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Drug Class Update with New Drug Evaluation: Insulins

Date of Review: October 2026

Date of Last Review: June 2024
Dates of Literature Search: 04/01/2024 - 06/19/2026
Brand Name (Manufacturer): Awiqli (Novo Nordisk)
Dossier Received: no

Generic Name: insulin icodec-abae

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

Purpose for Class Update:
Evaluate new evidence for the use of insulins published since the last review presented to the Pharmacy and Therapeutics (P&T) Committee in 2024. Evidence for the effectiveness and safety of a new insulin product, insulin icodec, will also be evaluated and presented.

Plain Language Summary:
- This review identifies new evidence for insulin medications used to treat people with type 1 diabetes (T1D) and type 2 diabetes (T2D).
- Insulin works by helping the body absorb glucose (sugar) from foods into muscle and fat so it can be used by the body. In people without diabetes, the body naturally produces enough insulin to absorb glucose from the things they eat or drink. In people with diabetes the body does not make enough insulin or use insulin as well as it should. Additional insulin is needed and given by a shot or by breathing it in through the mouth.
- If there is not enough insulin to keep glucose levels normal then conditions such as heart disease, vision loss, and kidney disease can occur due to excess sugar in the body.
- Insulin is available as basal, or long-acting, insulin which works over a long period of time and is usually given once a day or less often, twice a day. Other insulins work quickly, called bolus or prandial insulin, and they are given at or near mealtimes.
- Two high-quality guidelines, one from the Scottish Intercollegiate Guidelines Network and the other from the National Institute for Health and Care Excellence recommend the use of insulin in patients with T2D but do not recommend one over another.
- The American Diabetes Association recommends the use of basal and prandial insulin for patients with T1D but do not recommend any specific type of insulin.
- A guideline by the Scottish Intercollegiate Guidelines Network for people with diabetes who are also pregnant recommend insulin to reduce blood glucose levels.
- Three new insulins were approved for use. KIRSTY and MERILOG/MERIGLOG Solostar are new formulations that are biosimilar and interchangeable with insulin aspart. LANGLARA is a biosimilar and interchangeable with insulin glargine. A biosimilar means you can switch from the original product and expect comparable blood glucose control and safety.

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- A new long-acting insulin was approved for use which is called insulin icodec, brand name Awiqli. It is used once a week which is different than other insulins. It was found to work similar to insulin degludec and insulin glargine. The risk of very low blood sugars, also called hypoglycemia, was higher with insulin icodec compared to insulin degludec. Very low blood sugars are concerning because they can cause shakiness, sweating, headache, confusion and dizziness.
- The Drug Use Research and Management Group recommends that coverage for insulins continue without changes after reviewing the current evidence. Costs of insulin products should be reviewed in deciding preferred and non-preferred products.

Research Questions:

1. In patients with diabetes, what is the comparative evidence for efficacy or harms for insulins for important outcomes (e.g., hemoglobin A1c [HbA1C], microvascular outcomes, macrovascular outcomes and mortality)?
2. Are there subpopulations of patients with diabetes for which certain insulins may be more effective or associated with less harm?
3. What is the evidence for the effectiveness and harms of insulin icodec in patients with type 2 diabetes (T2D)?
4. Are there specific subpopulations for which insulin icodec may be specifically indicated, more effective, or associated with less harm?

Conclusions:

- There are 4 new guidelines, 3 new formulations, and one new drug review included in this class update.
- The Scottish Intercollegiate Guidelines Network (SIGN) updated guidance for the treatment of T2D. Recommendations for insulin use include the addition of NPH insulin to metformin as initial therapy or the use of basal insulin (high-quality evidence). Insulin choice should be based on hypoglycemia risk. Additional recommendations are presented below.[1]
- The National Institute for Health and Clinical Excellence (NICE) recommends the use of insulin for patients with T2D that are consistent with the current fee-for-service (FFS) policy.[2] No one particular insulin is preferred over another.
- The American Diabetes Association (ADA) recommends that patients with T1D should be treated with continuous subcutaneous insulin infusion or multiple daily doses of prandial and basal insulin (Grade A).[3] Patients with T2D should be managed with non-insulin agents initially if severe hyperglycemia is not present (Grade A).[3]
- A SIGN guideline on the management of diabetes in pregnancy recommends the use of metformin or insulin to manage glucose levels as first-line therapies.
- Three new formulations of biosimilar insulins were approved since the last review. KIRSTY (insulin aspart-xjhz) and MERILOG and MERIGLOG Solostar (insulin aspart-szjj) are biosimilars to insulin aspart and LANGLARA (insulin glargine-aldy) is a biosimilar to insulin glargine.[4,5,6]
- Insulin icodec, a new once-weekly formulation of insulin, was approved in March of 2026.[7] It was found to be noninferior to once-daily (OD) basal insulin comparators (insulin glargine and insulin degludec) in five trials, ONWARD 1-5.[8–12] Insulin icodec demonstrated statistically greater HbA1c reductions than once-daily basal insulin in four trials with a greater HbA1c treatment reduction of -0.16% to -0.22%. Hypoglycemia events were higher with insulin icodec compared to insulin degludec with a number needed to harm (NNH) of 10-32 over 26-52 weeks and compared to insulin glargine with a NNH of 50 over 26 weeks.[9,10]

Recommendations:

- No changes to the preferred drug list (PDL) are recommended based on review of the current evidence.
- Recommend that insulin icodec remain non-preferred on the PDL.

- After evaluation of costs at executive session: Aspart pens and vials were made preferred; Novolin N pen was made preferred; Humulin 70/30 Kwikpen, Humalog 75/25 Kwikpen, and Humalog Kwikpen 50/50 were made non-preferred.

Summary of Prior Reviews and Current Policy

- Previous review of the insulin class has not found evidence of significant differences in glucose lowering between long-acting insulin products or between short-acting products.
- The insulin class was reviewed in a literature scan in October of 2024. There were no changes to the PDL after review of the clinical evidence. After evaluation of costs in executive session, insulin levemir preparations, insulin aspart (NOVOLOG and generics) preparations, insulin glulisine (APIDRA) preparations, and insulin aspart mix (NOVOLOG mixes and generic) preparations were made non-preferred.
- Current PDL status of preferred and non-preferred products is available in **Appendix 1**. Non-preferred products are subject to prior authorization (PA).

Background:

Approximately 9.1% of Oregonians have been diagnosed with diabetes based on data from 2022.[13] Diabetes is prevalent in Oregon Health Plan (OHP) patients with 14.2% having the diagnosis.[13] Diabetes is a major cause of morbidity and mortality with diabetes being the eighth leading cause of death in Oregon in 2022.[13] Medical expenses are 2.3 times higher for people with diabetes compared to those who do not have the disease.[14]

The ADA recommends an HbA1c goal of less than 7.0% for most adults with diabetes.[15] Obtaining target glucose levels are important in reducing the risk of macrovascular and microvascular complications. Insulins are important and highly effective pharmacotherapy used in the management of both T1D and T2D. In patients with T1D the destruction of pancreatic beta-cells results in the need for lifelong insulin replacement. Management usually consists of multiple daily injections of basal and rapid acting insulin analogs or use of continuous subcutaneous insulin infusion. Hyperglycemia in patients with T2D is the result of insulin resistance and impaired insulin secretion. While evidence has shown the importance of lifestyle modifications, such as diet and exercise changes, antidiabetic treatments are necessary to reduce glucose levels in most patients with T2D.[3] Most patients with T2D are started on oral therapy but over time, commonly 11-15 years after diagnosis, insulin is needed to obtain glucose targets. The standard of care for most patients is to continue oral or injectable non-insulin anti-diabetic medications when adding insulin to facilitate goal HbA1c.[3] Some glucose-lowering medication doses may need to be reduced, or discontinued, to prevent hypoglycemia.

Important outcomes in patients with diabetes are reducing the risk of microvascular and macrovascular complications, mortality, HbA1c reduction, severe adverse events and hypoglycemia. Hemoglobin A1C reduction is often used as a surrogate marker to assess comparative efficacy of different antidiabetic therapies, as hyperglycemia is associated with increased microvascular complications, and possibly macrovascular outcomes as well. A clinically relevant change in HbA1c is considered to be 0.3% or more.[16] Available data for most new drugs are limited to short-term studies, which prevents the assessment of the durability of most antidiabetic treatments to control glucose levels long-term.

The insulin class represents a modest spend to the OHA with over 600 claims for Quarter 2 of 2026. There is a slightly higher spend for short-acting insulin products compared to long and intermediate acting insulins.

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), NICE, Department of Veterans Affairs, Canada's Drug Agency (CDA-AMA), and the SIGN 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.

Systematic Reviews:
No high-quality systematic reviews were identified.

After review, 6 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:
High-Quality Guidelines:

<u>SIGN – Pharmacological Management of Glycemia Control in People with T2DM</u>
A revised edition of SIGN recommendations for glucose lowering treatments for people with T2DM was issued in 2024 to update the original 2017 publication.[1] Accreditation of the guideline process used by SIGN is endorsed by NICE. Recommendations are graded from High-quality (1++) down to Expert opinion (4) based on type and quality of evidence.[1] Recommendations pertaining to insulin therapies will be presented. All recommendations are in addition to lifestyle measures and consistent with other guidelines. SIGN recommends the HbA1c goal should be 7.0% for most people with T2D.[1]

Recommendations:
- Bedtime NPH should be used when adding insulin to metformin. The type of basal insulin analogue should be based on hypoglycemia risk (i.e., those who suffer from recurrent episodes of hypoglycemia or require assistance with insulin injections) (1+ to 1++).[1]
- Bedtime basal insulin should be initiated, dosed and titrated based on morning (fasting) glucose, when initiating insulin therapy (1+ to 1++). Additional prandial insulin should be started if HbA1c does not meet target levels.[1]
- To improve or maintain target glucose levels, soluble human insulin or rapid-acting insulin analogues can be used when intensifying insulin regimens (1+).[1]

<u>NICE – Type 2 Diabetes Management</u>
Guidelines for T2D management in adults from NICE was updated February 2026.[2] Recommendations regarding the use of non-insulin therapy are presented elsewhere. The use of insulin in people with T2D will be presented.

Recommendations:[2]
- When initiating insulin in patients with T2D continue metformin if the individual is already taking it.
- Other diabetes lowering medication used for glucose control alone should be discontinued.

- The risks and benefits of continuing other medications for the benefit of cardiovascular (CV) protection or weight management should be discussed with benefits and risks of therapy.
- Basal insulin is recommended for once or twice daily use in those initiating insulin.
- Consider insulin as an initial therapy in those presenting with an HbA1c of 9.0% or greater. Consider combining basal insulin once or twice daily and short or rapid acting insulin (given separately or as a biphasic insulin).
- Insulin choice should be based on the following considerations:
    - Need for assistance when using insulin
    - Concern over nocturnal hypoglycemia
    - Preference for once-daily injections
- Cost should be considered when multiple basal type insulins are appropriate.
- Pre-mixed insulins should be considered that include insulin analogues compared to human insulin if the patient prefers injecting insulin immediately before a meal, issues with hypoglycemia, or blood glucoses rise considerably after a meal.
- Consider need for short or rapid acting insulin before meals for those on a basal insulin regimen.
- Consider alternate insulin regimens if glucose targets are not being met.

ADA – Standards of Care in Diabetes 2026

The ADA updates recommendations for standards of care for the management of diabetes on an annual basis.[3] Recommendations are graded from A to E, with A having the highest quality of evidence for support and E are recommendations based on expert opinion. Recommendations regarding insulin drug treatment will be presented.

The guidelines recommend that most adults with T1D should be treated with continuous subcutaneous insulin infusion (CSII) or multiple daily doses of prandial and basil insulin (Grade A).[3] Insulin analogs or inhaled insulin are recommended over injectable human insulin to minimize the risk of hypoglycemia (Grade A). Mealtime insulin doses should be matched to individual carbohydrate, fat and protein consumption (Grade B).[3] Glycemic goals and insulin needs and behaviors should be reassessed every 3-6 months.

In patients with T2D glucagon-like peptide-1 receptor agonists (GLP-1 RA) are preferred over insulin if the patient does not have severe hyperglycemia or hyperglycemia crisis (Grade A).[3] If insulin is initiated in patients with T2D glucose-lowering therapy should be continued (Grade A). In patients with T1D or T2D, automated insulin delivery systems should be offered if they are taking insulin (Grade A).[3]

SIGN –Management of Diabetes in Pregnancy

A 2024 guideline was published by SIGN outlined treatment and management of women with T1D and T2D during pregnancy.[17] Recommendations were considered ‘strong’ by being described as ‘should’ be used while ‘conditional’ recommendations are described as ‘considered’.[17] Recommendations for insulin therapy will be included.

Pregnant women who require insulin may benefit from continuous glucose monitoring and insulin delivery via a pump.[17] The guideline recommends that women with T1D have access to continuous glucose monitoring (CGM) as achieving glucose targets has been associated with improved outcomes, such as reduction in hypertensive disorders and diabetes-related distress (high-quality evidence).[17]

In women who have T2D, the use of DPP-4 inhibitors, GLP-1 agonists, SGLT-2 inhibitors, sulfonylureas, and thiazolidinedione (TZD) should be avoided during pregnancy. There were no differences noted between outcomes with the use of metformin compared to insulin, based on expert opinion.[17] The guidelines recommend that women with gestational diabetes should be offered metformin or insulin first-line.[17]

New Formulations or Indications:

New Formulations:

KIRSTY (insulin aspart-XJHZ): A new formulation of insulin aspart was approved in July of 2025 as insulin apart-xjhz.[4] It is the biosimilar and interchangeable with insulin aspart. The new formulation comes in multi-dose vial (100 units/mL) for intravenous (IV) or SC use and single-patient-use prefilled pen (100 units/mL) for SC use. The approved use for KIRSTY is as a rapid acting insulin analog indicated for glycemic control in adults and pediatric patients with diabetes.[4]

MERILOG and MERIGLOG Solostar (insulin aspart-szjj): MERILOG (10 mL multiple-dose vial) and MERILOG Solostar (3 mL single-patient use prefilled pens) were approved in February 2025.[5] Both the vial and pen contain 100 units/mL (U-100) of insulin aspart. Insulin aspart-szjj is a biosimilar to insulin aspart approved to improve glycemic control in adults and pediatric patients with DM.

LANGLARA (insulin glargine-aldy): A new biosimilar to insulin glargine was approved in April of 2026 to improve glycemic control in adult and pediatric populations with diabetes.[6] Insulin glargine-aldy was approved based on evidence that it is highly similar to the reference product, insulin glargine.

New FDA Safety Alerts:

Table 1. 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 glargine/lixisenatide[18]	SOLIQUA 100/33	March 2026	Warnings and Precautions	Severe gastrointestinal reactions have been reported with GLP-1 RAs.
		November 2024	Warnings and Precautions	Serious risk of pulmonary aspiration for patients undergoing elective surgery or procedures requiring general anesthesia or deep sedation.
Insulin lispro[19]	HUMALOG	May 2025	Warnings and Precautions	Do not transfer insulin lispro U-200 from the insulin lispro prefilled pens to a syringe as the doses are not equivalent and can result in overdosage and severe hypoglycemia.
Insulin degludec/liraglutide[20]	XULTOPHY 100/3.6	October 2025	Warnings and Precautions	Acute pancreatitis has been observed with GLP-1 RAs.
			Adverse Reactions	Severe gastrointestinal adverse reactions, including some severe, have been reported.
		November 2024	Warnings and Precautions	Serious risk of pulmonary aspiration for patients undergoing elective surgery or procedures requiring

				general anesthesia or deep sedation who had residual gastric contents.
Abbreviations: GLP-1 RAs = glucagon-like peptide-1 receptor agonist				

Randomized Controlled Trials:
A total of 81 citations were manually reviewed from the initial literature search. After further review, all 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), except for the RCTs included in the new drug review.

NEW DRUG EVALUATION:

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations. Pharmacology and pharmacokinetic properties are listed in **Appendix 5**.

Clinical Efficacy:
Insulin icodec is long-acting insulin indicated as an adjunct to diet and exercise to improve blood glucose control in patients with T2D.[7] Insulin icodec is administered once-weekly on the same day of the week. The recommended starting dose is 70 units subcutaneously in insulin naïve patients. The maximum plasma concentration is at approximately 16 hours after administration with a peak effect on days 2-4 of the weekly dosing interval.[21] The half-life is approximately 196 hours.

Approval of insulin icodec was based on 4 open-label, treat to target, active controlled, RCTs and one double-blind RCT (ONWARD 1-5)(**Table 2**).[8–12] Insulin icodec was compared to two basal insulin comparators, insulin glargine and insulin degludec. Insulin icodec was found to be noninferior to basal insulin based on an upper bound of 95% confidence interval < 0.3% noninferiority margin in all 5 trials for the primary outcome of HbA1c lowering at week 26 or 52.[21] Insulin icodec was found to be statistically superior to comparator basal insulin for HbA1c reduction in ONWARD trials 1-3 with a treatment difference of -0.16% to -0.22%.[21]

In ONWARDS-1 insulin icodec once weekly was compared to insulin glargine U100 daily in a treat to target, non-inferiority (NI), open-label (OL) design lasting 52 weeks (main phase) with 26-week follow-up (extension phase).[8] Patients were adults with T2D with no prior insulin use. The mean age was 59 years, mean body mass index (BMI) of 30 and mean HbA1c of 8.5%. Participants were on non-insulin lowering therapy at screening including metformin, SGLT-2 inhibitors, GLP-1 RAs and sulfonylureas. Sulfonylureas and glinides were discontinued upon randomization, due to risk of hypoglycemia when combined with insulin, and all other glucose lowering therapies were continued. Titrations were based on pre-breakfast fasting self-monitoring blood glucose (SMBG) with a target of 80-130 mg/dL. The primary outcome was the change in HbA1c from baseline at 52 weeks. Insulin icodec was NI and superior to insulin glargine with HbA1c changes of -1.55% vs. -1.35%, respectively (**Table 2**).[8]

A second trial, ONWARDS-2 was a 26-week NI, OL, RCT comparing once-weekly insulin icodec to insulin degludec once-daily.[9] Patients with T2D were inadequately controlled on once or twice-daily basal insulin for study inclusion. Patients had a mean age of 63 years, HbA1c of 8.13%, and mean diabetes duration of 17 years. The most common insulin use at baseline was insulin glargine and insulin degludec U100. Insulin was titrated weekly to achieve a pre-breakfast target glucose of 80-130 mg/dL.[9] The most common non-insulin anti-diabetic therapies used were metformin, SGLT-2 inhibitors, and GLP-1 RAs. Insulin

icodec was noninferior and superior to insulin degludec for the primary endpoint of change in HbA1c from baseline at 26 weeks (estimated treatment difference [ETD] -0.22; 95% confidence interval [CI], -0.37 to -0.08).[9] More patients taking insulin icodec obtained an HbA1c of <7.0% compared to insulin degludec, 40% and 26%, respectively.[9]

ONWARDS-3 was a double-blind, NI, 26-week RCT comparing once weekly insulin icodec with daily placebo injection with daily insulin degludec with weekly placebo injections.[10] There were 588 patients included that had T2D, a mean BMI of 29 kg/m^2 and mean age of 59 years old. Patients eligible for enrollment had to have no prior insulin use but non-insulin treatment at baseline was permitted and continued through the study duration. There was a higher number of patients in the insulin icodec group on non-insulin oral therapies, such as SGLT-2 inhibitors and GLP-1 RAs.[10] Titrations were based on mean prebreakfast fasting SMBG with a target of 80-130 mg/dL The primary outcome was change in HbA1c from baseline with a non-inferiority margin set at 0.3%.[10] Insulin icodec was found to be noninferior and superior in HbA1c reduction at 26 weeks compared to insulin degludec ETD -0.2 (95% CI, -0.3 to -0.1; p= 0.001 for noninferiority and p=0.002 for superiority).[10]

A fourth trial, ONWARDS-4, was an open-label, multi-center, noninferiority trial in patients with T2D on a basal-bolus regimen at baseline.[11] Patients were randomized to weekly insulin icodec plus 2-4 daily injections of insulin aspart compared to once-daily insulin glargine U100 plus 2-4 daily injections of insulin aspart. Pre-trial non-insulin glucose lowering meds were continued throughout the trial, except sulfonylureas, which were discontinued due to risk of hypoglycemia. Insulin was titrated from week 2 on to attain a pre-breakfast SMBG value of 80-130 mg/dL.[11] Aspart doses were based on pre-prandial SMBG and bedtime SMBG values measure on the previous 3 days before titration. The primary outcome was change in HbA1c from baseline with a non-inferiority margin set at 0.3%. Insulin icodec + aspart was found to be noninferior to insulin glargine + aspart (ETD -0.82; 95% CI, -0.58 to -1.17; p<0.001).[11] Groups were similar in the percent of patients obtaining an HbA1c <7% at week 26 (estimated odds ratio [EOR] 0.82; 95% CI, 0.58 to 1.17; p = 0.27).[11]

The ONWARDS-5 trial was an open-label, phase 3a, RCT in which patients with T2D were randomized to insulin icodec with dose titration via an app compared to OD analogue dosing of degludec, glargine U100 or glargine U300 as recommended via labeling.[12] The dosing guide application (app) used with insulin icodec provided automated dose guidance for participants via a dedicated study phone with a locked operating system. Health care providers were able to view and adjust dose recommendations. Patients randomized to OD insulin analogues had doses titrated based on standards of practice. Glucoses were tracked via SMBGs measured prebreakfast.[12] The primary endpoint was change in HbA1c from baseline at week 52. The noninferiority margin was set at 0.3%. Secondary endpoints were patient recorded outcomes based on 2 validated scales: Treatment Related Impact Measure for Diabetes (TRIM-D) and compliance score determined by the change in Diabetes Treatment Satisfaction Questionnaire (DTSQ) score.[12] Insulin icodec was noninferior (p<0.001) and superior (P = 0.009) to OD insulin (ETD -0.38; 95% CI, -0.66 to -0.09).[12] Patient reported outcomes for the TRIM-D and DTSQ also favored insulin icodec over OD insulin.[12] This trial was not included in the labeling due to the confounded effect of the use of the app to manage dosage titrations.[21]

In a separate RCT in patients with T1D, insulin icodec was compared to once-daily insulin degludec.[22] Insulin icodec was found be NI to insulin degludec; however, insulin icodec had approximately 50% higher incidence of clinically significant hypoglycemia or severe hypoglycemia. For this reason, approval was not extended to patients with T1D.

Clinical Safety:

The most common adverse effect associated with the use of insulin icodec was hypoglycemia, hypersensitivity reactions (i.e., urticaria and swelling of the face and lips), injection site reactions, lipodystrophy, pruritus, rash, edema and weight gain.[7] There is a warning of the risk of hypoglycemia with the use of icodec due to medication-errors if mistaken for another insulin product and/or changes in insulin regimen. Severe adverse reactions such as anaphylaxis can occur.[7]

Hypokalemia and fluid retention and heart failure (HF) with concomitant use of TZDs may occur. The use of Awiqli FlexTouch pens should never be shared between patients.

In trials the risk of level 2 hypoglycemia (plasma glucose < 54 mg/dL) and level 3 hypoglycemia (severe cognitive impairment requiring external assistance for recovery) were higher for insulin icodec compared to basal insulin but overall numbers were low and safety was considered comparable to basal insulins.[21] The risk of deaths, serious adverse events and discontinuations due to adverse events were similar between groups.[21]

The use of insulin icodec has not been studied in patients that are pregnant. Use of insulin icodec beyond 52 weeks is unknown and evidence of long-term use would be helpful since T2D is a chronic condition.

Look-alike / Sound-alike Error Risk Potential: None identified

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) HbA1c lowering
2) Mortality
3) Microvascular and macrovascular complications
4) Serious adverse events (e.g., hypoglycemia)

Primary Study Endpoint:
1) Change in HbA1c from baseline at 26 and 52 weeks

Table 2. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1.Rosenstock, et al[8] (ONWARDS-1) MC, NI, OL, Phase 3a, RCT, TTT	1. Insulin icodec once weekly treat to target* 2. Insulin glargine U100 once daily treat to target* * Doses were adjusted to enable participants to reach prebreakfast self-measured blood glucoses of 80-130 mg/dL	Demographics: Male: 56.5% Mean age: 59 years Mean BMI: 30 Mean HbA1c: 8.50% Mean diabetes duration: 11.5 years GLP-1 RA use: 17.8% SGLT-2 use: 36.5% Metformin use: 90% Key Inclusion Criteria: - Adults 18 years of age and older - T2D - HbA1c 7-11% - No prior insulin use	ITT: 1. 492 2. 492 PP: 1. 475 2. 479 Attrition: 1. 17 (4%) 2. 13 (3%)	Primary Endpoint: Change in HbA1c from baseline to week 52: 1. -1.55% 2. -1.35% ETD -0.19% (95% CI, -0.36 to -0.03) Noninferiority; P<0.001 Superiority P=0.02 Secondary Endpoint: Time spent in in glycemic range 70-180 mg/dL in weeks 48 to 52: 1. 71.9% 2. 66.9% ETD 4.27 (95 % CI, 1.92 to 6.62)	NA for all	Clinically Significant Hypoglycemia: 1. 48 (9%) 2. 49 (10.0%) Severe Hypoglycemia: 1. 1 (0.2%) 2. 3 (0.6%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) Participants assigned in 1:1 ratio via an interactive web-response system. More females were in the insulin glargine group. Performance Bias: (high) Medication was administered in prefilled pen injectors. Insulin treatment was not blinded which may influence patient management. Detection Bias: (unclear) All analysis was done by manufacturer. Attrition Bias: (low) Low attrition in both groups. Reporting Bias: (low) Trial was conducted as reported and outcomes were prespecified, Other Bias: (unclear) Funded by manufacturer. **Applicability**:

	Duration: 52 weeks	- BMI 40 or less Key Exclusion Criteria: - Pregnant or breastfeeding - MI, stroke or unstable angina within 180 days - Treatment for T2D or obesity not stated as allowed inclusion criteria		P<0.001				Patient: Patients are representative of patients with T2D. The use of non-insulin hypoglycemic therapies is common and appropriate in this population. An 11-year history of diabetes is typical before needing insulin. Intervention: Based on prior studies the starting dose of insulin icodec is appropriate. Comparator: Insulin glargine is a long-acting insulin that is widely used is an appropriate comparator. Outcomes: HbA1c and time spent in glucose range of 70-180 mg/dL are appropriate outcomes. Setting: Conducted in 123 sites in 12 countries.
2. Philis-Tsimikas, et al[10] (ONWARDS-2) MC, NI, OL, Phase 3a, RCT	1. Insulin icodec once weekly treat to target* 2. Insulin degludec once-daily Duration: 26 weeks	Demographics: Male: 57% Mean age: 63 years Mean BMI: 29 kg/m^2 Mean HbA1c: 8.13% Mean diabetes duration: 17 years White: 57% Asian: 37% Insulin glargine U100: 42% Insulin degludec: 28% Insulin glargine U300: 16% Metformin: 84% SGLT2 inhibitor: 33% GLP-1 RA: 26% Key Inclusion Criteria: - T2D - HbA1c 7.0-10% - Inadequately controlled on once- or twice-daily basal insulin	ITT: 1. 263 2. 263 PP: 1. 256 2. 253 Attrition: 1. 7 (3%) 2. 10 (4%)	Primary Endpoint: Change in HbA1c from baseline to week 26: 1. -0.93 2. -0.71 ETD -0.22 (95% CI, -0.37 to -0.08) P<0.001 for noninferiority P=0.0028 for superiority Secondary Endpoints: Participants obtaining an HbA1c of less than 7%: 1. 105 (40%) 2. 68 (26%) EOR 1.88 (95% CI, 1.26 to 2.79) P=0.0019 Mean change in body weight from baseline to week 26: 1. 1.40 kg 2. -0.30 kg TD 1.70 (95% CI, 0.76 to 2.63) P=0.0004	NA ARR 14/ NNH 7	Hypoglycemia (level 1 -blood glucose ≥54 mg/dL and <70 mg/dL): 1. 145 (55%) 2. 118 (45%) ERR 1.88 (95% CI, 1.34 to 2.63) P=0.0002 Clinically significant hypoglycemia (level 2 - <54 mg/dL): 1. 37 (14%) 2. 19 (7%) ERR 1.98 (95% CI, 0.95 to 4.12) P=0.067 Serious adverse events: 1. 22 (8%) 2. 16 (6%) ERR 1.98 (95% CI, 0.95 to 4.12) P=0.067	ARR 10/ NNH 10	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) Randomized 1:1 via a centrally randomized using an interactive web response system. Performance Bias: (high) Insulin treatment was not blinded which may influence patient management. Detection Bias: (high) All analysis was done by manufacturer. Attrition Bias: (low) Attrition was low in both groups. Reporting Bias: (low) Trial was conducted as reported. Other Bias: (unclear) Funded by the manufacturer. **Applicability**: Patient: Patients were representative of people with T2D. Intervention: Based on prior studies the starting dose of insulin icodec is appropriate. Comparator: Insulin degludec is a long-acting insulin that is widely used is an appropriate comparator. Outcomes: HbA1c is an appropriate outcome. Setting: Seventy-one sites in 9 countries.

		- With or without non-insulin glucose-lowering agents (e.g., metformin, SU, meglitinides, DPP-4s, TZDs, SGLT2s, alpha-glucosidase inhibitors, GLP-1 RAs - BMI ≤40 kg/m^2 Key Exclusion Criteria: - Pregnant or breastfeeding - Chronic renal or cardiac disease - Treatment with antidiabetic agents not included above						
3. Lingvay, et al[9] (ONWARDS-3) DB, MC, NI, Phase 3a, RCT	1. Insulin icodec once weekly (70 U starting) +placebo injection once-daily 2. Insulin degludec once daily (10 U starting) + once-weekly placebo injection Duration: 26 weeks	Demographics: Male: 63% Mean age: 59 years Mean BMI: 29 kg/m^2 Mean HbA1c: 8.5% Mean diabetes duration: 11 years White: 60% Asian: 28% Metformin: 90% SGLT2 inhibitor: 36% GLP-1 RA: 19% Key Inclusion Criteria: - T2D - HbA1c 7.0-11% - No prior insulin use	ITT: 1. 291 2. 291 PP: 1. 281 2. 283 Attrition: 1. 13 (4%) 2. 11 (4%)	Primary Endpoint: Change in HbA1c from baseline to week 26: 1. -1.6% 2. -1.4% ETD -0.2 (95% CI, -0.3 to -0.1) P<0.001 for noninferiority P=0.002 for superiority Secondary Endpoint: Mean change in body weight from baseline to week 26: 1. 2.8 kg 2. 2.3 kg ETD 0.46 (95% CI, -0.19 to 1.10) P=0.17	NA for all	Hypoglycemia (level 2): 1. 24 (8.9%) 2. 17 (5.8%) ERR 3.12 (95% CI, 1.30 to 7.51) P=0.01 Clinically significant hypoglycemia (level 2 or 3): 1. 24 (8.2%) 2. 13 (4.4%) ERR 3.12 (95% CI, 1.3 to 7.51) P=0.01 Severe adverse events: 1. 14 (4.4%) 2. 4 (1.4%)	ARR 3.1/NNH 32 ARR 3.8/NNH 26	**Risk of Bias (low/high/unclear)**: Selection Bias: (high) Randomized 1:1 via a centrally randomized using an interactive web response system. A higher percentage of participants in the insulin icodec were on oral agents, specifically SGLT-2 inhibitors and GLP-1 RAs, compared to insulin degludec. Performance Bias: (low) Treatments were given via a pen device using a double dummy design. Trial was described as double blind but no details were given. Detection Bias: (Unclear) Not described. Attrition Bias: (low) Attrition was low in both groups. Reporting Bias: (low) Trial was conducted as reported. Other Bias: (unclear) Funded by manufacturer. **Applicability**: Patient: Patients were representative of people with T2D. Many patients also had HTN (65%) and other comorbidities as well as use of common non-insulin therapies to manage glucose levels.

		Key Exclusion Criteria: - Pregnant or breastfeeding - Participation in a clinical trial within previous 90 days - History of DKA within previous 90 days - MI, stroke or hospitalization for unstable angina within the previous 180 days CHF Class IV at screening - Impaired renal or liver function				ERR 1.98 (95% CI, 0.95 to 4.12) P-value not provided Injection site reactions: 1. 25 (8.5%) 2, 13 (4.4%)		Intervention: Based on prior studies the starting dose of insulin icodec is appropriate. Comparator: Insulin degludec is a long-acting insulin that is widely used is an appropriate comparator. Outcomes: HbA1c is an appropriate outcome. Setting: Conducted in 11 countries and 92 sites.
4. Mathieu, et al[11] (ONWARDS-4) MC, NI, OL, Phase 3a, RCT	1. Insulin icodec once weekly plus 2-4 daily bolus insulin aspart injections 2. Insulin glargine U100 once-daily plus 2-4 daily bolus insulin aspart injections Duration: 26 weeks	Demographics: Male: 53% Mean age: 59 years Mean BMI: 30 kg/m^2 Mean HbA1c: 8.3% Mean diabetes duration: 17 years Total daily insulin dose: 68 U Metformin: 66% SGLT2 inhibitor: 29% GLP-1 RA: 13% Key Inclusion Criteria: - T2D - ≥ 18 years - HbA1c 7-10% - Use of a basal-bolus regimen (once-daily injections of basal insulin and 2-4	ITT: 1. 291 2. 291 PP: 1. 274 2. 269 Attrition: 1. 17 (6%) 2. 22 (8%)	Primary Endpoint: Change in HbA1c from baseline to week 26: 1. - 1.16% 2. -1.18% ETD -0.02 (95% CI, -0.11 to 0.15) P<0.0001 for noninferiority Secondary Endpoint: Participants obtaining an HbA1c of less than 7%: 1. 41% 2. 45% EOR 0.82 (95% CI, -0.52 to 2.79) P=0.27	NA NS	Hypoglycemia (level 1): 1. 244 (84%) 2. 251 (86%) ERR 1.25 (95% CI, 1.03 to 1.52) P=0.025 Clinically significant hypoglycemia (level 2): 1. 54 (19%) 2. 71 (24%) ERR 0.74 (95% CI, 0.47 to 1.15) P=0.18 Serious adverse events: 1. 13 (4%) 2. 12 (4%) P = NR	ARR 2/ NNH 50 NS	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Randomized 1:1 via a centrally randomized using an interactive web response system. The icodec group had a slightly longer duration of diabetes (1.7 years longer) and higher bodyweight (2.4 kg higher). Performance Bias: (Low) Masked continuous glucose monitoring. Detection Bias: (High) All analysis was done by manufacturer. Attrition Bias: (Low) Attrition was low in both groups. Reporting Bias: (Low) Trial was conducted as reported. Other Bias: (Unclear) Funded by the manufacturer. **Applicability**: Patient: The patient population is representative of individuals requiring long-acting insulin to manage their diabetes. Additional information on comorbidities would be helpful to extrapolate results. Intervention: Based on prior studies the starting dose of insulin icodec is appropriate.

		injections daily of bolus insulin) - With or without non-insulin glucose-lowering agents (e.g., metformin, SU, meglitinides, DPP-4s, TZDs, SGLT2s, alpha-glucosidase inhibitors, GLP-1 RAs) Key Exclusion Criteria: - Pregnant or breastfeeding - Treatment for diabetic ketoacidosis within 90 days prior to screening - Chronic renal or cardiac disease						Comparator: Based on phase 2 trials demonstrating similar glucose lowering effect as glargine U100. Outcomes: HbA1c is an appropriate outcome. Setting: Eighty sites from 9 countries.
4. Bajaj H, et al (ONWARDS-5) MC, OL, PG, Phase 3a, RCT	1. Insulin icodec once weekly + app 2. Use of once-daily basal insulin analogue (OD) (insulin degludec, insulin glargine U100 or insulin glargine U300) Duration: 52 weeks	Demographics: Male: 58% Mean age: 59 years Mean BMI: 33 kg/m^2 Mean HbA1c: 8.9% Mean diabetes duration: 12 years Metformin: 92% SGLT2 inhibitor: 43% GLP-1 RA: 28% HTN: 75% Coronary artery disease: 8.5% Key Inclusion Criteria: - T2D - ≥ 18 years	ITT: 1. 542 2. 543 PP: 1. 483 2. 493 Attrition: 1. 59 (11%) 2. 50 (9%)	Primary Endpoint: Change in HbA1c from baseline to week 52: 1.- 1.68% 2. -1.31% ETD -0.38 (95% CI, -0.66 to -0.09) P<0.001 for noninferiority P = 0.009 for superiority Secondary Endpoints: Treatment Related Measure for Diabetes [TRIM-D] scores: 1. 4.68 points 2. 3.90 points ETD 0.78 (95% CI, 0.10 to 1.47) p-value not provided	NA for all	Hypoglycemia: 1. 200 (37%) 2. 153 (28%) Clinically significant hypoglycemia (< 54 mg/dL): 1. 64 (11.8%) 2. 42 (7.8%) Serious Adverse Events: 1. 45 (8.3%) 2. 57 (10.6%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Randomized 1:1. Patients were randomized using an interactive web response system. Baseline characteristics were well matched. Insulin degludec was the most commonly (70%) assigned insulin in the OD analogue group. Performance Bias: (High) Differences in glucose titration management could influence goal HbA1c obtainment. Open-label study design may influence how patients were managed. Detection Bias: (High) All analysis was done by manufacturer. Attrition Bias: (Low) Attrition was low in both groups; however, slightly higher in the insulin icodec group. Reporting Bias: (Low) Trial was conducted as reported. Other Bias: (Unclear) Funded by the manufacturer.

		- HbA1c > 7% - Insulin naïve but required insulin initiation - With or without non-insulin glucose-lowering agents (e.g., metformin, SU, meglitinides, DPP-4s, TZDs, SGLT2s, alpha-glucosidase inhibitors, GLP-1 RAs) on stable doses Key Exclusion Criteria: - Pregnant or breastfeeding - Any disorder that may jeopardize a patient's safety		Diabetes Treatment Satisfaction Questionnaire [DTSQ] score: 1. 90.42 2. 87.37 ETD 3.04 (95% CI, 1.28 to 4.81) p-value not provided				**Applicability**: Patient: The patient population is representative of individuals requiring long-acting insulin to manage their diabetes. Clinic visits every 3 months mimic clinical practice. Intervention: Based on prior studies the starting vb. Setting: Seven countries and 176 sites.
Abbreviations: ARR = absolute risk reduction; CHF = congestive heart failure; CI = confidence interval; DKA = diabetic ketoacidosis; DPP-4 = dipeptidyl pepdidase-4; ERR = estimated rate ratio; ETD = estimated treatment difference; EOR = estimated odds ratio; GLP-1 RAs= glucagon-1 peptide -1; ITT = intention to treat; MI = myocardial infarction; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NI = noninferiority; NNT = number needed to treat; NR = not reported; NS = not significant; OD = once daily; PG = parallel group; PP = per protocol; RCT = randomized controlled trial; SGLT-2 = sodium-glucose co-transporter 2; SU = sulfonylurea; T2D = type 2 diabetes; TD = treatment difference; TTT = treat to target; TZD = thiazolidinedione.								

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6. Langlara (insulin glargine-aldy) [prescribing information]. Philadelphia, PA; Lannett Company, Inc. April 2026.

7. Awiqli (insulin icodec-abae)[prescribing information]. Plainsboro, NJ; Novo Nordisk Inc. March 2026.

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19. Humalog (insulin lispro)[prescribing information]. Indianapolis, IN; Eli Lilly and Company. May 2025.

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL
insulin glargine,hum.rec.anlog	LANTUS SOLOSTAR	INSULN PEN	SQ	Y
insulin glargine,hum.rec.anlog	LANTUS	VIAL	SQ	Y
insulin lispro	HUMALOG	CARTRIDGE	SQ	Y
insulin lispro	HUMALOG JUNIOR KWIKPEN	INS PEN HF	SQ	Y
insulin lispro	INSULIN LISPRO JUNIOR KWIKPEN	INS PEN HF	SQ	Y
insulin lispro	HUMALOG KWIKPEN U-100	INSULN PEN	SQ	Y
insulin lispro	HUMALOG KWIKPEN U-200	INSULN PEN	SQ	Y
insulin lispro	HUMALOG TEMPO PEN U-100	INSULN PEN	SQ	Y
insulin lispro	INSULIN LISPRO KWIKPEN U-100	INSULN PEN	SQ	Y
insulin lispro	HUMALOG	VIAL	SQ	Y
insulin lispro	INSULIN LISPRO	VIAL	SQ	Y
insulin lispro protamin/lispro	HUMALOG MIX 50-50 KWIKPEN	INSULN PEN	SQ	Y
insulin lispro protamin/lispro	HUMALOG MIX 75-25 KWIKPEN	INSULN PEN	SQ	Y
insulin lispro protamin/lispro	INSULIN LISPRO PROTAMINE MIX	INSULN PEN	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 U-500 KWIKPEN	INSULN PEN	SQ	Y

insulin regular, human	HUMULIN R	VIAL	IJ	Y
insulin regular, human	NOVOLIN R	VIAL	IJ	Y
insulin aspart	INSULIN ASPART PENFILL	CARTRIDGE	SQ	N
insulin aspart	NOVOLOG PENFILL	CARTRIDGE	SQ	N
insulin aspart	INSULIN ASPART FLEXPEN	INSULN PEN	SQ	N
insulin aspart	NOVOLOG FLEXPEN	INSULN PEN	SQ	N
insulin aspart	INSULIN ASPART	VIAL	SQ	N
insulin aspart	NOVOLOG	VIAL	SQ	N
insulin aspart (niacinamide)	FIASP PENFILL	CARTRIDGE	SQ	N
insulin aspart (niacinamide)	FIASP FLEXTOUCH	INSULN PEN	SQ	N
insulin aspart (niacinamide)	FIASP	VIAL	SQ	N
insulin aspart prot/insuln asp	INSULIN ASPART PROT MIX 70-30	INSULN PEN	SQ	N
insulin aspart prot/insuln asp	NOVOLOG MIX 70-30 FLEXPEN	INSULN PEN	SQ	N
insulin aspart prot/insuln asp	INSULIN ASPART PROT MIX 70-30	VIAL	SQ	N
insulin aspart prot/insuln asp	NOVOLOG MIX 70-30	VIAL	SQ	N
insulin aspart/B3/pump cart	FIASP PUMPCART	CARTRIDGE	SQ	N
insulin aspart-szjj	MERILOG SOLOSTAR	INSULN PEN	SQ	N
insulin aspart-szjj	MERILOG	VIAL	SQ	N
insulin aspart-xjhz	KIRSTY PEN	INSULN PEN	SQ	N
insulin aspart-xjhz	KIRSTY	VIAL	SQ	N
insulin degludec	INSULIN DEGLUDEC PEN (U-100)	INSULN PEN	SQ	N
insulin degludec	INSULIN DEGLUDEC PEN (U-200)	INSULN PEN	SQ	N
insulin degludec	TRESIBA FLEXTOUCH U-100	INSULN PEN	SQ	N
insulin degludec	TRESIBA FLEXTOUCH U-200	INSULN PEN	SQ	N
insulin degludec	INSULIN DEGLUDEC	VIAL	SQ	N
insulin degludec	TRESIBA	VIAL	SQ	N
insulin degludec/liraglutide	XULTOPHY 100-3.6	INSULN PEN	SQ	N
insulin detemir	LEVEMIR FLEXPEN	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	BASAGLAR TEMPO PEN U-100	INSULN PEN	SQ	N
insulin glargine,hum.rec.anlog	INSULIN GLARGINE MAX SOLOSTAR	INSULN PEN	SQ	N
insulin glargine,hum.rec.anlog	INSULIN GLARGINE SOLOSTAR	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 glargine-aglr	REZVOGLAR KWIKPEN	INSULN PEN	SQ	N
insulin glargine-yfgn	INSULIN GLARGINE-YFGN	INSULN PEN	SQ	N
insulin glargine-yfgn	SEMGLEE (YFGN) PEN	INSULN PEN	SQ	N
insulin glargine-yfgn	INSULIN GLARGINE-YFGN	VIAL	SQ	N

insulin glargine-yfgn	SEMGLEE (YFGN)	VIAL	SQ	N
insulin glulisine	APIDRA SOLOSTAR	INSULN PEN	SQ	N
insulin glulisine	APIDRA	VIAL	SQ	N
insulin lispro	ADMELOG SOLOSTAR	INSULN PEN	SQ	N
insulin lispro	ADMELOG	VIAL	SQ	N
insulin lispro-aabc	LYUMJEV KWIKPEN U-100	INSULN PEN	SQ	N
insulin lispro-aabc	LYUMJEV KWIKPEN U-200	INSULN PEN	SQ	N
insulin lispro-aabc	LYUMJEV TEMPO PEN U-100	INSULN PEN	SQ	N
insulin lispro-aabc	LYUMJEV	VIAL	SQ	N
insulin NPH human isophane	HUMULIN N KWIKPEN	INSULN PEN	SQ	N
insulin NPH human isophane	NOVOLIN N FLEXPEN	INSULN PEN	SQ	N
insulin regular, human	AFREZZA	CART INHAL	IH	N
insulin regular, human	NOVOLIN R FLEXPEN	INSULN PEN	SQ	N
insulin regular in 0.9 % NaCl	MYXREDLIN	PLAST. BAG	IV	

Appendix 2: Abstracts of Comparative Clinical Trials

None

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to June 19, 2026
Search Strategy:

#	Searches	Results
1	aspart.mp.	1744
2	degludec.mp.	1102
3	detemir.mp.	1157
4	glargine.mp. or Insulin Glargine/	3913
5	glulisine.mp.	383
6	Insulin Lispro/ or lispro.mp.	1567
7	NPH.mp.	3661
8	insulin regular.mp.	1200
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	10654
10	limit 9 to (english language and humans and yr="2024 -Current")	606
11	limit 10 to (clinical trial, phase iii or clinical trial, phase iv or guideline or meta-analysis or practice guideline or "systematic review")	81

Appendix 4: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

Awiqli (insulin icodec-abae) injection, for subcutaneous use
Initial U.S. Approval: 2026

INDICATIONS AND USAGE

Awiqli is a long-acting human insulin analog indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (1)

DOSAGE AND ADMINISTRATION

- Individualize dose based on type of diabetes, metabolic needs, blood glucose monitoring results and glycemic control goals. (2.1)
- See Full Prescribing Information for important administration instructions (2.2)
- Inject Awiqli subcutaneously into the thigh, upper arm, or abdomen. (2.2)
- Rotate injection sites to reduce risk of lipodystrophy and localized cutaneous amyloidosis. (2.2)
- See Full Prescribing Information for the recommended starting dosage in insulin naïve patients (2.3) and recommendations for switching patients from daily basal insulin. (2.4)
- Closely monitor glucose when switching to Awiqli. (2.4)

DOSAGE FORMS AND STRENGTHS

Injection: 700 units/mL (U-700) available as a clear and colorless solution:

- 3 mL single-patient-use FlexTouch prefilled pen (containing 2,100 units) (3)
- 1.5 mL single-patient-use FlexTouch prefilled pen (containing 1,050 units) (3)
- 1 mL single-patient-use FlexTouch prefilled pen (containing 700 units) (3)

CONTRAINDICATIONS

- During episodes of hypoglycemia (4)
- Hypersensitivity to insulin icodec-abae or any of the excipients in Awiqli (4)

WARNINGS AND PRECAUTIONS

- *Hypoglycemia Due to Medication Errors and Accidental Overdoes:* Accidental mix-ups between insulin products can occur. Advise patients to always check the product label before each injection to confirm they are using Awiqli and not another insulin or injectable antidiabetic medicine.. DO NOT transfer Awiqli from the Awiqli FlexTouch pen into a syringe for administration as overdosage and severe hypoglycemia can result. (5.1)
- *Hypoglycemia:* May be life-threatening. Increase monitoring with changes to: insulin dosage, co-administered glucose lowering medications, meal pattern, physical activity, and in patients with renal impairment, hepatic impairment or hypoglycemia unawareness. (5.2)
- *Hyperglycemia or Hypoglycemia with Changes in Insulin Regimen:* Make changes to a patient's insulin regimen (e.g., insulin strength, manufacturer, type, injection site or method of administration) under close medical supervision with increased frequency of blood glucose monitoring. (5.3)
- *Hypersensitivity Reactions:* Severe, life-threatening, generalized allergy, including anaphylaxis, can occur. Discontinue Awiqli FlexTouch, monitor and treat if indicated. (5.4)
- *Hypokalemia:* May be life-threatening. Monitor potassium levels in patients at risk for hypokalemia and treat if indicated. (5.5)
- *Never share* an Awiqli FlexTouch pen between patients, even if the needle is changed. (5.6)
- *Fluid Retention and Heart Failure with Concomitant Use of Thiazolidinediones (TZDs):* Observe for signs and symptoms of heart failure; consider dosage reduction or discontinuation if heart failure occurs. (5.7)

ADVERSE REACTIONS

Adverse reactions commonly associated with Awiqli are:

- hypoglycemia, hypersensitivity reactions (e.g., urticaria, swelling face and lips), injection site reactions, lipodystrophy, pruritus, rash, edema, and weight gain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk at 1-844-668-6463 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- *Drugs that may increase the risk of hypoglycemia:* antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, salicylates, somatostatin analog (e.g., octreotide), sulfonamide antibiotics, GLP-1 receptor agonists, DPP-4 inhibitors, and SGLT-2 inhibitors. (7)
- *Drugs that may decrease the blood glucose lowering effect:* atypical antipsychotics, corticosteroids, danazol, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones. (7)
- *Drugs that may increase or decrease the blood glucose lowering effect:* Alcohol, beta-blockers, clonidine, lithium salts, and pentamidine. (7)
- *Drugs that may blunt the signs and symptoms of hypoglycemia*: beta-blockers, clonidine, guanethidine, and reserpine. (7)

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

Revised: 03/2026

Appendix 5. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	Stimulation of peripheral glucose update by binding to human insulin receptor
Absorption	Steady state after 2-3 weeks. Maximum concentration 15 hours post dose.
Distribution and Protein Binding	>99% protein bound
Elimination	Degradation similar to human insulin with no active metabolites
Half-Life	Approximately 1 week independent of dose
Immunogenicity	No clinically significant effect of anti-insulin icodec antibodies on safety or effectiveness

Appendix 6: Key Inclusion Criteria

Population	Individuals with type 1 diabetes, type 2 diabetes or gestational diabetes
Intervention	Insulin products
Comparator	Other insulin products
Outcomes	Glucose lowering (i.e., HbA1c), microvascular and macrovascular complications, morality and hypoglycemia.
Timing	New and existing 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

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:** Approve for up to 12 months	**No:** Pass to RPh; deny and recommend a trial of one of the preferred insulin products

P&T / DUR Review: *10/26 (KS); 6/24 (SF); 2/20(KS); 9/19; 11/18; 9/17; 3/16; 11/15; 9/10*
Implementation: *1/1/27; 11/1/2019; 11/1/17; 10/13/16; 1/1/11*