETD -0.04% 95% -0.11 to 0.03; p<0.001 for noninferiority	-Noninferiority design (margin 4.4 mmol/mol [0.4%]) -165 study centers, 17 countries -Industry funded
PRONTO-T1D[19] Phase III DB/OL, RCT	1. URLi DB mealtime (n=451) 2. Lispro DB mealtime (n=442) 3. URLi OL postmeal (n=329) 1 injected 0-2 min prior to meals 2 Injected at mealtime 3 Injected up to 20 min after start of meal 4:4:3 randomization	Adults with T1DM (≥ 18 y) Baseline HbA1c 7.0-9.5% BMI ≤ 35 kg/m^2	HbA1C change from baseline to 26 weeks (LSM) 1. -1.4 mmol/mol (-0.13%) 2. -0.9 mmol/mol (-0.05%) 3. 0.8 mmol/mol (0.08%)	1 vs. 2 ETD -0.08% 95% CI -0.16 to 0.00 P=0.06 for noninferiority 3 vs. 2 ETD 0.13% 95% CI 0.04 to 0.22 P=0.003 for noninferiority	-Noninferiority design (margin 4.4 mmol/mol [0.4%]) -8-week lead in to optimize basal insulin (glargine or degludec) -166 study centers, 18 countries -Industry funded
PRONTO-T2D[20] Phase III DB, RCT	1. URLi (n=336) 2. Lispro (n=337) Inject 0-2 min prior to meals	Adults with T2DM Baseline HbA1c 7.0-10.0% Up to 3 oral hypoglycemics at enrollment but	HbA1C mean change from baseline to 26 weeks 1. -0.38% 2. -0.43%	1 vs. 2 EDT 0.06% 95% CI -0.05 to 0.16	-Noninferiority design (margin 4.4 mmol/mol [0.4%]) -May continue metformin and/or SGLT2-I -8-week lead-in to optimize basal insulin, remained on prestudy basal (degludec, glargine) -Industry funded

		discontinued all except metformin and SGLT2-I during lead-in			
PRONTO-Peds[21] Phase III, RCT, DB/OL	1. URLi DB premeal (n=280) 2. Lispro DB premeal (n=298) 3. URLi OL postmeal (n=138) 1 & 2 injected 0-2 min prior to meals 3 injected up to 20 min after start of meal 2:2:1 randomization	Children and Adolescents with T1DM (1 to <18 y)	HbA1C change from baseline to 26 weeks (LSM) 1. 0.71 mmol/mol (0.06%) 2. 0.94 mmol/mol (0.09%) 3. 0.77 mmol/mol (0.07%)	1 vs. 2 LSM difference -0.23 mmol/mol 95% CI -1.84 to 1.39 ETD -0.02% 95% CI -0.17 to 0.13 3 vs. 2 LSM difference -0.17 mmol/mol 95% CI -2.15 to 1.81 ETD -0.02% 95% CI -0.20 to 0.17	-Noninferiority design (margin 4.4 mmol/mol [0.4%]) -4-week lead-in to optimize basal insulin, remained on prestudy basal (degludec, detemir, glargine) -Industry funded
SWITCH PRO[22] Phase IV, RCT, crossover, OL	1. degludec U100 (n=249 degludec first) 2. glargine U100 (n=249 glargine first) 41 week duration	Adults with T2DM and $\geq$1 hypoglycemia risk factor ($\geq$ 18 y) Baseline HbA1c $\leq$ 9.5% BMI $\leq$ 45 kg/m^2	TIR assessed by CGM (time spent in range of 3.9 to 10.0 mmol/L during weeks 17-18 and 35-36)	1. 72.1% 2. 70.7% ETD 1.43% (20.6 min/d) 95% CI 0.12 to 2.74; p=0.032	- 67 study sites, 5 countries -22 patients withdrew during first study period and 8 during second -20 patients excluded due to insufficient CGM data -n=488 in final analysis set -Industry funded

Abbreviations: ARR = absolute risk reduction; BMI = body mass index; CGM = continuous glucose monitoring; CI = confidence interval; CrI = credible interval; DB = double blind; ETD = estimated treatment difference; faster aspart = fast-acting insulin aspart, FIASP; GLA-100 = insulin glargine 100 unit/mL; GLA-300 = insulin glargine 300 unit/mL; HbA1C = glycated hemoglobin; LSM = least squares mean; $iAUC_{0\text{-}2\,h}$ = Incremental area under curve from 0 to 2 h after meals; IAsp = insulin aspart; LGA = large for gestational age; NICU = neonatal intensive care unit; NS = not significant; OL = open label; OR = odds ratio; RCT = randomized clinical trial; RR = rate ratio; SGLT2-I = sodium-glucose cotransporter 2 inhibitor; SOC-BI = standard of care-basal insulin analogues; TIR = time in range; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; URLi = ultra rapid lispro, LYUMJEV; y = years.

Appendix 3: Abstracts of Comparative Clinical Trials

Detemir vs neutral protamine Hagedorn insulin for diabetes mellitus in pregnancy: a comparative effectiveness, randomized controlled trial[14]

BACKGROUND: Insulin detemir, being used increasingly during pregnancy, may have pharmacologic benefits compared with neutral protamine Hagedorn.
OBJECTIVE: We evaluated the probability that compared with treatment with neutral protamine Hagedorn, treatment with insulin detemir reduces the risk for adverse neonatal outcome among individuals with type 2 or overt type 2 diabetes mellitus (gestational diabetes mellitus diagnosed at <20 weeks' gestation).
STUDY DESIGN: We performed a multiclinic randomized controlled trial (September 2018 to January 2020), which included women with singleton gestation with type 2 or overt type 2 diabetes mellitus who sought obstetrical care at <=21 weeks' gestation. Participants were randomized to receive either insulin detemir or neutral protamine Hagedorn by a clinic-stratified scheme. The primary outcome was a composite of adverse neonatal outcomes, including shoulder dystocia, large for gestational age, neonatal intensive care unit admission, respiratory distress (defined as the need of at least 4 hours of respiratory support with supplemental oxygen, continuous positive airway pressure or ventilation at the first 24 hours of life), or hypoglycemia. The secondary neonatal outcomes included gestational age at delivery, small for gestational age, 5-minute Apgar score of <7, lowest glucose level, need for intravenous glucose, respiratory distress syndrome, need for mechanical ventilation or continuous positive airway pressure, neonatal jaundice requiring therapy, brachial plexus injury, and hospital length of stay. The secondary maternal outcomes included hypoglycemic events, hospital admission for glucose control, hypertensive disorder of pregnancy, maternal weight gain, cesarean delivery, and postpartum complications. We used the Bayesian statistics to estimate a sample size of 108 to have >75% probability of any reduction in the primary outcome, assuming 80% power and a hypothesized effect of 33% reduction with insulin detemir. All analyses were intent to treat under a Bayesian framework with neutral priors (a priori assumed a 50:50 likelihood of either intervention being better; National Clinical Trial identifier 03620890).
RESULTS: There were 108 women randomized in this trial (57 in insulin detemir and 51 in neutral protamine Hagedorn), and 103 women were available for analysis of the primary outcome (n=5 for pregnancy loss before 24 weeks' gestation). Bayesian analysis indicated an 87% posterior probability of reduced primary outcome with insulin detemir compared with neutral protamine Hagedorn (posterior adjusted relative risk, 0.88; 95% credible interval, 0.61-1.12). Bayesian analyses for secondary outcomes showed consistent findings of lower adverse maternal outcomes with the use of insulin detemir vs neutral protamine Hagedorn: for example, maternal hypoglycemic events (97% probability of benefit; posterior adjusted relative risk, 0.59; 95% credible interval, 0.29-1.08) and hypertensive disorders (88% probability of benefit; posterior adjusted relative risk, 0.81; 95% credible interval, 0.54-1.16).
CONCLUSION: In our comparative effectiveness trial involving individuals with type 2 or overt type 2 diabetes mellitus, use of insulin detemir resulted in lower rates of adverse neonatal and maternal outcomes compared with neutral protamine Hagedorn.

Risk of hypoglycaemia with insulin degludec versus insulin glargine U300 in insulin-treated patients with type 2 diabetes: the randomised, head-to-head CONCLUDE trial[15]

AIMS/HYPOTHESIS: A head-to-head randomised trial was conducted to evaluate hypoglycaemia safety with insulin degludec 200 U/ml (degludec U200) and insulin glargine 300 U/ml (glargine U300) in individuals with type 2 diabetes treated with basal insulin.
METHODS: This randomised (1:1), open-label, treat-to-target, multinational trial included individuals with type 2 diabetes, aged >=18 years with HbA_{1c} <=80 mmol/mol (9.5%) and BMI <=45 kg/m². Participants were previously treated with basal insulin with or without oral glucose-lowering drugs (excluding insulin secretagogues) and had to fulfil at least one predefined criterion for hypoglycaemia risk. Both degludec U200 and glargine U300 were similarly titrated to a fasting blood glucose target of 4.0-5.0 mmol/l. Endpoints were assessed during a 36 week maintenance period and a total treatment period up to 88 weeks. There were three hypoglycaemia endpoints: (1) overall symptomatic hypoglycaemia (either severe, an event requiring third-party assistance, or confirmed by blood glucose [<3.1 mmol/l] with symptoms); (2) nocturnal symptomatic hypoglycaemia (severe or confirmed by blood glucose with symptoms, between 00:01 and 05:59 h); and (3) severe hypoglycaemia. The primary endpoint was the number of overall symptomatic hypoglycaemic events in the maintenance period. Secondary hypoglycaemia endpoints included the number of nocturnal symptomatic events and number of severe hypoglycaemic events during the maintenance period.
RESULTS: Of the 1609 randomised participants, 733 of 805 (91.1%) in the degludec U200 arm and 734 of 804 (91.3%) in the glargine U300 arm completed the trial (87.3% and 87.8% completed on treatment, respectively). Baseline characteristics were comparable between the two treatment arms. For the primary endpoint, the rate of overall symptomatic hypoglycaemia was not significantly lower with degludec U200 vs glargine U300 (rate ratio [RR] 0.88 [95% CI 0.73, 1.06]). As there was no significant difference between treatments for the primary endpoint, the confirmatory testing procedure for superiority was stopped. The pre-specified confirmatory secondary hypoglycaemia

endpoints were analysed using pre-specified statistical models but were now considered exploratory. These endpoints showed a lower rate of nocturnal symptomatic hypoglycaemia (RR 0.63 [95% CI 0.48, 0.84]) and severe hypoglycaemia (RR 0.20 [95% CI 0.07, 0.57]) with degludec U200 vs glargine U300.
CONCLUSIONS/INTERPRETATION: There was no significant difference in the rate of overall symptomatic hypoglycaemia with degludec U200 vs glargine U300 in the maintenance period. The rates of nocturnal symptomatic and severe hypoglycaemia were nominally significantly lower with degludec U200 during the maintenance period compared with glargine U300.
TRIAL REGISTRATION: ClinicalTrials.gov NCT03078478 FUNDING: This trial was funded by Novo Nordisk (Bagsvaerd, Denmark).

Efficacy and Safety of Insulin Glargine 300 Units/mL (Gla-300) Versus Insulin Glargine 100 Units/mL (Gla-100) in Children and Adolescents (6-17 years) With Type 1 Diabetes: Results of the EDITION JUNIOR Randomized Controlled Trial[16]

OBJECTIVE: To compare efficacy and safety of insulin glargine 300 units/mL (Gla-300) and 100 units/mL (Gla-100) in children and adolescents (6-17 years old) with type 1 diabetes.
RESEARCH DESIGN AND METHODS: EDITION JUNIOR was a noninferiority, international, open-label, two-arm, parallel-group, phase 3b trial. Participants were randomized 1:1 to Gla-300 or Gla-100, titrated to achieve fasting self-monitored plasma glucose levels of 90-130 mg/dL (5.0-7.2 mmol/L), with continuation of prior prandial insulin. The primary end point was change in HbA_{1c} from baseline to week 26. Other assessments included change in fasting plasma glucose (FPG), hypoglycemia, hyperglycemia with ketosis, and adverse events.
RESULTS: In 463 randomized participants (Gla-300, n = 233; Gla-100, n = 230), comparable least squares (LS) mean (SE) reductions in HbA_{1c} were observed from baseline to week 26 (-0.40% [0.06%] for both groups), with LS mean between-group difference of 0.004% (95% CI -0.17 to 0.18), confirming noninferiority at the prespecified 0.3% (3.3 mmol/mol) margin. Mean FPG change from baseline to week 26 was also similar between groups. During the 6-month treatment period, incidence and event rates of severe or documented (<=70 mg/dL [<=3.9 mmol/L]) hypoglycemia were similar between groups. Incidence of severe hypoglycemia was 6.0% with Gla-300 and 8.8% with Gla-100 (relative risk 0.68 [95% CI 0.35-1.30]). Incidence of any hyperglycemia with ketosis was 6.4% with Gla-300 and 11.8% with Gla-100.
CONCLUSIONS: Gla-300 provided similar glycemic control and safety profiles to Gla-100 in children and adolescents with type 1 diabetes, indicating that Gla-300 is a suitable therapeutic option in this population.

Insulin degludec versus insulin detemir, both in combination with insulin aspart, in the treatment of pregnant women with type 1 diabetes (EXPECT): an open-label, multinational, randomised, controlled, non-inferiority trial[17]

BACKGROUND: Insulin degludec (degludec) is a second-generation basal insulin with an improved pharmacokinetic-pharmacodynamic profile compared with first-generation basal insulins, but there are few data regarding its use during pregnancy. In this non-inferiority trial, we aimed to compare the efficacy and safety of degludec with insulin detemir (detemir), both in combination with insulin aspart (aspart), in pregnant women with type 1 diabetes.
METHODS: This open-label, multinational, randomised, controlled, non-inferiority trial (EXPECT) was conducted at 56 sites (hospitals and medical centres) in 14 countries. Women aged at least 18 years with type 1 diabetes who were between gestational age 8 weeks (+0 days) and 13 weeks (+6 days) or planned to become pregnant were randomly assigned (1:1), via an interactive web response system, to degludec (100 U/mL) once daily or detemir (100 U/mL) once or twice daily, both with mealtime insulin aspart (100 U/mL), all via subcutaneous injection. Participants who were pregnant received the trial drug at randomisation, throughout pregnancy and until 28 days post-delivery (end of treatment). Participants not pregnant at randomisation initiated the trial drug before conception. The primary endpoint was the last planned HbA_{1c} measurement before delivery (non-inferiority margin of 0.4% for degludec vs detemir). Secondary endpoints included efficacy, maternal safety, and pregnancy outcomes. The primary endpoint was assessed in all randomly assigned participants who were pregnant during the trial. Safety was assessed in all randomly assigned participants who were pregnant during the trial and exposed to at least one dose of trial drug. This study is registered with ClinicalTrials.gov, NCT03377699, and is now completed.
FINDINGS: Between Nov 22, 2017, and Nov 8, 2019, from 296 women screened, 225 women were randomly assigned to degludec (n=111) or detemir (n=114). Mean HbA_{1c} at pregnancy baseline was 6.6% (SD 0.6%; approximately 49 mmol/mol; SD 7 mmol/mol) in the degludec group and 6.5% (0.8%; approximately 48 mmol/mol; 9 mmol/mol) in the detemir group. Mean last planned HbA_{1c} measurement before delivery was 6.2% (SE 0.07%; approximately 45 mmol/mol; SE 0.8 mmol/mol) in the degludec group and 6.3% (SE 0.07%; approximately 46 mmol/mol; SE 0.8 mmol/mol) in the detemir group (estimated treatment difference -0.11% [95% CI -

0.31 to 0.08]; -1.2 mmol/mol [95% CI: -3.4 to 0.9]; p_{non-inferiority}<0.0001), confirming non-inferiority. Compared with detemir, no additional safety issues were observed with degludec.
INTERPRETATION: In pregnant women with type 1 diabetes, degludec was found to be non-inferior to detemir.
FUNDING: Novo Nordisk.

A Randomized Trial Evaluating the Efficacy and Safety of Fast-Acting Insulin Aspart Compared With Insulin Aspart, Both in Combination With Insulin Degludec With or Without Metformin, in Adults With Type 2 Diabetes (ONSET 9)[18]

OBJECTIVE: To evaluate the efficacy and safety of fast-acting insulin aspart (faster aspart) compared with insulin aspart (IAsp), both with insulin degludec with or without metformin, in adults with type 2 diabetes not optimally controlled with a basal-bolus regimen.
RESEARCH DESIGN AND METHODS: This multicenter, double-blind, treat-to-target trial randomized participants to faster aspart (n = 546) or IAsp (n = 545). All available information, regardless of treatment discontinuation or use of ancillary treatment, was used for evaluation of effect.
RESULTS: Noninferiority for the change from baseline in HbA_{1c} 16 weeks after randomization (primary end point) was confirmed for faster aspart versus IAsp (estimated treatment difference [ETD] -0.04% [95% CI -0.11; 0.03]; -0.39 mmol/mol [-1.15; 0.37]; P < 0.001). Faster aspart was superior to IAsp for change from baseline in 1-h postprandial glucose (PPG) increment using a meal test (ETD -0.40 mmol/L [-0.66; -0.14]; -7.23 mg/dL [-11.92; -2.55]; P = 0.001 for superiority). Change from baseline in self-measured 1-h PPG increment for the mean over all meals favored faster aspart (ETD -0.25 mmol/L [-0.42; -0.09]); -4.58 mg/dL [-7.59; -1.57]; P = 0.003). The overall rate of treatment-emergent severe or blood glucose (BG)-confirmed hypoglycemia was statistically significantly lower for faster aspart versus IAsp (estimated treatment ratio 0.81 [95% CI 0.68; 0.97]).
CONCLUSIONS: In combination with insulin degludec, faster aspart provided effective overall glycemic control, superior PPG control, and a lower rate of severe or BG-confirmed hypoglycemia versus IAsp in adults with type 2 diabetes not optimally controlled with a basal-bolus regimen.

Ultra rapid lispro improves postprandial glucose control compared with lispro in patients with type 1 diabetes: Results from the 26-week PRONTO-T1D study[19]

AIMS: To evaluate the efficacy and safety of ultra rapid lispro (URLi) versus lispro in adults with type 1 diabetes in a 26-week, treat-to-target, phase 3 trial. MATERIALS AND METHODS: After an 8-week lead-in to optimize basal insulin glargine or degludec, patients were randomized to double-blind mealtime URLi (n = 451) or lispro (n = 442), or open-label post-meal URLi (n = 329). The primary endpoint was change from baseline glycated haemoglobin (HbA1c) to 26 weeks (non-inferiority margin 0.4%), with multiplicity-adjusted objectives for postprandial glucose (PPG) excursions after a meal test. RESULTS: Both mealtime and post-meal URLi demonstrated non-inferiority to lispro for HbA1c: estimated treatment difference (ETD) for mealtime URLi -0.08% [95% confidence interval (CI) -0.16, 0.00] and for post-meal URLi +0.13% (95% CI 0.04, 0.22), with a significantly higher endpoint HbA1c for post-meal URLi versus lispro (P = 0.003). Mealtime URLi was superior to lispro in reducing 1- and 2-hour PPG excursions during the meal test: ETD -1.55 mmol/L (95% CI -1.96, -1.14) at 1 hour and - 1.73 mmol/L (95% CI -2.28, -1.18) at 2 hours (both P < 0.001). The rate and incidence of severe, documented and postprandial hypoglycaemia (<3.0 mmol/L) was similar between treatments, but mealtime URLi demonstrated a 37% lower rate in the period >4 hours after meals (P = 0.013). Injection site reactions were reported by 2.9% of patients on mealtime URLi, 2.4% on post-meal URLi, and 0.2% on lispro. Overall, the incidence of treatment-emergent adverse events was similar between treatments. CONCLUSIONS: The results showed that URLi provided good glycaemic control, with non-inferiority to lispro confirmed for both mealtime and post-meal URLi, while superior PPG control was demonstrated with mealtime dosing.

Randomized Double-Blind Clinical Trial Comparing Ultra Rapid Lispro With Lispro in a Basal-Bolus Regimen in Patients With Type 2 Diabetes: PRONTO-T2D[20]

OBJECTIVE: To evaluate the efficacy and safety of ultra rapid lispro (URLi) versus lispro in patients with type 2 diabetes on a basal-bolus insulin regimen.
RESEARCH DESIGN AND METHODS: This was a phase 3, treat-to-target, double-blind 26-week study. After an 8-week lead-in to optimize basal insulin glargine or degludec in combination with prandial lispro treatment, patients were randomized to blinded URLi (n = 336) or lispro (n = 337) injected 0-2 min prior to meals. Patients could continue metformin and/or a sodium-glucose cotransporter 2 inhibitor. The primary end point was change in HbA_{1c} from baseline to 26 weeks (noninferiority margin 0.4%), with multiplicity-adjusted objectives for postprandial glucose (PPG) excursions during a standardized meal test.

RESULTS: HbA_{1c} improved for both URLi and lispro, and noninferiority was confirmed: estimated treatment difference (ETD) 0.06% (95% CI -0.05; 0.16). Mean change in HbA_{1c} was -0.38% for URLi and -0.43% for lispro, with an end-of-treatment HbA_{1c} of 6.92% and 6.86%, respectively. URLi was superior to lispro in controlling 1- and 2-h PPG excursions: 1-h ETD, -0.66 mmol/L (95% CI -1.01, -0.30); 2-h ETD, -0.96 mmol/L (-1.41, -0.52). Significantly lower PPG excursions were evident from 0.5 to 4.0 h postmeal with URLi treatment. There were no significant treatment differences in rates of severe or documented hypoglycemia (<3.0 mmol/L). Incidence of overall treatment-emergent adverse events was similar between treatments.
CONCLUSIONS: URLi compared with lispro in a basal-bolus regimen was confirmed to be noninferior for HbA_{1c} and superior to lispro for PPG control in patients with type 2 diabetes.

Efficacy and safety of ultra-rapid lispro versus lispro in children and adolescents with type 1 diabetes: The PRONTO-Peds trial[21]

AIMS: To evaluate the efficacy and safety of ultra-rapid lispro (URLi) versus lispro in a paediatric population with type 1 diabetes (T1D) in a Phase 3, treat-to-target study.
MATERIALS AND METHODS: After a 4-week lead-in to optimize basal insulin, participants were randomized to double-blind URLi (n = 280) or lispro (n = 298) injected 0 to 2 minutes prior to meals (mealtime), or open-label URLi (n = 138) injected up to 20 minutes after start of meals (postmeal). Participants remained on pre-study basal insulin (degludec, detemir or glargine). The primary endpoint was glycated haemoglobin (HbA1c) change from baseline after 26 weeks (noninferiority margin 4.4 mmol/mol [0.4%]).
RESULTS: Both mealtime and postmeal URLi demonstrated noninferiority to lispro for HbA1c: estimated treatment difference (ETD) for mealtime URLi -0.23 mmol/mol (95% confidence interval [CI] -1.84, 1.39) and postmeal URLi -0.17 mmol/mol (95% CI -2.15, 1.81). Mealtime URLi reduced 1-hour postprandial glucose (PPG) daily mean (P = 0.001) and premeal to 1 hour postmeal PPG excursion daily mean (P < 0.001) versus lispro. The rate and incidence of severe, nocturnal or documented hypoglycaemia (<3.0 mmol/L [54 mg/dL]) were similar for all treatments. With mealtime URLi versus lispro, the rate of postdose hypoglycaemia (<3.0 mmol/L) was higher at </=2 hours (P = 0.034). The incidence of treatment-emergent adverse events was similar for all treatments. More participants reported an injection site reaction with mealtime URLi (7.9%) versus postmeal URLi (2.9%) and lispro (2.7%). CONCLUSIONS: In children and adolescents with T1D, URLi demonstrated good glycaemic control, and noninferiority to lispro in HbA1c change for mealtime and postmeal URLi. When dosed at the beginning of meals, URLi reduced 1-hour PPG and PPG excursions versus lispro.

Effect of insulin degludec versus insulin glargine U100 on time in range: SWITCH PRO, a crossover study of basal insulin-treated adults with type 2 diabetes and risk factors for hypoglycaemia[22]

AIMS: To compare time in range (TIR) with use of insulin degludec U100 (degludec) versus insulin glargine U100 (glargine U100) in people with type 2 diabetes.
MATERIALS AND METHODS: We conducted a randomized, crossover, multicentre trial comparing degludec and glargine U100 in basal insulin-treated adults with type 2 diabetes and >=1 hypoglycaemia risk factor. There were two treatment periods, each with 16-week titration and 2-week maintenance phases (with evaluation of glucose using blinded professional continuous glucose monitoring). The once-weekly titration (target: 3.9-5.0 mmol/L) was based on pre-breakfast self-measured blood glucose. The primary endpoint was percentage of TIR (3.9-10.0 mmol/L). Secondary endpoints included overall and nocturnal percentage of time in tight glycaemic range (3.9-7.8 mmol/L), and mean glycated haemoglobin (HbA1c) and glucose levels.
RESULTS: At baseline, participants (n = 498) had a mean (SD) age of 62.8 (9.8) years, a diabetes duration of 15.1 (7.7) years and an HbA1c level of 59.6 (11.0) mmol/mol (7.6 [1.0]%). Noninferiority and superiority were confirmed for degludec versus glargine U100 for the primary endpoint, with a mean TIR of 72.1% for degludec versus 70.7% for glargine U100 (estimated treatment difference [ETD] 1.43% [95% confidence interval (CI): 0.12, 2.74; P = 0.03] or 20.6 min/d). Overall time in tight glycaemic range favoured degludec versus glargine U100 (ETD 1.5% [95% CI: 0.15, 2.89] or 21.9 min/d). Degludec also reduced nocturnal time below range (TBR; <3.9 mmol/L) compared with glargine U100 (ETD -0.88% [95% CI: -1.34, -0.42] or 12.7 min/night; post hoc) and significantly fewer nocturnal hypoglycaemic episodes of <3.0 mmol/L were observed.
CONCLUSIONS: Degludec, compared with glargine U100, provided more TIR and time in tight glycaemic range, and reduced nocturnal TBR in insulin-treated people with type 2 diabetes.

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to November 20, 2023, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations November 10, 2023
Literature search repeated 5/6/24 using same search criteria and updated dates resulting in 179 additional articles; 178 were excluded and 1 systematic review was included in this literature scan.

☐	1	Insulin Aspart/	805
☐	2	Insulin Detemir/	589
☐	3	Insulin Glargine/	2273
☐	4	insulin glulisine.mp.	265
☐	5	Insulin Lispro/	971
☐	6	Insulin/	200189
☐	7	Insulin, Isophane/	1058
☐	8	insulin degludec.mp.	808
☐	9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	202404
☐	10	limit 9 to (english language and yr="2020 -Current")	15802
☐	11	limit 10 to humans	11542
☐	12	limit 11 to (adaptive clinical trial or clinical trial, phase iii or clinical trial, phase iv or comparative study or controlled clinical trial or "corrected and republished article" or equivalence trial or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	2181
☐	13	Diabetes Mellitus, Type 1/ or Diabetes, Gestational/ or Diabetes Mellitus/ or Diabetes Complications/ or Diabetes Mellitus, Type 2/	417414
☐	14	12 and 13	1354

Appendix 5: Key Inclusion Criteria

Population	Patients with type 1 or 2 diabetes mellitus, or gestational diabetes
Intervention	Insulins
Comparator	Other insulin products
Outcomes	Mortality, micro or 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 insulins
- Select preferred insulin pens (Novolin® 70/30 and Humulin® 70/30)

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. 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 #3
3. Is the request for an insulin pen or cartridge?	**Yes:** Go to #4	**No:** Approve for up to 12 months

Approval Criteria		
4. Has the patient tried and failed or have contraindications to any of the preferred pens or cartridges? Note: Documentation of trial and failure or contraindication to a long-acting or basal preferred product is required for non-preferred long-acting or basal insulin requests.	**Yes:** Go to #5	**No:** Pass to RPh; deny and recommend a trial of one of the preferred insulin products
5. 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

P&T / DUR Review: *6/24 (SF); 2/20(KS); 9/19; 11/18; 9/17; 3/16; 11/15; 9/10*
Implementation: *11/1/2019; 11/1/17; 10/13/16; 1/1/11*