Hypoglycemics, Insulins and Related Agents

Therapeutic Class Review (TCR)

February 1, 2023

FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
Rapid-Acting Insulins		
human insulin inhalation powder (Afrezza®)[1]	Mannkind	To improve glycemic control in adults with diabetes mellitus
insulin aspart (Fiasp®)[2]	Novo Nordisk	To improve glycemic control in adults and pediatric patients with diabetes mellitus
insulin aspart (Novolog®)[3]	generic*, Novo Nordisk	To improve glycemic control in adults and children with diabetes mellitus
insulin glulisine (Apidra®)[4]	Sanofi-Aventis	To improve glycemic control in adults and children with diabetes mellitus
insulin lispro† (Admelog®)[5]	Sanofi-Aventis	To improve glycemic control in adults and children 3 years of age and older with T1DM and adults with T2DM
insulin lispro (Humalog®, Humalog Junior)[6,7]	generic*, Eli Lilly	To improve glycemic control in adults and children 3 years of age and older with T1DM and adults with T2DM
insulin lispro-aabc† (Lyumjev®)[8]	Eli Lilly	To improve glycemic control in adults and children with diabetes mellitus
Regular (R) Insulins		
human insulin (Humulin® R)[9,10]	Eli Lilly	To improve glycemic control in adults and children with diabetes mellitus; human insulin 500 U/mL (Humulin R U-500) is for use in patients requiring daily doses > 200 units
human insulin (Novolin® R)[11]	Novo Nordisk	
Intermediate (N) Insulins		
human insulin NPH (Humulin N)[12]	Eli Lilly	To improve glycemic control in adults and children with diabetes mellitus
human insulin NPH (Novolin N)[13]	Novo Nordisk	
Long-Acting Insulins		
insulin degludec (Tresiba®)[14]	Novo Nordisk, Novo Nordisk	To improve glycemic control in patients 1 year of age or older with diabetes mellitus‡
insulin detemir (Levemir®)[15]	Novo Nordisk	To improve glycemic control in adults and children with diabetes mellitus
insulin glargine U-100† (Basaglar®)[16]	Eli Lilly	To improve glycemic control in adults and children with T1DM and adults with T2DM
insulin glargine U-100 (Lantus®)[17]	Winthrop, Sanofi-Aventis	To improve glycemic control in adult and pediatric patients with diabetes mellitus
insulin glargine-yfgn U-100†,§ ¶(Semglee)[18]	Mylan, Mylan	To improve glycemic control in adults and children with T1DM and adults with T2DM
insulin glargine U-300 (Toujeo®)[19]	Sanofi-Aventis	To improve glycemic control in adults and pediatric patients 6 years and older with diabetes mellitus

NPH = neutral protamine Hagedorn; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus
* Authorized generic available.
† Biosimilar agents
‡ Insulin degludec (Tresiba) is not recommended in pediatric patients who require doses of < 5 units.
§ Interchangeable biosimilar
¶ Non-interchangeable insulin glargine (Semglee®) has been phased out of the US market; this product, insulin glargine-yfgn (Semglee) is an interchangeable biosimilar to reference product insulin glargine (Lantus).[20]

FDA-Approved Indications (continued)

Drug	Manufacturer	Indication(s)
Rapid/Intermediate-Acting Combination Insulins		
insulin aspart 70/30 (Novolog® Mix)[21]	generic*, Novo Nordisk	To improve glycemic control in patients with diabetes mellitus
insulin lispro 50/50, 75/25 (Humalog® Mix)[22,23]	Eli Lilly*, Eli Lilly	For the treatment of patients with diabetes mellitus for the control of hyperglycemia
Regular/Intermediate-Acting Combination Insulins		
human insulin 70/30 (Humulin® 70/30)[24]	Eli Lilly	To improve glycemic control in adults with diabetes mellitus
human insulin 70/30 (Novolin 70/30)[25]	Novo Nordisk	

NPH = neutral protamine Hagedorn; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus

* Authorized generic available.

Insulin degludec (Tresiba), insulin detemir (Levemir), insulin glargine (Basaglar, Lantus, Semglee, Toujeo), insulin glargine-yfgn (Semglee), and insulin inhalation powder (Afrezza) are not recommended for the treatment of diabetic ketoacidosis.

In June 2019, the FDA approved the first ready-to-use insulin for intravenous (IV) infusion, insulin human in 0.9% sodium chloride injection (Myxredlin; Baxter) 100 units/100 mL in a single-dose container.[26,27] Myxredlin is intended for use in a hospital or other acute care setting and will not be detailed in this therapeutic class review.

OVERVIEW

It is estimated that over 37 million Americans have diabetes mellitus (DM).[28] Diabetes is responsible for increased morbidity and mortality. Adequate glycemic control is crucial to minimize chronic microvascular (e.g., blindness, renal dysfunction) and macrovascular (e.g., cardiovascular disease [CVD]) complications.[29]

Exogenous insulin supplements deficient levels of endogenous insulin, and temporarily restores the ability of the body to properly utilize carbohydrates, fats, and proteins. Multiple insulin products are available and are used as replacement therapy in the management of T1DM and T2DM when glycemic goals are not met with oral antidiabetic agents.

The World Health Organization (WHO) classifies DM based on clinical parameters to identify diabetes subtypes, and it includes the following types: T1DM (absolute insulin deficiency), T2DM (insulin resistance), hybrid forms of diabetes (e.g., slowly evolving immune-mediated, ketosis-prone T2DM), specific types (e.g., monogenic, drug- or chemical-induced, infection-related), unclassified diabetes, and hyperglycemia first detected during pregnancy (e.g., gestational diabetes mellitus [GDM]).[30]

The American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) have partnered to create the Precision Medicine in Diabetes Initiative (PMDI). Their first consensus report, published in 2020, focuses on clarifying the etiological heterogenicity of diabetes using risk factor measures, biomarkers and genomics, and lifestyle and pharmacological intervention.[31] They describe precision medicine as a tailored approach to diagnosis, prevention, and treatment of diabetes using the patient's unique biology, environment and/or context. Precision medicine emphasizes tailoring the diagnostics or therapeutics (prevention or treatment) to subgroups of populations that share similar characteristics, and in doing so optimizing therapeutic efficacy and minimizing error and risk. Precision diagnostics may involve testing for genetic variants, biomarkers, or autoantibodies to subclassify a diabetes diagnosis, which could help manage future expectations around the disease course and predict drug outcomes. The next ADA/EASD PMDI consensus report will focus on precision diagnostics and therapeutics and is expected to be released in early 2023.[32,33]

In 2021 the ADA and EASD released a consensus report on the management of T1DM in adults. The panel emphasizes the importance of an accurate diabetes diagnosis.[34] Misclassification of T1DM in adults is common and over 40% of those diagnosed with T1DM after the age of 30 years were initially thought to have T2DM. Distinguishing features of T1DM include younger age at diagnosis (< 35 years), lower body mass index (BMI; < 25 kg/m^2), unintended weight loss, ketoacidosis, and glucose > 360 mg/dL. A family history of T1DM or a history of autoimmune disease may also be present. ADA/EASD recommends that patients with suspected T1DM be tested for islet autoantibodies (e.g., glutamic acid decarboxylase [GAD] [primary], islet tyrosine phosphatase 2 [IA2], zinc transporter 8 [ZNT8]) where available. However, a negative antibody test does not necessarily eliminate a diagnosis of T1DM, as seen in 5% to 10% individuals with new-onset T1DM, and islet antibodies may also disappear over time. The ADA and EASD recommend insulin therapy in patients with suspected T1DM, regardless of the presence of T2DM features (e.g., BMI ≥ 25 kg/m^2, absence of weight loss, absence of ketoacidosis, less marked hyperglycemia) or absence of islet antibodies. If the clinical course suggests T2DM, then non-insulin treatment may be tried. However, if the diabetes type is still unclear after 3 years of insulin therapy, a C-peptide test may be performed. Low (< 200 pmol/L) or absent C-peptide confirms T1DM and persistent C-peptide > 600 pmol/L strongly suggests T2DM. Levels between 200 to 600 pmol/L may indicate monogenic diabetes, a rare diabetes subtype of with an onset < 35 years of age that is often mistaken for T1DM. It is important to distinguish monogenic diabetes from T1DM since patients with monogenic diabetes may achieve better glycemic control with oral antidiabetic agents than with insulin.

Exogenous insulin therapy is necessary in all patients with T1DM.[35] ADA considers all forms of diabetes mediated by autoimmune β-cell destruction under the category of T1DM, including latent autoimmune diabetes in adults (LADA).[36] The ADA 2023 Standards of Medical Care in Diabetes advises that most adults and children with T1DM be treated with multiple daily insulin injections of prandial and basal insulin, or continuous subcutaneous (SC) insulin infusion.[37] Rapid-acting insulin analogs are typically used to reduce hypoglycemia risk. Continuous glucose monitoring should be considered in most patients. Automated insulin delivery systems are recommended to improve glycemic control and reduce hypoglycemia in this population. The rapid-acting insulins, insulin aspart (Fiasp, Novolog, generic), insulin glulisine (Apidra), insulin lispro (Admelog, Humalog U-100, generic), insulin lispro-aabc 100 units/mL (Lyumjev), and insulin lispro/protamine lispro (Humalog Mix 50/50 and 75/25, generic) are approved for use with insulin pumps.

The American College of Physicians (ACP) 2018 guidance for pharmacologic treatment of T2DM states that glycemic goals should be individualized based on the patients' preferences, general health, and life expectancy as well as treatment burden.[38] They recommend a goal hemoglobin A1c (HbA1c) level between 7% and 8% in most patients. They advise clinicians to consider deintensifying pharmacologic therapy in patients who achieve HbA1c levels < 6.5%. Prescribed treatment should minimize symptoms related to hyperglycemia and avoid HbA1c target levels in patients with a life expectancy < 10 years due to advanced age (≥ 80 years) because the harms outweigh the benefits in this population.

The ADA 2023 Standards of Medical Care in Diabetes also advocates that glycemic goals be tailored to individual patient needs.[39] A reasonable HbA1c goal for nonpregnant adults without significant hypoglycemia is < 7%. In patients using an ambulatory glucose profile/glucose management indicator to assess glycemia, a parallel goal is a time in range of > 70% with time below range < 4%. More stringent HbA1c goals (< 7%) are reasonable for selected patients (e.g., those with short duration of diabetes, long life expectancy, and no significant CVD) and may be considered if this can be achieved without significant hypoglycemia. Less stringent HbA1c goals (< 8%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with long-standing diabetes in whom the general goal is difficult to attain. ADA defines clinically significant hypoglycemia as serum glucose < 54 mg/dL and glucose alert value of ≤ 70 mg/dL. For pediatric patients, the ADA recommends a target HbA1c < 7% for all age groups, although individualization is still supported.[40] A reasonable HbA1c goal for older individuals (≥ 65 years of age) who are otherwise healthy with intact cognitive function is < 7% to 7.5%.[41] This goal may be relaxed (< 8%) in older individuals to reduce the risk of hypoglycemia, particularly in those with chronic comorbidities, cognitive impairment, or functional dependence. An HbA1c target of < 6% for pregnant women is recommended, which can be relaxed depending on hypoglycemia risk during pregnancy.[42] Moreover, due to increased red blood cell turnover during pregnancy, HbA1c levels may decrease and thereby not fully reflect glycemic parameters. The ADA advises HbA1c be used as a secondary measure during pregnancy, next to self-monitoring of blood glucose.

According to the ADA, selection of antidiabetic medication should be based on patient-related variables, such as comorbidities, hypoglycemia risk, patient preference; and agent-related variables, such as its effect on body weight, adverse effect profile, and cost.[43] It is generally agreed that metformin, unless contraindicated and if tolerated, is a first-line option, in addition to lifestyle management, in the treatment of T2DM. In patients with T2DM with or at high risk for atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), and/or chronic kidney disease (CKD), glucagon-like peptide 1 receptor agonists (GLP-1RA) and sodium-glucose cotransporter-2 (SGLT2) inhibitors, with or without metformin based on glycemic needs, are appropriate independent of HbA1c as initial or add-on therapy. In general, a GLP1-RA is preferred over insulin when possible, and if insulin is used, the addition of a GLP-1RA is recommended to improve efficacy and durability of effect. Early use of insulin should be considered if there is evidence of ongoing catabolism (weight loss) or if there are symptoms of hyperglycemia, or if high HbA1c (> 10%) or blood glucose levels (≥ 300 mg/dL) are present. If initial therapy at maximum tolerated doses does not achieve or maintain the HbA1c target after 3 months, another agent from a different class should be added. On average, any second agent is typically associated with a further reduction in HbA1c of approximately 1%. However, not all treatment intensification results in sequential add-on therapy, rather it may entail switching therapy or weaning current therapy to accommodate therapeutic changes.

Insulin therapy is the treatment of choice for T1DM and for T2DM during pregnancy.[44] Unlike metformin and glyburide, insulin does not cross the placenta to a measurable degree.

According to the ADA, metformin is preferred in most pediatric patients with T2DM as initial treatment if HbA1c is < 8.5% and the patient is asymptomatic.[45] Basal insulin is appropriate as initial therapy if the patient cannot take metformin, or as an add-on to initial metformin titration if HbA1c is ≥ 8.5% or if blood glucose is ≥ 250 mg/dL and the patient is symptomatic. Since the GLP-1RAs liraglutide (Victoza®), exenatide extended-release (Bydureon®), and dulaglutide (Trulicity®) received FDA approval to manage T2DM in patients ages ≥ 10 years, the ADA recommends that they be considered in this population if glucose levels are not adequately controlled with metformin ± basal insulin and if there are no contraindications for use. Insulin is recommended in those with cystic fibrosis-related diabetes.

The ADA and the EASD 2022 position statement on the management of T2DM supports a diabetes care decision cycle for person-centered glycemic management of T2DM to prevent complications and optimize quality of life.[46] It includes factors that impact treatment choice, such as HbA1c target; the agent's impact on weight and hypoglycemia; and its side effect profile, the frequency and mode of administration, and probability of patient adherence.

In 2022, the American Association of Clinical Endocrinology (AACE) published an update to its guideline on development of a diabetes comprehensive care plan.[47] AACE recommends a goal HbA1c ≤ 6.5% for most nonpregnant adults if it can be achieved safely. Patients with a history of severe hypoglycemia, hypoglycemia unawareness, limited life expectancy, advanced renal disease, extensive comorbidities, or long-standing DM can aim for a less stringent HbA1c goal ≤ 8%. Pharmacotherapy recommendations center around individualization based on glucose-lowering, avoidance of hypoglycemia and weight gain, and reduction of cardio-renal risk. The guideline recommends the use of GLP-1RAs and SGLT2 inhibitors with proven CV benefits for patients with established ASCVD or who are at high risk for ASCVD. Metformin is often the preferred initial therapy, and early combination therapy should be considered for some recently diagnosed T2DM patients with HbA1c ≥ 7.5% who are unlikely to reach their HbA1c goal on monotherapy. Patients with an HbA1c ≥ 9% should be initiated on dual or triple combination therapy regimens, typically including metformin. The use of basal insulin as initial therapy in combination with noninsulin therapy is recommended for patients with an HbA1c > 10%.

AACE states that when insulin therapy is indicated in patients with T2DM, therapy with long-acting basal insulin analogs (degludec, glargine, and detemir) should be the initial choice in most cases; basal insulin analogs (degludec, detemir, glargine) are preferred over intermediate-acting neutral protamine Hagedorn (NPH) because basal insulin analogs provide a relatively flat serum insulin level and are associated with less hypoglycemia.[48] Additionally, glargine U-300 and degludec can be associated with less hypoglycemia than glargine U-100 and detemir. The guideline discusses that patients on a basal insulin who do not achieve adequate glycemic control should be started on a GLP-1RA or switched to a fixed ratio insulin-GLP-1RA product before adding mealtime insulin. Rapid-acting insulin analogs (aspart, glulisine, lispro, inhaled insulin) are preferred over regular insulin for postprandial hyperglycemia because they have a more rapid onset and offset of action and result in less hypoglycemia. Premixed insulin analog therapy, which contains rapid- and long-acting components in the same vial or pen, may be appropriate for patients in whom adherence to a drug regimen is problematic; although, these preparations lack component dosing flexibility and may increase the risk for hypoglycemia compared with basal insulin or basal-bolus insulin. Basal-bolus insulin therapy is flexible and is recommended for intensive insulin therapy. The preferred treatment for postprandial hyperglycemia in pregnant women is regular or rapid-acting insulin analogs; basal insulin needs can be met with the use of rapid-acting insulin via infusion pump or long-acting insulin.

The AACE and American College of Endocrinology (ACE) 2020 diabetes management algorithm, which serves as a supplement to AACE's 2022 clinical practice guidelines for developing a diabetes care plan, generally recommends diabetes treatment with a goal HbA1c ≤ 6.5% if it can be reached without substantial hypoglycemia or other adverse effects.[49] A goal HbA1c > 6.5% is appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced renal disease or macrovascular complications, extensive comorbid conditions, or long-standing T2DM in which the HbA1c goal has been difficult to attain. Choice of antidiabetic agent should be based on glycemic profile, HbA1c, body weight, age, comorbid conditions, ease of use, and affordability. Minimizing the risks of hypoglycemia and weight gain are a main concern. AACE/ACE suggests patients with T2DM and HbA1c < 7.5% start with monotherapy, preferably with metformin. Alternatives to metformin as initial therapy (in order of preference) include GLP-1RAs, SGLT2 inhibitors, DPP-4 inhibitors, and α-glucosidase inhibitors (AGI); monotherapy with a thiazolidinedione (TZD) or sulfonylurea (SU) should be used with caution. Patients with an HbA1c ≥ 7.5% to ≤ 9% should begin with dual therapy with metformin (unless contraindicated) plus a second agent, including a GLP-1RA, SGLT2 inhibitor, DPP-4 inhibitor, TZD, SU, basal insulin, colesevelam, bromocriptine (quick release), or AGI; TZDs, basal insulin, and SUs should be used with caution. Patients with an HbA1c > 9% and no symptoms of hyperglycemia may start with maximum doses of 2 or 3 antihyperglycemic agents; patients with an HbA1c > 9% with symptoms of hyperglycemia should begin insulin therapy with or without other agents. The HbA1c should be reassessed every 3 months and failure to improve glycemic control may warrant additional complementary therapy for optimal glycemic control. An updated version of this algorithm is anticipated to be published in May 2023.[50]

The Endocrine Society (ES) published a guideline in 2022 on the management of diabetes in individuals who are at high risk for hypoglycemia.[51] The guideline suggests the use of long-acting insulin analogs rather than insulin NPH, as well as rapid-acting insulin analogs rather than regular (short-acting) human insulins for adults and pediatric patients who are at risk of hypoglycemia.

In 2018, the World Health Organization (WHO) released guidelines regarding diabetes treatment intensification.[52,53,54] WHO recommends introduction of human insulin in patients with T2DM who do not achieve glycemic control with metformin and/or a SU. In adults with T1DM or adults with T2DM for whom insulin is indicated, human insulin should be used to manage blood glucose, and long-acting insulin analogues should be considered for T1DM or adults with T2DM who experience frequent, severe hypoglycemia with human insulin.

In 2021, the American Academy of Pediatrics (AAP) issued a review on the management of T2DM in children and adolescents.[55] In alignment with the ADA Standards of Medical Care for Children and Adolescents, insulin is suggested in obese youth with T2D to control severe metabolic decompensation (e.g., diabetic ketoacidosis) or in those with HbA1c > 8.5% during metformin titration. For pediatric patients without severe symptoms with confirmed T2DM, liraglutide is recommended to be considered if metformin and lifestyle changes are inadequate; insulin is an alternative. AAP notes insulin can usually be discontinued following recovery and addition of lifestyle changes, metformin, and liraglutide. Insulin is also recommended for pediatric patients without adequate blood glucose control (HbA1c level > 7%) following the addition of liraglutide.

In 2019, the Endocrine Society (ES) issued guidelines on diabetes screening and treatment in patients aged ≥ 65 years.[56] They recommend diabetes regimens geared toward minimizing risk for hypoglycemia. Metformin is recommended as first-line oral therapy for T2DM unless the patient has significant renal impairment or gastrointestinal intolerance. If the addition of another agent is required to achieve glycemic goals, the ES advises avoiding those associated with high risk for hypoglycemia (e.g., SUs and glinides) and using insulin sparingly.

SC insulins can be administered to a single patient via a multidose insulin cartridge, vial, or a prefilled insulin pen device. Insulin inhalation powder (Afrezza) may be an option for patients with T1DM and T2DM who have barriers to injectable administration, such as visual impairment or neuropathy.

Insulin glargine 100 U/mL products, Basaglar and Semglee, were approved as *follow-on* products for Lantus in December 2016 and June 2020, respectively. In December 2017, Sanofi-Aventis's insulin lispro 100 U/mL (Admelog), a *follow-on* to Humalog 100 U/mL, was also approved. *Follow-on* products are defined as copies of biological products approved under the Food, Drug and Cosmetic (FD&C) Act 505(b)(2) pathway.[57] Effective March 23, 2020, certain biologics previously approved under the FD&C 505 pathway that were designated as drugs are now considered to be biologics under section 351 of the Public Health Service Act (PHSA).[58,59,60] This transition allows products, such as insulin, to receive competition through the biosimilar pathway. The biosimilar pathway for approval also allows biologic products to receive additional designation as an *interchangeable* biosimilar.[61,62] Interchangeable biosimilar products can be substituted for the reference product without the intervention of the prescriber at the pharmacy, depending on state substitution laws.[63] In June 2020, insulin lispro-aabc (Lyumjev) became the first commercially available insulin in the United States (US) that was approved under the under section 351(a) of the Public Health Service Act.[64] In July 2021, insulin glargine-yfgn (Semglee) became the first product in the US to receive a determination of interchangeability for its reference product insulin glargine (Lantus).[65] Insulin glargine-yfgn (Semglee) is expected to provide the same clinical result and safety profile in any given patient as insulin glargine (Lantus), and switching between the products does not diminish efficacy. Commercial availability has been transitioned from insulin glargine U-100 (Semglee) to insulin glargine-yfgn, and insulin glargine U-100 (Semglee) has been phased out of the US market.[66] Authorized generic insulins, available for insulin aspart (Novolog) and insulin lispro (Humalog), may also be substituted for their corresponding brand product because they are identical to the brand product.

PHARMACOLOGY[67,68]

Insulin, secreted from the pancreatic beta cells, lowers blood glucose levels by stimulating peripheral glucose uptake by skeletal muscle and fat, and by inhibiting gluconeogenesis. Insulin also inhibits lipolysis in the adipocyte, inhibits proteolysis, and enhances protein synthesis. Exogenous insulin is derived from recombinant DNA technology with *E. coli* or yeast.

PHARMACOKINETICS[69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99]

Comparison of Insulin Products

Drug	Composition of Insulin	Onset (hrs)	Peak (hrs)	Duration (hrs)	Compatibility for Mixing
Rapid-Acting					
human insulin (Afrezza)	Consists of human insulin adsorbed onto carrier particles consisting of fumaryl diketopiperazine (FDKP) and polysorbate 80	~0.2	~0.6-0.9	1.5-4.5	--
insulin aspart (Fiasp)	Consists of human insulin aspart in a clear aqueous solution; Created when the amino acid proline is substituted with aspartic acid at position B28; Inclusion of niacinamide (vitamin B_3) increases the speed of initial insulin absorption	0.27-0.33	1.5-2.2	5-7	infusion fluids (5% dextrose or 0.9% sodium chloride)
insulin aspart (Novolog)	Consists of human insulin aspart in a clear aqueous solution; Created when the amino acid proline is substituted with aspartic acid at position B28	0.25	0.75-1.5	3-5	NPH
insulin glulisine (Apidra)	Created when the amino acid asparagine at position B3 is replaced by lysine and the lysine at position B29 is replaced by glutamic acid	0.33	0.92	5.3	NPH
insulin lispro (Admelog, Humalog)	Consists of zinc-insulin lispro crystals dissolved in clear aqueous fluid; Created when the amino acids at positions 28 and 29 on the insulin B-chain are reversed	0.25-0.5	0.5-1.5	3-4	Admelog: None
				3-5	Humalog: NPH
insulin lispro-aabc (Lyumjev)	Consists of insulin lispro in a clear aqueous fluid; Created when the amino acids at positions 28 and 29 on the insulin B-chain are reversed	0.25-0.28	2-2.9	4.6-7.3	None

Comparison of Insulin Products (continued)

Drug	Composition of Insulin	Onset (hrs)	Peak (hrs)	Duration (hrs)	Compatibility for Mixing
Rapid/Intermediate-acting combinations					
insulin aspart (Novolog Mix)	Suspension containing insulin aspart protamine crystals and soluble insulin aspart	0.17-0.33	1.6-3.2	Up to 24 hours	None
insulin lispro (Humalog Mix)	Suspension containing insulin lispro protamine suspension and insulin lispro solution	0.25-0.5	0.8-6.5	Similar to corresponding Humulin mixes	None
Regular-acting					
human insulin regular 100 U/mL (Humulin R, Novolin R)	Crystalline regular insulin is prepared by precipitation in the presence of zinc chloride at a neutral pH	0.5	2.5-5	8-12	NPH
human insulin 500 U/mL (Humulin R U-500)	A solution identical to human insulin that is produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of *Escherichia coli*	< 0.25	4-8	13-24	None
Regular/Intermediate-acting combinations					
human insulin (Humulin 70/30, Novolin 70/30)	Crystalline regular insulin and isophane (NPH) is modified, crystalline protamine zinc insulin	0.5-0.8	2.2-5	Up to 24	None
Intermediate-acting					
human insulin NPH (Humulin N, Novolin N)	Isophane (NPH) is modified, crystalline protamine zinc insulin; Its effects are comparable to a mixture of 2:1 to 3:1 regular insulin and protamine zinc insulin	1.5	4-12	Up to 24	Regular, aspart (Novolog), lispro, and glulisine

Comparison of Insulin Products (continued)

Drug	Composition of Insulin	Onset (hrs)	Peak (hrs)	Duration (hrs)	Compatibility for Mixing
Long-acting					
insulin degludec (Tresiba)	Created when the amino acid threonine in position B30 is omitted and a side-chain consisting of glutamic acid and a C16 fatty acid is attached	1	12	> 42	None
insulin detemir (Levemir)[100]	Created when the amino acid threonine in position B30 is omitted and a C14 fatty acid chain is added to amino acid B29	0.8-2	6-8	Up to 24	None
insulin glargine U-100 (Basaglar)	Created when the amino acids at position A21 of human insulin are replaced by glycine and 2 arginines are added to the C-terminus of the B-chain	nr	12*	Up to 24	None
insulin glargine U-100 (Lantus)		nr	5*		
insulin glargine-yfgn U-100 (Semglee)		nr	11.3*		
insulin glargine U-300 (Toujeo)[101]		6	12-16	Up to 36	

nr = not reported

* Based on median time to maximum serum insulin concentration. No pronounced peak is detected with insulin glargine U-100 (Basaglar, Lantus, Semglee) and insulin glargine-yfgn (Semglee) since the drug is released slowly over 24 hours.

In clinical studies, the onset of action of insulin aspart (Fiasp) was 5 minutes earlier and time to maximum glucose reduction was 11 minutes earlier compared to insulin aspart (Novolog, generic).[102]

In clinical studies, the steady state for the 24-hour glucose lowering effect of insulin glargine 300 U/mL (Toujeo) was approximately 27% lower than an equivalent dose of insulin glargine 100 U/mL (Lantus). The glucose lowering effect of insulin glargine 300 U/mL increases with subsequent daily administration.

The AACE/ACE state that the newer basal insulins, insulin glargine 300 units/mL (Toujeo) and insulin degludec (Tresiba), have more prolonged and stable pharmacokinetics compared to other long-acting insulins (insulin glargine 100 units/mL, insulin detemir).[103] Insulin glargine 300 units/mL (Toujeo) and insulin degludec (Tresiba) have demonstrated similar glycemic control and lower incidence of severe or confirmed hypoglycemia compared to insulin glargine 100 units/mL and insulin detemir. Insulin degludec may also result in a more stable day-to-day variability compared to insulin glargine 300 units/mL. Insulin U-500 displays a delayed onset and longer duration of action and characteristics more in-line with an intermediate-acting (NPH) insulin.[104]

CONTRAINDICATIONS/WARNINGS[105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128]

Insulin therapy is contraindicated during episodes of hypoglycemia.

Changes in insulin dosages should only be made under medical supervision.

A product should not be used in a patient with known hypersensitivity to the active ingredient or its excipients.

Patients with T1DM prescribed insulin inhalation powder (Afrezza) must also receive a long-acting insulin. Insulin inhalation powder is contraindicated in patients with hypersensitivity to regular human insulin. Insulin inhalation powder should not be used in patients who smoke or who have recently stopped smoking (< 6 months ago), as safety and efficacy have not been established in this population.

Insulin inhalation powder is contraindicated in patients with chronic lung disease, such as asthma or chronic obstructive pulmonary disease (COPD), since acute bronchospasm has been experienced in these patients. Prior to starting therapy, all patients should be evaluated for potential lung disease, including detailed medical history, physical examination, and spirometry. In long-term (up to 2 years) clinical studies, patients without chronic lung disease experienced a small decline (40 mL) in lung function as measured by forced expiratory volume in 1 second (FEV_1). This decline was observed within the first 3 months of therapy and persisted throughout the studies. The impact of treatment > 2 years and reversal of impairment after discontinuation has not been assessed. Pulmonary function should be monitored at baseline, after 6 months of therapy, and annually in all patients; more frequent monitoring is needed in those with symptoms such as wheezing, bronchospasm, cough, or difficulty breathing. Alternative therapy should be considered in patients who experience a decline of at least 20% in FEV_1 from baseline.

In clinical trials, the incidence of lung cancer was reported in patients treated with insulin inhalation powder (2 cases per 2,750 patient-years). In both cases, the patients had prior history of heavy tobacco use. Two additional cases of lung cancer (squamous cell and lung blastoma) in non-smokers who were treated with insulin inhalation powder were reported after clinical trial completion. These data are insufficient to establish an associated of insulin inhalation powder with respiratory tract tumors. Caution should be used in patients with current or previous lung cancer or who are at increased risk for lung cancer.

In clinical trials with T1DM patients, more patients using insulin inhalation powder experienced diabetic ketoacidosis (DKA) than those receiving comparators (0.43% versus 0.14%, respectively). In patients at risk for DKA, such as those with an acute illness or infection, carefully monitor blood glucose and switch to an alternate route of administration if necessary.

Precautions

Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin therapy.

As with all therapeutic proteins, insulin administration may cause anti-insulin antibodies to form; however, no clinically relevant impact on HbA1c or total daily insulin dose has been found.

Injectable insulins contain metacresol in varying concentrations. Metacresol has been reported to cause localized reactions and generalized myalgias. Select human insulin products (Humulin N, Humulin 70/30, Novolin N, and Novolin 70/30), insulin aspart products (Fiasp, Novolog, Novolog Mix), insulin degludec (Tresiba), and insulin lispro protamine/insulin lispro (Humalog Mix 75/25) contain approximately half the amount of metacresol compared to insulin glulisine (Apidra), and insulin lispro (Admelog, Humalog), and insulin lispro-aabc (Lyumjev).

All insulins can cause a shift in potassium from the extracellular to intracellular space, potentially leading to hypokalemia that if left untreated may cause respiratory paralysis, ventricular arrhythmia, and death. Caution should be used in patients who may be at risk for hypokalemia.

Changes in insulin strength, manufacturer, type, or method or site of administration may affect glycemic control and increase the risk of hypoglycemia or hyperglycemia. Patients and caregivers must be educated to recognize and manage these risks. All insulins may require a dose adjustment for patients with renal or hepatic impairment as they may be at higher risk of hypoglycemia. The recovery from hypoglycemia may be delayed with long-acting insulins compared to short-acting insulins.

The full glucose lowering effect of insulin glargine 300 U/mL (Toujeo) may not be seen for at least 5 days, which should be considered prior to stopping intravenous insulin therapy in patients with T1DM.

A single insulin pen should not be used to give medication to multiple patients. Sharing insulin pens and needles could result in the transmission of human immunodeficiency virus (HIV), the hepatitis viruses, and other blood-borne diseases. All insulin pens are approved only for single-patient use and product labeling warns against sharing of devices.[129] The FDA requires prescribing information and carton labeling of all injectable pen insulin products to specify that pens be dispensed to a single patient in the original sealed carton.[130]

The FDA also issued a Safety Communication regarding the use of devices for diabetes management that are unauthorized for sale in the US.[131] Devices that are unauthorized have not received FDA review and approval to assure their safety and efficacy. As a result, use of these devices could lead to incorrect blood glucose level measurements and/or an improper dose of insulin which could result in serious or potentially life-threatening medical complications. In addition, combining devices not appropriate for use with other devices also should be avoided. The FDA recommends that patients only use diabetes management devices that have received authorization from the FDA for sale in the US.

Pump or infusion set malfunction during continuous insulin administration can rapidly lead to hyperglycemia and ketoacidosis. Prompt correction is essential, during which time interim SC injections may be required.

DRUG INTERACTIONS[132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154,155]

Beta-blockers and clonidine are commonly used drugs that may mask the signs and symptoms of hypoglycemia. In addition, beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood glucose-lowering effect of insulin. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.

Substances that may decrease insulin requirements include oral antidiabetic agents, monoamine oxidase inhibitors (MAOIs), angiotensin converting enzyme (ACE) inhibitors, fibrates, fluoxetine, sulfonamide antibiotics, nonselective beta-blockers, and alpha-adrenergic blockers.

Drugs that may increase insulin requirements include oral contraceptives, thiazides, glucocorticoids, growth hormone, isoniazid, niacin, sympathomimetic agents, atypical antipsychotics, and thyroid hormones.

Thiazolidinediones (TZDs) (e.g., pioglitazone and rosiglitazone) are peroxisome proliferator-activated receptor (PPAR)- gamma agonists and can cause dose-related fluid retention, particularly when used in combination with insulin.

ADVERSE EFFECTS[156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172,173,174,175,176,177,178,179]

The most common adverse effect with all insulin products is hypoglycemia. Compared to human insulin, long-acting injectable agents decrease episodes of hypoglycemia by 25% to 50% and decrease nocturnal hypoglycemic episodes by 25% to 33%.

Injection site reactions can occur with any type of injectable insulin. Other possible adverse effects of injectable insulins include lipodystrophy, localized cutaneous amyloidosis, pruritus, and rash.

In clinical trials, insulin glargine U-100 (Lantus) had treatment-emergent injection site pain in 2.7% of patients versus 0.7% of patients on NPH insulin. Treatment discontinuation was not required. Insulin detemir (Levemir) was associated with more frequent mild injection site reactions than with insulin NPH. In clinical trials, injection site reactions occurred in 3.8% of patients treated with insulin degludec. In clinical trials, injection site reactions occurred in ≥ 5% of patients treated with insulin glargine (Basaglar). In clinical trials with insulin aspart (Fiasp), injection site reactions were reported in 1.6% of patients treated, which included 4.2% of pediatric patients with T1DM. In separate clinical trials, pediatric patients treated with insulin lispro-aabc (Lyumjev) reported a higher incidence of injection site reactions (6.2%) than adults (2.7%).

Use of insulin inhalation powder (Afrezza) is associated with cough (26.9%) and throat pain or irritation (4.8%). Coughing usually occurred within 10 minutes, was generally mild, dry, intermittent, and tended to decrease over time. Postmarketing experience of bronchospasm has been reported.

The potential for weight gain is associated with insulin therapy.[180] In clinical studies, insulin detemir was associated with a mean change in body weight in adults with T1DM and T2DM ranging from -0.3 kg to 0.5 kg and 0.5 kg to 1.2 kg, respectively. In clinical trials with insulin glargine (Lantus), mean change in body weight in adults with T1DM and T2DM ranged from 0.1 kg to 1 kg and 0.4 kg to 3.7 kg, respectively. In clinical trials with insulin aspart (Fiasp), average weight gain experienced by patients with T1DM and T2DM was 0.7 kg and 2.2 kg, respectively. Clinical trials in patients with T1DM noted modest weight loss with insulin inhalation powder (Afrezza) in contrast to weight gain with comparator insulin. In insulin-using patients with T2DM, insulin inhalation powder was associated with a more modest weight gain than comparator over the 52-week trial duration. Adverse effects data are obtained from prescribing information and therefore, should not be considered comparative or all-inclusive.

Insulin therapy may cause sodium retention and edema, particularly if treatment is intensified after poor metabolic control.

As with all therapeutic proteins, insulin therapy has the potential for immunogenic antibody formation.

SPECIAL POPULATIONS[181,182,183,184,185,186,187,188,189,190,191,192,193,194,195,196,197,198,199,200,201,202,203,204]

Pediatrics

Safety and efficacy of insulin inhalation powder (Afrezza) have not been established in pediatric patients. Human insulin (Humulin R, Humulin N, Novolin R) products have been used in all age groups. Although no well-controlled studies of human insulin 500 U/mL (Humulin R U-500) have been performed in children, standard precautions for its use in adults can be applied to children.

Insulin lispro (Admelog, Humalog, generic) can be used in children ≥ 3 years of age with T1DM, and insulin lispro-aabc (Lyumjev) can be used in children ≥ 1 year of age, but these agents have not been studied in pediatric patients with T2DM. Human insulin aspart (Fiasp, Novolog, generic) can be given to pediatric patients ≥ 2 years of age with T1DM or T2DM. Insulin degludec (Tresiba) is approved for use in patients ≥ 1 year of age with T1DM or T2DM. Insulin glulisine (Apidra) is approved for use in pediatric patients with T1DM from 4 to 17 years of age. The safety and efficacy of insulin NPH combinations with insulin aspart (Novolog, generic) and insulin lispro in children have not been evaluated by the FDA, and little data exist.

The labeling for insulin glargine (Lantus) has been updated to advise that the safety and efficacy of its use have been established in pediatric patients with diabetes mellitus; however, labeling for the other insulin glargine products (Basaglar, Toujeo) continue to state that the safety and efficacy of their use have not been established in patients < 6 years of age with T1DM and pediatric patients with T2DM. The safety and efficacy of insulin glargine-yfgn (Semglee) have not been established in patients < 6 years of age with T1DM and pediatric patients with T2DM. The safety and efficacy of insulin detemir (Levemir) have been established in pediatric patients with T1DM and T2DM. In general, intermediate- and long-acting insulins can have slightly higher exposure (area-under-the-curves) and maximum concentrations in children.

Insulin aspart (Fiasp, Novolog, generic), insulin glulisine (Apidra), and insulin lispro U-100 (Admelog, Humalog, generic) are approved for use in a continuous insulin infusion pump in the pediatric population.

Pregnancy

Available data from published studies over decades have not established an association between use of human insulin (Humulin R, Humulin N, Novolin R, Novolin N) or human insulin isophane/human insulin (Novolin 70/30) during pregnancy and major birth defects, miscarriage, or adverse maternal or fetal outcomes.

There are no clinical studies of the use of insulin glargine 300 U/mL (Toujeo) in pregnant women; it should not be used during pregnancy unless the potential benefit justifies the potential risk. Labeling for insulin aspart (Fiasp) advises that there are no data available in pregnant women to inform of drug-associated risk for birth defects and miscarriage.

In 2012, the pregnancy category for insulin detemir was modified from C to B. In an open-label study that included 310 women with T1DM who were pregnant or intended to become pregnant, no differences in pregnancy outcomes or the health of the fetus and newborn between groups treated with insulin detemir or NPH insulin.

Labeling for the remaining products in this class review generally advise that available data on their use in pregnant women have not established an association with adverse fetal or maternal outcomes.

In general, poorly controlled diabetes during pregnancy increases maternal and fetal risks.

Geriatrics

In elderly patients with diabetes, the initial dosing, dose adjustments, and maintenance dosage should be conservative to reduce the risk of hypoglycemia.

Renal impairment

Renally impaired patients are subject to increased levels of circulating insulin and are at increased risk of hypoglycemia. More frequent insulin dose adjustments may be warranted in this patient population.

No differences in safety or effectiveness were observed in a subgroup analysis of insulin degludec-treated patients with T2DM who had with eGFR < 60 mL/min/1.73 m^2 or eGFR < 30 mL/min/1.73 m^2.

Hepatic impairment

Due to an increased risk of hypoglycemia, more frequent dose adjustments and blood glucose monitoring may be needed in patients with hepatic impairment.

Other

For categories such as age, gender, and obesity, there are no significant data that suggest a difference in drug effect in these patients.

DOSAGES[205,206,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221,222,223,224,225,226,227,228,229]

Drug	Dosing	Time of administration related to mealtime	Availability
Rapid-Acting Insulins			
human insulin inhalation powder (Afrezza)	Dosing should be titrated to glycemic control in combination with a long-acting insulin	At the beginning of the meal	Cartridge: 4 units, 8 units, and 12 units packaged as: ▪ 90 x 4-unit cartridges ▪ 90 x 8-unit cartridges ▪ 90 x 12-unit cartridges ▪ 90 x 4-unit + 90 x 8-unit cartridges ▪ 90 x 8-unit + 90 x 12-unit cartridges ▪ 60 of each 4-unit/8-unit/12-unit 2 inhalers are contained per package
insulin aspart (Fiasp)	Dosing should be titrated to glycemic control in combination with an intermediate- or long-acting insulin (and/or with oral antidiabetic agents for T2DM)	At start of a meal or within 20 minutes after starting a meal	100 units/mL: ▪ 10 mL vial ▪ 3 mL prefilled FlexTouch® pen ▪ 3 mL PenFill cartridges
insulin aspart (Novolog)		5 to 10 minutes before eating	100 units/mL: ▪ 10 mL vial *,† ▪ 3 mL prefilled FlexPen®*,† ▪ 3 mL PenFill cartridges*
insulin glulisine (Apidra)	Dosing should be titrated to glycemic control in combination with an intermediate- or long-acting insulin (and/or with oral antidiabetic agents for T2DM)	Within 15 minutes before a meal or within 20 minutes after starting a meal	100 units/mL: ▪ 10 mL vial ▪ 3 mL prefilled SoloStar® pen
insulin lispro (Admelog, Humalog, Humalog Junior)	Dosing should be titrated to glycemic control in combination with an intermediate- or long-acting insulin (and/or with oral antidiabetic agents for T2DM)	No more than 15 minutes before a meal or immediately after a meal	100 units/mL: ▪ 3 mL vial (Admelog; Humalog) ▪ 10 mL vial (Admelog; Humalog*) ▪ 3 mL prefilled pen (Admelog SoloStar; Humalog KwikPen®*, Humalog Tempo Pen™) ▪ 3 mL prefilled pen (Humalog Junior KwikPen)* ▪ 3 mL cartridge (Humalog) 200 units/mL: ▪ 3 mL prefilled pen (Humalog KwikPen)
insulin lispro-aabc (Lyumjev)	Dosing should be titrated to glycemic control in combination with an intermediate- or long-acting insulin (and/or with oral antidiabetic agents for T2DM)	No more than 20 minutes before a meal or immediately after a meal	100 units/mL: ▪ 10 mL vial ▪ 3 mL prefilled pen (KwikPen, Tempo Pen) 200 units/mL: ▪ 3 mL prefilled pen (KwikPen)

* Authorized generic available.

† FDA approved 10 mL vial and 3 mL FlexPen versions under the marketing of the ReliOn® brand and distributed by Walmart.

Dosages (continued)

Drug	Dosing	Time of administration related to mealtime	Availability
Rapid-Acting Insulins *(continued)*			
human insulin‡ (Humulin R, Novolin R)	Dosing should be titrated to glycemic control in combination with an intermediate or long-acting insulin (and/or with oral antidiabetic agents for T2DM)	30 minutes prior to meal	100 units/mL: ▪ 3 mL vials (Humulin R U-100) ▪ 3 mL pen (Novolin R FlexPen†) ▪ 10 mL multi-dose vials (Humulin R U-100; Novolin R U-100†) 500 units/mL: ▪ 3 mL prefilled pen (Humulin R KwikPen) ▪ 20 mL vials (Humulin R U-500)
Intermediate (N) Insulins			
human insulin NPH‡ (Humulin N, Novolin N)	Dosing should be titrated to glycemic control; Can be used in combination with a quick- or long-acting insulin (and/or with oral antidiabetic agents for T2DM); Total daily dose given as 1 to 2 injections/day	30 to 60 minutes prior to meal or bedtime	100 units/mL: ▪ 3 mL vials (Humulin N) ▪ 10 mL vials (Humulin N; Novolin N†) ▪ 3 mL prefilled pen (Humulin N KwikPen; Novolin FlexPen†)
Long-Acting Insulins			
insulin degludec (Tresiba)	Dosing should be individualized based on the type of diabetes and whether the patient is insulin-naïve; Initial dose in patients with T1DM is one-third of the total daily insulin requirements; Short-acting, pre-meal insulin should be used to satisfy the remainder of the daily insulin requirement	*Adults:* Administer SC once daily any time during the day There should be a minimum interval of 8 hours after the last injection *Pediatrics:* Administer SC once daily at the same time each day; for patients requiring < 5 units each day, use the U-100 vial	100 U/mL: ▪ 10 mL vial ▪ 3 mL FlexTouch pen 200 U/mL: ▪ 3 mL FlexTouch pen
insulin detemir (Levemir)		Once daily (with the evening meal or at bedtime) or twice daily (with the evening meal, at bedtime, or 12 hours after the morning dose)	100 units/mL: ▪ 10 mL vial ▪ 3 mL prefilled pen (FlexTouch pen, FlexPen)§
insulin glargine (Basaglar)		Administer SC once daily at any time during the day, at the same time every day	100 units/mL: ▪ 3 mL prefilled pen (KwikPen, Tempo Pen)
insulin glargine (Lantus)			100 units/mL: ▪ 10 mL vial ▪ 3 mL SoloStar pen
insulin glargine-yfgn (Semglee)			100 units/mL: ▪ 10 mL vial ▪ 3 mL pen

* Authorized generic available.
† FDA approved 10 mL vial and 3 mL FlexPen versions under the marketing of the ReliOn® brand and distributed by Walmart.
‡ Human insulin U-100 (Humulin 70/30, Humulin N, Humulin R, Novolin 70/30, Novolin N, Novolin R) is available over-the-counter.
§ Levemir FlexTouch pen will be discontinued as of February 2023 and replaced by Levemir FlexPen.[230]

Dosages (continued)

Drug	Dosing	Time of administration related to mealtime	Availability
Long-Acting Insulins *(continued)*			
insulin glargine (Toujeo)	Dosing should be individualized based on the type of diabetes and whether the patient is insulin-naïve; Initial dose in patients with T1DM is one-third of the total daily insulin requirements; Short-acting, pre-meal insulin should be used to satisfy the remainder of the daily insulin requirement	Administer SC once daily at any time during the day, at the same time every day	300 units/mL: ▪ 1.5 mL SoloStar prefilled pen ▪ 3 mL Max SoloStar prefilled pen
Rapid/Intermediate-Acting Combination Products			
insulin aspart/ protamine aspart (Novolog Mix 70/30)	Dosing should be titrated to glycemic control	Within 15 minutes before meal initiation or immediately after a meal Typically dosed on a twice-daily basis (breakfast and dinner)	▪ 10 mL vial*,† ▪ 3 mL prefilled FlexPen*,†
insulin lispro/ protamine lispro (Humalog Mix 75/25, Humalog Mix 50/50)	Dosing should be titrated to glycemic control	Within 15 minutes before meal initiation or immediately after a meal	▪ 10 mL vial (Humalog Mix 50/50, Humalog Mix 75/25) ▪ 3 mL prefilled KwikPen (Humalog Mix 50/50, Humalog Mix 75/25*)
human insulin (Humulin 70/30, Novolin 70/30)	Dosing should be titrated to glycemic control in combination with an intermediate or long acting insulin (and/or with oral antidiabetic agents for T2DM)	30 to 60 minutes prior to meal	▪ 3 mL vials (Humulin 70/30) ▪ 10 mL vials (Humulin 70/30; Novolin 70/30†) ▪ 3 mL prefilled pen (Humulin 70/30 KwikPen, Novolin 70/30 FlexPen†)

* Authorized generic available.
† FDA approved 10 mL vial and 3 mL FlexPen versions under the marketing of the ReliOn® brand and distributed by Walmart.

Injectable insulins may be administered via subcutaneous (SC) injection into the thigh, upper arm, and abdomen regions. Injection sites should be rotated within the same region.

Regular insulin (Humulin R U-100 and U-500) may be diluted with sterile diluent for Humulin R for SC injection only under medical supervision. Diluted insulin may be used for 14 days when stored at 30°C (86°F) or 28 days when stored at 5° C (41°F). See prescribing information for more details.

Regular insulin, insulin glulisine (Apidra), insulin lispro 100 units/mL (Admelog, Humalog U-100, generic), insulin lispro-aabc 100 units/mL (Lyumjev), and insulin aspart (Fiasp, Novolog, generic) can be administered intravenously (IV) under medical supervision. Insulin lispro 200 units/mL (Humalog U-200), insulin aspart/protamine aspart (Novolog Mix), insulin lispro/protamine lispro (Humalog Mix), insulin detemir (Levemir), insulin glargine (Basaglar, Lantus, Toujeo), and insulin glargine-yfgn (Semglee) should not be given IV or used in insulin infusion pumps. See prescribing information for dilution and administration details.

Insulin aspart (Fiasp, Novolog, generic), insulin glulisine (Apidra), insulin lispro (Admelog, Humalog U-100, generic), insulin lispro-aabc 100 units/mL (Lyumjev), and insulin lispro/protamine lispro (Humalog Mix 50/50, Humalog Mix 75/25) may also be administered via continuous SC infusion in accordance with insulin infusion pump system instructions for use. Rotate infusion sites to reduce risk of lipodystrophy and localized cutaneous amyloidosis. Repeated insulin injections into areas of lipodystrophy or localized cutaneous amyloidosis or a sudden change in the injection site (to an unaffected area) may result in hyperglycemia.

The use of human insulin 500 U/mL in combination with other insulins and its use as a continuous SC infusion have not been established. Becton-Dickenson has created a syringe specific for U-500 insulin administration that does not require dose conversion as previously needed when using U-100 insulin/TB syringe to deliver U-500 insulin.[231] The syringes are only available by prescription and should be co-prescribed with U-500 insulin.

Doses of insulin should be individualized. Generally, for both children and adults, an initial dose is 0.5 to 1 unit/kg/day. Insulin requirements may be altered during major illness, emotional disturbances, stress, or changes in exercise, meal patterns, or coadministered drugs. The duration of action of all insulins will vary according to the dose, injection site, blood flow, temperature, and level of physical activity.

In patients with T1DM, use insulin degludec, insulin detemir, and insulin glargine (Lantus) concomitantly with a short- or rapid-acting insulin. Start insulin degludec and insulin detemir at the same unit dose as the total daily long- or intermediate-acting insulin unit dose when switching from other insulin therapies. Dosage adjustment may be required to lower the risk of hypoglycemia.

To minimize risk of hypoglycemia, the starting dose of insulin degludec (Tresiba) in pediatric patients who are already on long- or intermediate-acting insulin therapy is 80% of the previous total daily insulin dose. Adults switching to insulin degludec may start at the same unit-per-unit dosage. Insulin degludec is not recommended in pediatric patients who require doses < 5 units. Healthcare professionals should be contacted if a dose is missed in pediatric patients receiving insulin degludec.

Two open-label phase 3 studies in patients with T1DM (n=493) or T2DM (n=687) evaluated insulin degludec given in flexible once-daily dosing intervals compared with insulin degludec and insulin glargine administered once daily at the same time each day. The flexible dosing intervals were predefined with variations between 8 and 40 hours. In patients with T1DM or T2DM, flexible dosing was shown to be non-inferior (upper limit of the 95% confidence interval [CI] for the treatment difference was ≤ 0.4%) with respect to HbA1c reduction versus same time dosing for insulin degludec and insulin glargine. In addition, nocturnal hypoglycemic events were reduced by 40% ($p < 0.01$) in the flexible dosing group versus the insulin glargine group. In patients with T2DM, rates for hypoglycemia were comparable between all groups.

The FlexPen delivery system is a disposable prefilled pen for insulin aspart (Novolog, generic), insulin aspart/protamine aspart (Novolog Mix), and insulin detemir (Levemir). The FlexPen is able to dial up to 60 units of insulin in 1-unit increments. The FlexTouch delivers from 1 to 80 units of insulins aspart (Fiasp), detemir (Levemir), and degludec U-100 and up to 160 units of insulin degludec U-200.

The KwikPen prefilled pen device for human insulin NPH (Humulin N), insulin NPH/regular (Humulin 70/30), insulin lispro (Humalog, generic), insulin lispro-aabc (Lyumjev), and insulin lispro/protamine lispro (Humalog Mix) can provide up to 60 units of insulin in 1-unit increments utilizing a dial mechanism. The KwikPen prefilled pen device for insulin glargine (Basaglar) can provide up to 80 units of insulin per injection in 1-unit increments. No dose conversion is needed when using the Humulin R U-500 KwikPen since the dose window shows the number of units to be injected. Humalog Junior KwikPen (and generic) contains 300 units of insulin lispro U-100 and can deliver doses in 0.5 unit of insulin to a maximum of 30 units in a single injection.

One refillable pen device is currently available for patients that may require smaller doses of insulin (e.g., children). The NovoPen Echo® provides half-unit dosing capabilities (from 0.5 to 30 units) and a memory function that records the dose and the date and time since the previous dose. NovoPen Echo should only be used with the Novo Nordisk product line of insulin cartridges.[232]

The SoloStar® prefilled pen devices for insulin glargine (Lantus, Toujeo), insulin glulisine (Apidra), and insulin lispro (Admelog) are useful for patients that require larger doses of insulin. This pen system is able to dial up to 80 units of insulin in 1-unit increments. Insulin glargine 300 units/mL (Toujeo) is also available in the 3 mL Max Solostar pen that delivers doses in 2-unit increments up to 160 units per injection. It is recommended for patients requiring at least 20 units/day. If switching from the Toujeo SoloStar to Max SoloStar pen, increase or decrease dose by 1 unit, to match the dose increments on the prefilled pen.

The Tempo Pen™ is a prefilled insulin pen which is a component of the Tempo personalized diabetes management platform, available for insulin lispro-aabc (Lyumjev), insulin lispro (Humalog), and insulin glargine (Basaglar).[233] A Tempo Smart Button™ attaches to the pen, which then transfers insulin dose-related information to the TempoSmart™ app via Bluetooth® technology. The app can combine data from the insulin pen with readings from either a Tempo blood glucose meter or a Dexcom continuous glucose monitoring (CGM) system to assist in diabetes management. The Tempo system is indicated for use in patients ≥ 18 years who are diagnosed with T1DM or T2DM and is not indicated for patients with GDM nor those who use an insulin pump.

Semglee prefilled pens deliver insulin glargine-yfgn up to 80 units per injection and can be dialed in 1-unit increments.

People who are blind or have impaired vision should not use the prefilled pens without help from a person trained to use the pen. The FlexTouch (Fiasp, Novolog [and generic], Novolog Mix), KwikPen (Basaglar, Humulin, Humalog, Humalog Mix), Solostar (Admelog, Apidra, Lantus, Toujeo), and Semglee (insulin glargine-yfgn) prefilled pens should be used with caution in patients with visual impairment who may rely on audible clicks to dial their dose.

Do not transfer insulin degludec (Tresiba) or insulin glargine (Toujeo) from the prefilled pen/cartridge into a syringe as dosing errors may result.

Most pens and their compatible cartridges are refrigerated before use. Following the first use, these formulations should be stored at room temperature. Expiration dates are typically 10 to 14 days for regular insulin and insulin NPH, as well as mixes of regular insulin, insulin aspart, or insulin lispro with insulin NPH at room temperature. The rapid-acting insulins and insulin glargine cartridges and pens expire in 28 days, while those for insulin detemir last 42 days.

Insulin inhalation powder (Afrezza) should only be administered via oral inhalation using the breath-powered inhaler provided. The recommended initial mealtime dose is 4 units at each meal for insulin-naïve individuals. For patient using SC mealtime insulin, the mealtime inhalation dose should be determined by using the dose conversion table provided in the package insert, which instructs that 4 units of injected mealtime insulin is equal to 4 units of inhaled mealtime insulin. Doses should be rounded up to the nearest 4 units of insulin inhalation powder. For individuals using SC pre-mixed insulin, estimate the mealtime injected dose by dividing half of the total daily injected pre-mixed insulin dose equally among the 3 meals of the day. Then, convert each estimated injected mealtime dose to an appropriate insulin inhalation powder dose as outlined in the package insert and administer half of the total daily injected pre-mixed dose as an injected basal insulin dose.

Multiple cartridges are needed for insulin inhalation powder dosages > 12 units. Administer a single inhalation per cartridge. Only 1 inhaler should be used at a time. Replace the inhaler every 15 days. Insulin inhalation powder cartridges should be kept refrigerated and must be used within 10 days at room temperature and 3 days once the foil package is opened.

To administer insulin inhalation powder, fully exhale, close lips around the mouthpiece, tilt the inhaler downward while keeping the head level, inhale deeply and hold breath as long as comfortable. To avoid loss of drug powder once the drug cartridge has been inserted into the inhaler, the inhaler must be kept level with the white mouthpiece on top and the purple base on the bottom; the inhaler must not be shaken or dropped. If any of the above occurs, the cartridge should be replaced before use.

CLINICAL TRIALS

Search Strategies

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all brand names in this class. Randomized, comparative, controlled trials comparing agents within this class in an outpatient setting for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

Numerous studies were found meeting standard criteria. The data included here were further evaluated to remove studies that were found to be unacceptable for the following reasons: small treatment group, *post hoc* analysis, use of insulin pumps, studies relying on outcomes from self-reported data, inappropriate treatment duration, and unapproved formulation, dosage regimen, or route of administration.

The method of administration and associated monitoring makes it difficult to perform properly blinded studies with these drugs. Due to the lack of double-blind studies, open-label studies have been included; while these large studies may produce accurate results, the study design should be taken into consideration.

In countries outside of the US, blood glucose values are typically reported in mmol/L. For those studies reporting blood glucose values in mmol/L, the value in mg/dL can be estimated by multiplying the mmol/L value by 18.

Injectable insulin

insulin aspart (Fiasp) versus insulin aspart (Novolog)

Onset 1:[234,235] A 26-week, phase 3, multicenter, active-controlled, parallel-group trial evaluated the efficacy of faster-acting insulin aspart (Fiasp) compared to conventional insulin aspart (Novolog) in 1,143 adults with inadequately controlled T1DM (HbA1c, 7% to 9.5%). During an 8-week run-in period, patients were optimized on background basal insulin detemir (once- or twice-daily) and switched their bolus insulin to mealtime Novolog on a unit-to-unit basis. After run-in, patients were randomized 1:1:1 to blinded mealtime (0 to 2 minutes before a meal) Fiasp or Novolog, or open-label postmeal (20 minutes after start of a meal) Fiasp; insulin detemir was continued. Patients adjusted bolus insulin doses based on preprandial plasma glucose levels. The primary endpoint was change from baseline in HbA1c after 26 weeks of treatment. Fiasp met the prespecified noninferiority criteria (0.4%) for the primary endpoint (difference between mealtime Fiasp and Novolog, -0.15% [95% CI, -0.23 to -0.07]; difference between postmeal Fiasp and mealtime Novolog, 0.04% [95% CI, -0.4 to 0.12]). Compared to Novolog, the likelihood of achieving an HbA1c < 7% was statistically significantly higher with mealtime Fiasp (estimated odds ratio [OR], 1.47 [95% CI, 1.02 to 2.13]; p=0.04), but not with postmeal Fiasp. The difference in mean 1-hour and 2-hours postprandial plasma glucose (PPG) was statistically significantly lower with mealtime Fiasp compared to Novolog. However, when comparing the PPG for postmeal Fiasp and mealtime Novolog, the 1-hour PPG was statistically significantly lower for Novolog, but not significant difference was seen at 2-hours. Incidence of hypoglycemia, including severe episodes, was similar between the groups.

Onset 2:[236,237] In a 26-week, phase 3, double-blind trial, faster-acting insulin aspart (Fiasp) was compared to conventional insulin aspart (Novolog) in 689 adults with inadequately controlled T2DM with basal insulin and oral antidiabetic agents. During an 8-week run-in period, patients were optimized to basal insulin glargine (once-daily) and switched their bolus insulin to mealtime Novolog on a unit-to-unit basis. Patients were then randomized 1:1 to mealtime Fiasp or Novolog administered 0 to 2 minutes before each main meal, both with background insulin glargine and metformin. Bolus insulin dose adjustments were made daily by the patient base on plasma glucose levels and reviewed weekly by the investigator. The primary endpoint was change from baseline in HbA1c after 26 weeks of treatment. At 26-weeks mean HbA1c decreased to 6.6% in both groups; mean change was -1.38% for Fiasp and -1.36% for Novolog. Fiasp improved 1-hour PPG compared to Novolog, but no differences were seen in 2-hour PPG. Overall incidence of hypoglycemia was similar except for an increase in 0-2-hour postmeal hypoglycemia with Fiasp (2.27 versus 1.49 per patient-year of exposure).

insulin aspart (Fiasp) versus insulin aspart (Novolog) added to insulin degludec in pediatric patients

In a 26-week, active-controlled, parallel-group trial, 777 pediatric patients 2 to 17 years of age with T1DM were randomized 1:1:1 to blinded mealtime insulin aspart, blinded mealtime Novolog, or open-label postmeal Fiasp, all added to once daily insulin degludec.[238] Mealtime doses were administered 0 to 2 minutes before the meal, and postmeal doses were administered 20 minutes after the start of the meal. After 26 weeks, both mealtime and postmeal Fiasp demonstrated noninferiority to Novolog in change in HbA1c from baseline (difference from Novolog for mealtime Fiasp, -0.17% [95% CI, -0.3 to -0.03]; difference from Novolog for postmeal Fiasp, 0.13% [95% CI, -0.01 to 0.26]).

insulin aspart (Novolog) versus regular human insulin

A prospective, multicenter, randomized, parallel-group, open-label study was performed in 423 basal-bolus treated patients with T1DM.[239] Main outcome measures included blood glucose control assessed by HbA1c, 9-point self-monitored blood glucose profiles, insulin dose, quality of life, hypoglycemia, and adverse events. An algorithm-driven increase occurred in the dose and number of daily injections of basal insulin, particularly in the insulin aspart group. After 12 weeks of treatment, HbA1c was significantly lower in the insulin aspart group compared to regular human insulin groups by 0.17% (95% CI, 0.3 to 0.04; p<0.05). Comparison of the blood glucose profiles showed lower blood glucose levels with insulin aspart after breakfast (p<0.0001) and dinner (p<0.01). There were no differences between treatments in the incidence of hypoglycemic episodes or in the adverse event profiles. The WHO Diabetes Treatment Satisfaction Questionnaire score for perceived hyperglycemia was lower with insulin aspart (p=0.005).

In a 6-month, similarly designed trial in 1,070 adults with T1DM, HbA1c was significantly lower in the insulin aspart group (0.12% reduction in HbA1c) after 6 months.[240] The insulin aspart group had lower post-prandial blood glucose levels, but had higher preprandial glucose levels before breakfast and dinner (p<0.01). Major hypoglycemia episodes overall were similar in both treatment groups, but major hypoglycemia episodes occurring at night that required parenteral treatment occurred more often in the regular insulin group.

Another similarly designed study was performed over 6 months with a 6-month extension period. In 882 men and women with T1DM, HbA1c values were significantly lower with insulin aspart than with regular insulin (7.78% versus 7.93%; p=0.005) at 6 months.[241] In the extension period (n=714), the difference in HbA1c continued to remain significant at 12 months. The mean basal NPH dose at 12 months was significantly higher for the insulin aspart group than that for the regular insulin group (0.314 versus 0.296 units/kg; p=0.011). A similar percentage of patients in each treatment group had a major hypoglycemic episode by 6 months. Fewer subjects in the insulin aspart group than in the regular insulin group (4% versus 8%) experienced a major hypoglycemic episode during the night.

A trial was conducted in patients with T1DM who were randomized to mealtime insulin aspart with up to 4 daily NPH doses and a 25% increase in bedtime NPH dose (n=187) or to mealtime human unmodified insulin with once or twice daily basal NPH insulin (n=181).[242] Efficacy and safety were evaluated at 12 weeks (primary evaluation period) and 64 weeks. At 12 and 64 weeks, there was no statistically significant difference in HbA1c reduction between the insulin aspart and regular insulin groups (-0.09% and -0.14%, respectively). Post-prandial glucose values were lower with insulin aspart, and no significant differences were found in mild or severe hypoglycemia or adverse event rates. At 64 weeks, treatment satisfaction was higher in the insulin aspart group while quality of life was not different.

To compare quality of life (QOL) and treatment satisfaction, 424 patients were randomized to basal-bolus treatment with either insulin aspart (n=283) or regular human insulin (n=141) in a 6-month, multinational, randomized, open-label trial.[243] After 6 months, insulin aspart was associated with significantly greater improvement in treatment satisfaction than human insulin in 2 different scales (p<0.01), and in QOL with respect to diet restrictions (p<0.01). Improved satisfaction was mainly due to increased dietary and leisure time flexibility (p<0.0001).

In the multinational, double-blind, crossover trial, 155 patients with T1DM were randomized to two 16-week treatment periods with either insulin aspart or human insulin.[244] NPH insulin was given as basal insulin once or twice daily as needed. Treatment periods were separated by a 4-week washout. The rate of major nocturnal hypoglycemic episodes was 72% lower with insulin aspart than with human insulin (0.067 versus 0.225 events/month; p=0.001). The total rate of major hypoglycemia did not differ significantly between treatments (insulin aspart/human insulin relative risk, 0.72 [95% CI, 0.47 to 1.09]; p=0.12). Mean HbA1c remained constant, slightly below 7.7% on both treatments.

biphasic insulin aspart (Novolog Mix 70/30) versus human insulin 70/30

In a randomized, open-label, parallel trial, 177 patients with T2DM were assigned to meal-related injection of biphasic insulin aspart 3 times a day or biphasic human insulin twice a day over a study period of 24 weeks.[245] The mean difference between treatment groups in HbA1c after 24 weeks of treatment was 0.08% (p=0.6419). Significant differences in blood glucose levels were observed after lunch (156 versus 176 mg/dL, p=0.0289), before dinner (142 versus 166 mg/dL p=0.006), and after dinner (154 versus 182 mg/dL; p=0.002) in favor of biphasic insulin aspart. No differences were found regarding safety parameters in the 2 treatment groups.

The clinical efficacy and safety of 2 treatment regimens, biphasic insulin aspart at all 3 meals plus NPH insulin at bedtime versus premixed human insulin at breakfast and regular insulin at lunch and dinner plus NPH at bedtime, were compared in 167 adolescents with T1DM.[246] This open-label, parallel-group trial reported that after 4 months on biphasic insulin aspart therapy, HbA1c was not significantly different from that with human insulin (9.39% versus 9.3%, respectively). The body mass index increased in both groups, but significantly (p=0.005) less in the biphasic insulin aspart group. No significant group differences were found for the rate of hypoglycemic episodes.

insulin aspart (Novolog) versus regular human insulin versus insulin 70/30

A total of 231 patients with T2DM were randomized to insulin aspart (n=75), regular insulin (n=80), or insulin 70/30 (n=76) for 3 months with or without bedtime NPH insulin.[247] A total of 204 patients completed the trial according to protocol. The primary endpoint was change in HbA1c from baseline. HbA1c decreased 0.91% ± 1% for insulin aspart, 0.73% ± 0.87% for regular insulin, and 0.65% ± 1.1% for insulin 70/30. Postprandial blood glucose decreased more in the insulin aspart group compared with regular insulin and insulin 70/30. Incidence of hypoglycemic events per month were 0.56 with regular insulin, 0.4 with insulin aspart, and 0.19 with insulin 70/30.

biphasic insulin aspart (Novolog Mix 70/30) versus NPH human insulin

In a double-blind study of 403 patients with T2DM not controlled on oral hypoglycemic agents, patients were randomized to receive either biphasic insulin aspart or NPH insulin immediately before breakfast and dinner for 16 weeks.[248] Oral hypoglycemic agents were discontinued. In both groups, HbA1c decreased by greater than 0.6% (p<0.0001 versus baseline). The biphasic insulin aspart group had a decreased daily postprandial glycemic exposure (mean difference, 0.69 mmol/L; p<0.0001). Overall safety profile of both groups was similar.

biphasic insulin aspart (Novolog Mix 70/30) versus biphasic insulin lispro (Humalog Mix 75/25)

Patients (n=137) with T2DM currently receiving insulin treatment were randomized to a multicenter, open-label, crossover comparison of biphasic insulin aspart and biphasic insulin lispro.[249] Efficacy and safety profiles were assessed after 12 weeks of treatment. Treatment with biphasic insulin aspart was not inferior to treatment with biphasic insulin lispro. Adverse event profiles were similar between treatments, as was the incidence of hypoglycemic episodes (0.69 episodes/month with biphasic insulin aspart and 0.62 episodes/month with biphasic insulin lispro; p=not significant [NS]). For all device features assessed, the biphasic insulin aspart FlexPen consistently received higher scores (all p<0.005). Furthermore, 74.6% of patients preferred to continue using the FlexPen, whereas 14.3% preferred the biphasic insulin lispro pen (p<0.001).

insulin degludec (Tresiba) versus insulin detemir (Levemir)

The efficacy and safety of insulin degludec used in combination with mealtime insulin aspart for the treatment of T1DM were evaluated in an open-label, active-controlled clinical trial. A total of 455 patients with inadequately controlled diabetes were randomized to insulin degludec U-100 or insulin detemir once-daily in the evening.[250] After 8 weeks, insulin detemir could be dosed twice-daily. By trial end, 32.9% of patients on insulin detemir were dosed twice daily. At week 26, the difference in HbA1c reduction from baseline between insulin degludec and insulin detemir was -0.09% (95% CI, -0.23 to 0.05). Noninferiority was met. At week 26, 41.1% of patients on insulin degludec and 37.3% of those on insulin detemir achieved HbA1c < 7%. The incidence of severe hypoglycemia was similar between treatment groups (10.5% versus 10.6%). Mean weight gain reported was 1.5 kg for insulin degludec versus 0.4 kg for insulin detemir. In an open-label extension study, after 1 year the rate of nocturnal hypoglycemia was 33% lower with insulin degludec than insulin detemir (p<0.05).[251] Change in HbA1c was similar in both groups, but insulin degludec produced a significantly greater reduction in FPG than insulin detemir (difference degludec compared to detemir, -1.11 mmol/L [95% CI, -1.83 to -0.4]; p<0.05).

insulin degludec (Tresiba) versus insulin glargine (Lantus)

In a 52-week, open-label study, 629 patients with inadequately controlled T1DM were randomized to insulin degludec U-100 once-daily with the evening meal or insulin glargine U-100 once-daily according to the package insert.[252] Mealtime insulin aspart was also administered in both groups. At week 52, the difference in HbA1c reduction from baseline between insulin degludec and insulin glargine was -0.01% (95% CI, -0.14 to 0.11). Noninferiority was met. At week 52, 39.8% of patients on insulin degludec and 42.7% of those on insulin glargine achieved HbA1c < 7%. Severe hypoglycemia occurred in 12.3% of patients in the insulin degludec group and 10.4% in the insulin glargine group. Mean weight gain reported was comparable between the groups (2.1 kg versus 2 kg, respectively).

In a 26-week open-label study, 493 patients with inadequately controlled T1DM were randomized to insulin degludec U-100 injected once daily with the main evening meal, or insulin degludec injected once daily at any time of day, or insulin glargine dosed once daily in the evening.[253] Mealtime insulin aspart was administered in all groups. At week 26, the difference in HbA1c reduction from baseline between insulin degludec administered at the same time and at alternating times, each compared to insulin glargine was 0.16% and 0.17%, respectively. Noninferiority was met. Severe hypoglycemia occurred in 10.4% of patients in the insulin degludec flexible-dose group, 12.7% of patients in the insulin degludec evening meal dose group, and 9.9% in the insulin glargine group. Mean weight gain reported was 1.3 kg for insulin degludec flexible dose group, 0.9 kg in the insulin degludec evening meal dose group, and 1.7 kg in the insulin glargine group.

An open-label study randomized 1,030 insulin-naïve patients with inadequately controlled T2DM to insulin degludec U-100 once-daily with the evening meal or insulin glargine U-100 once-daily.[254] Background therapy consisted of metformin with or without a dipeptidyl peptidase-4 (DPP-4) inhibitor in both groups. At week 52, the difference in HbA1c reduction from baseline between insulin degludec and insulin glargine was 0.09% (95% CI, -0.04 to 0.22). Noninferiority was met. At week 52, 51.7% of patients on insulin degludec and 54.1% of those on insulin glargine achieved HbA1c < 7%. Severe hypoglycemia was reported in 0.3% of patients in the insulin degludec group, 1.9% of patients in the insulin glargine group.[255] Mean weight gain reported was similar between the groups (2.6 kg versus 2.3 kg, respectively).

A total of 457 insulin-naïve patients with T2DM were randomized to insulin degludec U-200 once-daily with the evening meal or insulin glargine U-100 once-daily in an open-label study.[256] Background therapy consisted of metformin with or without a DPP-4 inhibitor in both groups. At week 26, the difference in HbA1c reduction from baseline between insulin degludec and insulin glargine was 0.04% (95% CI, -0.11 to 0.19). Noninferiority was met. At week 26, 52.2% of patients on insulin degludec and 55.9% of those on insulin glargine achieved HbA1c < 7%. No incidences of severe hypoglycemia were reported it either group.[257] Mean weight gain reported was similar between the groups (2.3 kg versus 1.9 kg, respectively).

In an open-label study, 435 insulin-naïve patients with T2DM were randomized to insulin degludec U-100 once-daily with the evening meal or insulin glargine U-100 once-daily.[258] Background therapy with 1 or more oral anti-diabetic drugs (OADs) was continued. At week 26, the difference in HbA1c reduction from baseline between insulin degludec and insulin glargine was 0.11% (95% CI, -0.03 to 0.24). At week 26, 40.8% of patients on insulin degludec and 48.6% of those on insulin glargine achieved HbA1c < 7%. Noninferiority was met. No incidence of severe hypoglycemia was reported it either group.[259] Mean weight gain reported was similar between the groups (1.6 kg and 1.7 kg, respectively).

In an open-label study, 687 patients with T2DM were randomized to insulin degludec U-100 injected once-daily with the main evening meal, insulin degludec injected once daily at any time each day, or to insulin glargine U-100 injected once daily according to the approved labeling.[260] Background therapy with up to 3 of the following agents was continued, metformin, a sulfonylurea, a glinide, or a TZD. At week 26, the difference in HbA1c reduction from baseline between insulin degludec administered at the same time and at alternating times, each compared to insulin glargine was 0.18% and 0.04%, respectively. Noninferiority was met. The proportion of patients who achieved HbA1c < 7% were 40.8% for those given insulin degludec dosed at the same time each day, 38.9% for insulin degludec dosed at varying times, and 43.9% for insulin glargine. Severe hypoglycemia occurred in < 1% of patients in all treatment groups.[261] Mean weight gain reported was similar between the insulin degludec groups (1.9 kg and 1.6 kg).

A total of 992 patients with T2DM were randomized to insulin degludec U-100 injected once-daily with the main evening meal, or insulin glargine U-100 injected once-daily.[262] Insulin aspart was administered before each meal in both treatment arms in an open-label study. Metformin and/or pioglitazone were used as background therapy in both treatment arms. At week 52, the difference in HbA1c reduction from baseline between insulin degludec and insulin glargine was 0.08% (95% CI, -0.05 to 0.21). Noninferiority was met. A similar proportion of patients achieved HbA1c < 7% in each group. The incidence in severe hypoglycemia was similar between treatment groups (4.5% versus 4.4%).[263] Mean weight gain was also similar between the groups (3.2 kg versus 3.5 kg).

Two, 64-week, double-blind, crossover trials, SWITCH-1 and SWITCH-2, assessed hypoglycemic episodes with insulin degludec compared to insulin glargine 100 IU/mL in adults with T1DM (SWITCH-1; n=501) and T2DM (SWTICH-2; n=721).[264,265] In both studies, patients were randomized to receive once daily insulin degludec followed by insulin glargine 100 IU/mL or insulin glargine 100 IU/mL followed by insulin degludec. The studies consisted of two, 32-week treatment periods, each with a 16-week titration period and a 16-week maintenance period. During the maintenance period in both trials, insulin degludec demonstrated significantly lower rates of overall symptomatic hypoglycemia (SWITCH-1 rate ratio [RR] of 0.89 [95% CI, 0.85 to 0.94; p<0.001 for noninferiority and p<0.001 for superiority]; SWITCH-2 RR, 0.7 [95% CI, 0.61 to 0.8; p<0.001]). Similarly, insulin degludec was associated with a lower rate of severe hypoglycemic episodes and nocturnal symptomatic hypoglycemia. The SWITCH-PRO study (n=498) was similarly designed to SWITCH-2 and incorporated blinded professional continuous glucose monitoring (CGM) to analyze the primary endpoint of the percentage of time spent in the glycemic range of 3.9 to 10 mmol/L.[266] The study reported significantly more time in target range (3.9 to 10 L/L) with insulin degludec compared with insulin glargine U-100 (mean, 72.1% versus 70.7%, respectively; difference, 1.43%; 95% CI, 0.12 to 2.74; p=0.032) which demonstrated noninferiority and superiority of insulin degludec compared to insulin glargine U-100. This was equivalent to 20.6 minutes of additional time in range with insulin degludec versus insulin glargine U-100.

insulin degludec (Tresiba) versus insulin glargine U-100 (Lantus) on cardiovascular outcomes

The DEVOTE trial was a 2-year, phase 3b, multicenter, international, randomized, double-blind, active comparator-controlled trial that compared the cardiovascular safety of insulin degludec and insulin glargine U-100 (1:1) in 7,637 patients with T2DM when added to standard of care.[267] Patients enrolled had a history of CVD, chronic kidney disease, or multiple CV risk factors. The primary endpoint was the time to first occurrence of cardiovascular death, nonfatal MI, or nonfatal stroke. There was no statistically significant difference in occurrence of the primary endpoint between insulin degludec and insulin glargine U-100 (hazard ratio [HR], 0.91; in favor of insulin degludec). However, statistically significantly fewer patients in the degludec group experienced severe hypoglycemia (27% fewer patients; 40% reduction in severe hypoglycemia episodes overall; 54% relative risk reduction in severe nocturnal hypoglycemia).

insulin detemir (Levemir) versus insulin NPH (Novolin N)

A 6-month, prospective, randomized, open-label, controlled, parallel-group trial conducted at 92 sites included 749 men and women with T1DM with HbA1c < 12% who were already taking daily intermediate- or long-acting insulin and a fast-acting human insulin or insulin analog as bolus insulin.[268] Patients were randomized to insulin detemir or NPH insulin at bedtime in combination with human insulin with main meals. Main outcome measures included HbA1c, FPG, and hypoglycemia. After 6 months, FPG was lower with insulin detemir than with NPH insulin (difference, -1.16 mmol/L; p=0.001), whereas HbA1c did not differ significantly between treatments (difference, -0.12%; p=NS). Day-to-day variability in self-measured fasting blood glucose was lower with insulin detemir (2.82 versus 3.6 mmol/L; p<0.001). Lower glucose levels were seen before breakfast with insulin detemir compared to NPH (p<0.001). There was a 26% reduction in the relative risk of nocturnal hypoglycemia with insulin detemir compared with NPH (p=0.003). The adverse effect profiles were similar between treatment groups.

In a 26-week, open-label, randomized, parallel-group study, 347 children with T1DM, aged 6 to 17 years, received insulin detemir or NPH insulin once or twice daily plus insulin aspart before meals.[269] The mean HbA1c decreased by approximately 0.8% with both treatments. Within-subject variation in self-measured fasting plasma glucose was significantly lower with insulin detemir than with NPH insulin (p<0.001), as was mean fasting plasma glucose (8.4 versus 9.6 mmol/L; p=0.022). The risk of nocturnal hypoglycemia was 26% lower with insulin detemir (p=0.041).

A 1-year open-labeled, parallel group trial compared insulin detemir with NPH insulin, in combination with mealtime insulin aspart in 348 patients aged 2 to 16 years with T1DM.[270,271] Randomization was stratified by age (2 to 5 years, n=82; 6 to 16 years, n=265). Mean HbA1c was similar between groups at baseline (8.2% versus 8.1%), and changed little over 1 year (8.1% versus 8.3%). FPG was similar at baseline (8.44 versus 8.56 mmol/L) and decreased during the study (-1 versus -0.45 mmol/L). A lower rate of hypoglycemia was observed with insulin detemir compared with NPH (24-h; 50.6 versus 78.3 episodes per patient-year; nocturnal hypoglycemia, 8 versus 17.4 episodes per patient-year). No severe hypoglycemic episodes occurred with insulin detemir, while 3 subjects reported 6 episodes with NPH insulin.

In an open-label study, 310 women with T1DM who were pregnant or intended to become pregnant were randomized to insulin detemir (once or twice daily) or NPH insulin (1 to 3 times daily). Insulin aspart was administered before each meal. Mean HbA1c was < 7% at 10, 12, and 24 weeks of gestation in both arms. In the intent-to-treat population, the adjusted mean HbA1c at gestational week 36 was similar in each arm. There were no differences in pregnancy outcomes or the health of the fetus and newborn between the groups.

In a controlled, open-label, single-center, noninferiority trails, insulin detemir was compared to NPH insulin in women with pregestational and gestational T2DM.[272] Women who failed medical nutrition therapy or oral hypoglycemic therapy were randomized to receive detemir (n=42) or NPH insulin (n=45) between 14 and 32 weeks of gestation. Initial total daily insulin dose was 0.7, 0.8, and 0.9 units/kg of body weight during the first, second, and third trimester, respectively. Sixty percent of the total daily dose was given in the morning and 40% in the evening and 2/3 was given as basal insulin (detemir or NPH) twice a day and one-third as prandial rapid-acting insulin. Mean fasting blood glucose (101.2 versus 99.3, respectively), mean postprandial glucose (115.2 versus 113.4, respectively), proportion of women achieving overall glycemic control, time to achieve glycemic control, and maternal weight gain were all similar between the groups. In addition, birth weight, gestational age at delivery, Apgar score and neonatal hypoglycemia were also similar. However, insulin detemir was associated with a lower rate of hypoglycemia per week compared to NPH insulin (28 versus 102, respectively; p<0.001).

In the 20-week, multicenter, randomized, open-label, parallel-group trial, 504 (intent-to-treat group [ITT] n=498) patients with T2DM, poorly controlled on oral antidiabetic therapy, were randomly assigned to receive an evening SC injection of insulin detemir, a pre-breakfast injection of insulin detemir, or an evening injection of NPH insulin, in addition to their existing oral antidiabetic regimen.[273] Morning and evening detemir were associated with reductions in HbA1c similar to those receiving evening NPH (-1.58%, -1.48%, and -1.74%, respectively). Compared with evening NPH insulin, 24-hour and nocturnal hypoglycemia were reduced by 53% (p=0.019) and 65% (p=0.031), respectively, with evening insulin detemir. Incidences of hypoglycemia did not differ significantly between groups that received morning and evening insulin detemir, but nocturnal hypoglycemia was reduced further, by 87%, with morning insulin detemir compared with evening NPH insulin (p<0.001). Weight gain was 1.2 kg, 0.7 kg, and 1.6 kg with morning insulin detemir, evening insulin detemir, and NPH, respectively (p=0.005 for evening detemir versus NPH).

Patients with T2DM (n=476) with HbA1c 7.5% to 10% were randomized to add-on insulin detemir or NPH insulin twice daily to existing oral antidiabetic agent therapy in a parallel-group, open-label, multicenter trial.[274] At 24 weeks, HbA1c had decreased by 1.8% and 1.9% for insulin detemir and NPH insulin, respectively (p=NS). In both groups, 70% of participants achieved an HbA1c < 7%, but the proportion achieving this without hypoglycemia was higher with insulin detemir than with NPH insulin (26% versus 16%, p=0.008). Compared with NPH insulin, the risk for all hypoglycemia with insulin detemir was reduced by 47% (p<0.001) and nocturnal hypoglycemia by 55% (p<0.001). The mean weight gain was 1.2 kg with insulin detemir and 2.8 kg with NPH insulin (p<0.001).

A randomized, controlled noninferiority trial compared use of insulin detemir and NPH insulin for the treatment of gestational diabetes mellitus and T2DM in pregnancy.[275] Insulin aspart was added as needed. Patients were instructed to test blood glucose levels 4 times a day (fasting and 2-hour postprandial). Insulin dosages were adjusted to meet targets of FPG < 90 mg/dL and PPG < 120 mg/dL. The primary outcome was overall mean blood glucose during insulin treatment. Results from 87 women were analyzed. The difference in the mean blood glucose of the groups was 2.1 mg/dL (p=0.2937). The time to achieve glycemic control was similar in both groups. There were no differences in perinatal outcomes and maternal weight gain among the groups. There were more hypoglycemic events per patient in the NPH group.

insulin detemir (Levemir) versus insulin aspart (Novolog) versus biphasic insulin aspart (Novolog Mix 70/30)

In an open-label, controlled, multicenter trial, 708 patients with HbA1c levels between 7% to 10% who were receiving maximally tolerated doses of metformin and sulfonylurea were randomly assigned to receive biphasic insulin aspart twice daily, prandial insulin aspart 3 times daily, or basal insulin detemir once daily (twice if necessary).[276] The primary outcome measure at 1 year was HbA1c. Secondary measures included the proportion of patients with an HbA1c of ≤ 6.5%, the rate of hypoglycemia, and weight gain. At 1 year, HbA1c was similar in the biphasic group and the insulin aspart group (7.3% versus 7.2%, respectively; p=0.08), but higher in the basal group (7.6%, p<0.001 for both comparisons). The proportions of patients with a HbA1c ≤ 6.5% were similar in the biphasic and prandial groups (17% and 23.9%, respectively; p=0.08), but was lower in the basal group (8.1%; p≤0.01 for both comparisons). Mean numbers of hypoglycemic events per patient per year were 5.7%, 12%, and 2.3%, for the biphasic, prandial and basal groups, respectively; and mean weight gains were 4.7 kg, 5.7 kg, and 1.9 kg, respectively. Rates of adverse events were similar among the 3 groups.

insulin detemir (Levemir) versus insulin NPH (Novolin N) with insulin aspart (Novolog)

An open-label, parallel-group comparison study conducted at 46 centers in 5 countries included 448 patients (n=447 ITT) with T1DM. Patients were randomized to insulin detemir or NPH insulin before breakfast and at bedtime. Insulin aspart was given to both groups at meals.[277] After 6 months, comparable HbA1c levels were found between the 2 treatment groups. FPG was lower in patients treated with insulin detemir (-0.76 mmol/L), but this difference was not statistically significant (p=0.097). Within-subject variation of self-measured FPG was lower with insulin detemir than with NPH insulin (3.37 versus 3.78 mmol/L; p<0.001). Risk of hypoglycemia was 22% lower with insulin detemir than with NPH insulin (p<0.05) and 34% lower for nocturnal hypoglycemia (p<0.005). Nightly plasma glucose profiles were smoother and more stable with insulin detemir (p=0.05). Body weight was significantly lower with insulin detemir at the end of the trial (p<0.001).

Patients with T1DM (n=408) were randomized in a 16-week, open-label, parallel-group trial to insulin detemir administered twice daily either before breakfast and at bedtime or at a 12-hour interval or NPH insulin administered before breakfast and at bedtime.[278] Insulin aspart was the mealtime insulin. Although HbA1c for each insulin detemir group was not different from the NPH group at endpoint, HbA1c for the pooled insulin detemir groups was significantly lower than the NPH group (mean difference -0.18%; p=0.027). With both insulin detemir groups, clinician measured FPG was lower than with NPH insulin (-1.5 mmol/L, p=0.004; -2.3 mmol/L, p<0.001, respectively), as was self-measured pre-breakfast plasma glucose (p=0.006 and p=0.004, respectively). Within-person between-day variation of self-measured pre-breakfast plasma glucose was lower for both detemir groups (both p<0.001). The risk of minor hypoglycemia was lower in both insulin detemir groups (25%, p=0.046; 32%, p=0.002; respectively) compared with NPH insulin in the last 12 weeks of treatment, mainly attributable to a reduction in nocturnal hypoglycemia in the insulin detemir breakfast/bedtime group (p<0.001). Few severe hypoglycemic episodes were recorded, with no statistical differences between the groups. The NPH group gained weight during the study, but there was no clinically significant change in weight in either of the insulin detemir groups (-0.8 kg, p=0.006; -0.6 kg, p=0.04, respectively).

A multinational, open-label, parallel-group trial studied 505 patients with T2DM.[279] Patients were randomized to insulin detemir or NPH, receiving basal insulin either once or twice daily, according to their pretrial insulin treatment, and insulin aspart at mealtimes. After 26 weeks of treatment, significant reductions in HbA1c were observed for insulin detemir (p=0.004) and NPH insulin (p=0.0001), resulting in comparable levels at study end (detemir, 7.6%; NPH, 7.5%). The number of basal insulin injections administered per day had no effect on HbA1c levels (p=0.5). At study end, FPG concentrations were similar for the 2 treatment groups (p=0.66), as were reductions in FPG (detemir, 0.5 mmol/L; NPH, 0.6 mmol/L). However, within-subject day-to-day variation in fasting FPG was significantly lower with insulin detemir (p=0.021). The frequency of adverse events and the risk of hypoglycemia were comparable for the 2 treatment groups.

A multinational, 16-week, open-label, parallel-group trial included 400 people with T1DM randomized to insulin detemir in the morning and before dinner or morning and bedtime, or to NPH insulin morning and bedtime, all in combination with mealtime insulin aspart.[280] HbA1c was comparable among the 3 groups after 16 weeks, with reductions of 0.39% to 0.49% (p=0.64). Lower FPG was observed with insulin detemir morning/dinner and insulin detemir morning/bedtime compared with NPH groups (9.8 mmol/L and 9.1 mmol/L versus 11.1 mmol/L, p=0.006), but the insulin detemir groups did not differ significantly (p=0.15). Within-person variation in self-measured FPG was significantly lower for both insulin detemir regimens than for NPH insulin (SD: insulin detemir morning/dinner 2.5, insulin detemir morning/bedtime 2.6, NPH 3.1 mmol/L, p<0.001) but was comparable between the 2 insulin detemir groups (p=0.48). Ten-point plasma glucose profiles were lower between dinner and breakfast in the insulin detemir morning/dinner group (p=0.043) compared with the 2 other groups. Risk of overall and nocturnal hypoglycemia was similar for the 3 groups.

insulin detemir (Levemir) + insulin aspart (Novolog) versus insulin NPH (Novolin N) + regular insulin (Novolin R)

In an 18-week, randomized, open-label, parallel trial, 595 patients with T1DM received insulin detemir or NPH insulin in the morning and at bedtime in combination with mealtime insulin aspart or regular human insulin, respectively.[281] Glycemic control with insulin detemir/insulin aspart was improved in comparison with NPH insulin/regular human insulin (HbA1c: 7.88% versus 8.11%; p<0.001). Lower postprandial plasma glucose levels were seen in the insulin detemir/insulin aspart group (p<0.001), as well as lower within-person day-to-day variation in plasma glucose (SD: 2.88 versus 3.12 mmol/L; p<0.001). Risk of overall and nocturnal hypoglycemia was 21% (p=0.036) and 55% (p<0.001) lower in the insulin detemir/insulin aspart group than in the NPH insulin/regular human insulin group, respectively.

A 22-week, multinational, open-label, randomized, parallel-group trial enrolled 395 patients with T2DM. Patients were randomized to treatment with either basal insulin detemir in combination with insulin aspart at meals or basal insulin NPH in combination with regular human insulin at meals.[282] At 22 weeks, HbA1c was comparable between treatments (insulin detemir group: 7.46%, NPH group: 7.52%, p=0.515) with decreases from baseline of 0.65% and 0.58%, respectively. The insulin detemir group was associated with a significantly lower within-person variation in self-measured FPG (SD, 1.2 versus 1.54 mmol/L; p<0.001), as well as a lower body weight gain (0.51 kg versus 1.13 kg; p=0.038) than in the NPH group. The risk of nocturnal hypoglycemia was 38% lower with the insulin detemir group compared to the NPH group (p=0.14). The overall safety profile was similar between the 2 treatments.

insulin glargine 100 U/mL (Basaglar)

Basaglar was approved through an abbreviated approval pathway (505[b][2]). FDA approval was based on clinical trials that included patients with T1DM or T2DM, and on the safety and effectiveness data for Lantus.[283]

A 24-week, open-label, phase 3 trials demonstrated that Basaglar was non-inferior to another insulin glargine U-100 product (including Lantus and a non-US-approved insulin glargine U-100) in 535 adult patients with inadequately controlled T1DM.[284,285] Both insulin glargine products were given in combination with mealtime insulin lispro. The adjusted mean difference in change from baseline in HbA1c was 0.11% (95% CI, -0.002 to 0.219).

In a 24-week, double-blind trial, once-daily Basaglar or another insulin glargine U-100 product (including Lantus and a non-US-approved insulin glargine U-100) were given in combination with oral antidiabetic agents to 756 patients with inadequately controlled T2DM.[286,287] The difference in adjusted mean change from baseline in HbA1c was 0.05% (95% CI, -0.07 to 0.17); noninferiority of Basaglar was established.

insulin glargine 100 U/mL (Lantus) versus NPH human insulin

In an open-label study patients with T1DM were randomized to receive insulin glargine 100 U/mL once daily (n=310) or NPH insulin (n=309) over 16 weeks.[288] NPH insulin patients maintained their regimen of either once daily or twice daily injections whereas insulin glargine patients received once daily injections at bedtime. All patients continued to administer individually titrated insulin lispro before meals. Insulin glargine patients had lower self-reported fasting blood glucose concentrations. More patients achieved a fasting blood glucose concentration of less than 119 mg/dL in the insulin glargine group (29.6%) than in the NPH insulin group (16.8%). No differences were noted in the HbA1c or hypoglycemic episodes between the groups. Less variability of blood glucose concentrations was noted in the insulin glargine group. More injection site pain was reported in the insulin glargine group (6.1%) than in the NPH group (0.3%).

In a multicenter, randomized, open-label, parallel-group study, 534 patients with T1DM were randomized to receive pre-meal regular insulin and either daily insulin glargine 100 U/mL or NPH insulin (once or twice daily) for up to 28 weeks.[289] A small decrease in HbA1c levels was noted with both insulin glargine (-0.16%) and NPH insulin (-0.21%; p>0.05). Significant reductions in median FPG levels from baseline (-1.67 versus -0.33 mmol/L with NPH insulin, p=0.0145) were achieved with insulin glargine compared to NPH insulin. After the 1-month titration phase, significantly fewer subjects receiving insulin glargine experienced symptomatic hypoglycemia (39.9% versus 49.2%; p=0.0219) or nocturnal hypoglycemia (18.2% versus 27.1%; p=0.0116) compared with subjects receiving NPH insulin.

Patients with T1DM were treated for up to 28 weeks with once-daily insulin glargine 100 U/mL (n=199) or twice-daily NPH insulin (n=195) in addition to preprandial regular insulin in a randomized, parallel-group study.[290] A greater mean decrease in FBG was achieved at endpoint with insulin glargine compared with NPH insulin (-21 versus -10 mg/dL; p=0.015), and a greater percentage of patients treated with insulin glargine reached the target FBG (32.6% versus 21.3%; p=0.015). Similar percentages of patients in both treatment groups achieved HbA1c ≤ 7% at endpoint. After the 1-month titration phase, the percentage of patients who reported at least 1 symptomatic hypoglycemic event confirmed by a blood glucose < 50 mg/dL was significantly lower with insulin glargine than with NPH insulin (73.3% versus 81.7%; p=0.021). Severe hypoglycemia was also significantly reduced in insulin glargine patients.

Glycemic control and symptomatic hypoglycemia rates with insulin glargine 100 U/mL versus NPH insulin were studied in 125 poorly controlled T1DM patients.[291] Patients received preprandial insulin lispro and either insulin glargine or NPH insulin at bedtime for 30 weeks in a randomized, single-blinded fashion. Basal insulin dosage was titrated to achieve FBG < 5.5 mmol/L. At endpoint, mean HbA1c was 8.3% versus 9.1% for the insulin glargine versus NPH groups, but HbA1c was lower in the insulin glargine versus NPH group at study initiation (9.2% versus 9.7%). Adjusted least-squares mean change from baseline was -1.04% versus -0.51%, a significant treatment benefit in favor of insulin glargine (p<0.01). The mean values for end-point FBG were 7.9 versus 9 mmol/L in favor of insulin glargine (p<0.05). Significantly fewer moderate or severe nocturnal hypoglycemic episodes were observed in the insulin glargine group (p=0.04 and p=0.02, respectively).

In a multicenter, open-label, randomized, 6-month study, 349 T1DM patients ages 5 to 16 years received insulin glargine 100 U/mL once daily or NPH insulin either once or twice daily.[292] There was no difference between insulin glargine and NPH insulin in the primary efficacy measure of change in HbA1c from baseline to endpoint. Fasting blood glucose levels decreased significantly more in the insulin glargine group (-1.29 mmol/L) than in the NPH insulin group (-0.68 mmol/L; p=0.02). The percentage of patients that reported at least 1 symptomatic hypoglycemic episode was similar between groups; however, fewer patients in the insulin glargine group reported severe hypoglycemia (23% versus 29%, respectively) and severe nocturnal hypoglycemia (13% versus 18%, respectively), although these differences were not statistically significant. Fewer serious adverse events occurred in the insulin glargine group than in the NPH insulin group (p<0.02).

In an open-label, 24-week, multicenter trial, 765 patients with T2DM with inadequate glycemic control (HbA1c > 7.5%) while on 1 or 2 oral medications were randomized to either bedtime insulin glargine 100 U/mL or NPH insulin once daily, in addition to their prestudy medications.[293] Mean FPG at end point was similar with insulin glargine and NPH (117 versus 120 mg/dL), as was HbA1c (6.96% versus 6.97%). A majority of patients (approximately 60%) attained HbA1c < 7% with each insulin type. However, nearly 25% more patients attained this without documented nocturnal hypoglycemia (≤ 72 mg/dL) with insulin glargine (33.2% versus 26.7%; p<0.05). Rates of other categories of symptomatic hypoglycemia were 21% to 48% lower with insulin glargine.

A total of 518 patients with T2DM who were receiving NPH insulin with or without regular insulin for postprandial control were randomized to receive insulin glargine 100 U/mL once daily (n=259) or NPH insulin once or twice daily (n=259) for 28 weeks in an open-label, multicenter trial.[294] The treatment groups showed similar improvements in HbA1c from baseline to end point on intent-to-treat analysis. The mean change in HbA1c from baseline to endpoint was similar in the insulin glargine group (-0.41% ± 0.1%) and the NPH group (-0.59% ± 0.1%). The treatments were associated with similar reductions in fasting glucose levels. Overall, mild symptomatic hypoglycemia was similar in insulin glargine subjects (61.4%) and NPH insulin subjects (66%). However, nocturnal hypoglycemia in the insulin glargine group was reduced by 25% more than the NPH group during the treatment period after the dose-titration phase (26.5% versus 35.5%; p=0.0136). Patients in the insulin glargine group experienced less weight gain than those in the NPH group (0.4 versus 1.4 kg; p<0.0007).

In an open-label, randomized, controlled trial, 695 patients with T2DM previously treated with oral antidiabetic agents were randomized to treatment with morning insulin glargine 100 U/mL, bedtime NPH insulin, or bedtime insulin glargine for 24 weeks in addition to 3 mg of glimepiride.[295] HbA1c levels improved by -1.24% with morning insulin glargine, -0.96% with bedtime insulin glargine, and -0.84% with bedtime NPH insulin. HbA1c improvement was more pronounced with morning insulin glargine than with NPH insulin (p=0.001) or bedtime insulin glargine (p=0.008). Baseline to endpoint fasting blood glucose levels improved similarly in all 3 groups. Nocturnal hypoglycemia was less frequent with morning (17%) and bedtime insulin glargine (23%) than with bedtime NPH insulin (38%; p<0.001).

In a multicenter, open-label, randomized study, 570 patients with T2DM were treated with insulin glargine 100 U/mL or NPH insulin given once daily at bedtime.[296] Previous oral antidiabetic therapy was continued throughout the study. At 52 weeks, there was a trend toward a decrease in HbA1c values from baseline to endpoint with both drugs (insulin glargine: -0.46%; NPH insulin: -0.38%; p=0.415). Over the entire treatment period, NPH insulin-treated patients (41%) and insulin glargine-treated patients (35%) experienced a similar level of symptomatic hypoglycemia, but there was a statistically significant difference in the percentage of patients that experienced nocturnal hypoglycemia in NPH patients compared with those treated with insulin glargine in the overall population (24% versus 12%, respectively; p=0.002). The incidence of adverse events was similar for the 2 treatments.

An open-label, 24-week, randomized study compared the efficacy and safety of insulin glargine 100 U/mL and insulin NPH, both in combination with a daily fixed dose of glimepiride, in terms of glycemic control and incidence of hypoglycemia.[297] Patients with poorly controlled T2DM on oral antidiabetic agents (HbA1c 7.5% to 10.5%) received glimepiride plus insulin glargine (n=231) or NPH insulin (n=250) using a forced titration algorithm. Insulin glargine and insulin NPH achieved similar HbA1c reductions. Confirmed nocturnal hypoglycemia was significantly lower with insulin glargine versus NPH insulin (16.9% versus 30%; p<0.01).

insulin glargine 100 U/mL (Lantus) plus glimepiride and metformin versus human insulin 70/30

In a 24-week, multinational, multicenter, open-label, parallel-group clinical trial, 371 insulin-naïve patients with T2DM and poor glycemic control on a sulfonylurea plus metformin were randomized to daily morning insulin glargine 100 U/mL plus glimepiride and metformin or to insulin 70/30 twice daily without oral antidiabetic agents.[298] Mean HbA1c decrease from baseline was significantly more pronounced (-1.64% versus -1.31%; p=0.0003), and more patients reached HbA1c < 7% without confirmed nocturnal hypoglycemia (45.5% versus 28.6%; p=0.0013) with the insulin glargine arm than with insulin 70/30. Similarly, FBG decrease was greater in the insulin glargine group (adjusted mean difference, -17 mg/dL; p<0.0001), and more patients reached target FBG < 100 mg/dL with insulin glargine than with insulin 70/30 (31.6% versus 15%; p=0.0001). Insulin glargine patients had fewer confirmed hypoglycemic episodes than insulin 70/30 patients (4.07 versus 9.87 episodes/patient-year; p<0.0001).

insulin glargine 100 U/mL (Lantus) versus insulin detemir (Levemir)

In a 52-week multinational, open-label, parallel-group, treat-to-target, noninferiority trial 443 patients with T1DM and a mean age of 42 years; a mean body mass index of 26.5; a mean HbA1c of 8.1% and a mean duration of diabetes of 17.2 years were randomized to receive either insulin detemir or insulin glargine 100 U/mL for 52 weeks.[299] Insulin aspart was administered in both groups as the mealtime insulin. The basal insulin was initially administered once daily in the evening for both groups. If patients in the insulin detemir group achieved target plasma glucose levels before breakfast but not before dinner, administration was changed to twice a day regimen. Insulin glargine patients continued with once daily administration throughout the trial. The primary efficacy endpoint was HbA1c after 52 weeks while the secondary endpoints included the number of patients achieving an HbA1c ≤ 7% with or without a major hypoglycemic episode in the last month of treatment and FBG. Results after 52 weeks showed no significant differences in mean HbA1c between insulin detemir and insulin glargine groups (7.57% and 7.56%, respectively; mean difference, 0.01% [95% CI, -0.13 to 0.16]). Additionally, there was no significant difference in the proportion of patients receiving insulin detemir and insulin glargine in achieving an HbA1c value equal to or lower than 7% without major hypoglycemia (31.9% and 28.9%, respectively). In addition, there were no significant differences in estimated mean FPG (8.58 and 8.81 mmol/L; mean difference, -0.23 mmol/L [95% CI, -1.04 to 0.58]) or in basal insulin doses. The relative risks for total and nocturnal hypoglycemia were not significantly different between insulin detemir and insulin glargine (0.94 and 1.12, respectively; p=NS).

In a 24-week, multinational, open-label, treat-to-target trial, 973 insulin-naïve patients with T2DM and an HbA1c of 7% to 10.5% were randomized to insulin detemir twice daily or insulin glargine 100 U/mL once daily.[300] Patients in this study had been treated with metformin for 3 months or greater prior to the study. The primary outcome was the percentage of patients reaching an HbA1c < 7% without symptomatic hypoglycemia. In the insulin glargine and insulin detemir groups, 27.5% and 25.6% of patients, respectively, reached HbA1c < 7%. It was demonstrated that insulin glargine once-daily is non-inferior to insulin detemir twice-daily regarding the percentage of patients who achieve a target HbA1c without hypoglycemia. Insulin detemir-treated patients had less weight gain and more often achieved HbA1c < 6.5% (p=0.017). However, the drop-out rate and daily insulin doses were lower in the insulin glargine group.

insulin glargine 100 U/mL (Lantus) versus insulin detemir (Levemir) with insulin aspart (Novolog)

In a 26-week, multicenter, open-label, parallel-group trial, 320 patients with T1DM received either insulin detemir twice daily or insulin glargine 100 U/mL once daily, each in combination with pre-meal insulin aspart.[301] After 26 weeks, HbA1c decreased from 8.8% to 8.2% in the insulin detemir group and from 8.7% to 8.2% in the insulin glargine group. The overall risk of hypoglycemia was similar; however, the risk of severe and nocturnal hypoglycemia was 72% and 32% lower, respectively, with insulin detemir than with insulin glargine (p<0.05). Body weight gain was not significantly different between treatment arms.

insulin glargine 100 U/mL (Lantus) versus biphasic insulin aspart (Novolog Mix 70/30)

The 28-week parallel-group study randomized 233 insulin-naive patients on more than 1,000 mg daily metformin alone or in combination with other oral antidiabetic agents to receive biphasic insulin aspart twice daily or insulin glargine 100 U/mL at bedtime and titrated to target blood glucose.[302] At study end, the mean HbA1c value was lower in the biphasic insulin aspart group than in the insulin glargine group (6.91% versus 7.41%; p<0.01). The HbA1c reduction was greater in the biphasic insulin aspart group than in the insulin glargine group (-2.79% versus -2.36%; p<0.01), especially for subjects with baseline HbA1c > 8.5% (p<0.05). Minor hypoglycemia was greater in the biphasic insulin aspart group than in the insulin glargine group (3.4 and 0.7 episodes/year; p<0.05), and weight gain at study end was greater for biphasic insulin aspart-treated subjects than for insulin glargine-treated subjects (5.4 versus 3.5 kg; p<0.01).

In the randomized, open-label, parallel study, biphasic insulin aspart plus metformin twice daily were compared with insulin glargine 100 U/mL plus glimepiride daily in 255 insulin-naïve patients.[303] The primary endpoint was the difference in absolute change in HbA1c between groups after 26 weeks of treatment. HbA1c change was significantly greater in the insulin aspart group than the insulin glargine group (between-group difference, -0.5%; p=0.0002). During the maintenance phase, 1 major hypoglycemic episode occurred in each group; 20.3% and 9% of patients experienced minor hypoglycemic episodes in the insulin aspart and insulin glargine groups, respectively (p=0.0124). Insulin glargine patients experienced significant weight gain of 1.5 kg (p<0.0001); the weight change with insulin aspart patients of +0.7 kg was not statistically significant (p=0.0762).

In a 26-week, open-labeled, randomized, parallel-group, multinational, treat-to-target trial, 480 insulin-naïve patients with T2DM who were inadequately controlled on oral anti-diabetic medications were randomized to receive either biphasic insulin aspart prior to dinner or insulin glargine 100 U/mL at bedtime in combination with metformin and glimepiride.[304] A total of 433 patients completed the trial. At the end of treatment, biphasic insulin aspart and insulin glargine reduced the mean HbA1c levels by -1.41% and 1.25%, respectively (95% CI, -0.3 to -0.02; p=0.029). After 26 weeks, the mean HbA1c levels were 7.1% for the biphasic insulin aspart group and 7.3% for the insulin glargine group. The relative risk for a nocturnal hypoglycemic episode was greater in the biphasic insulin aspart group than for insulin glargine (relative risk, 2.41 [95% CI, 1.34 to 4.34]; p=0.003), although hypoglycemic rates were overall low with 3 major episodes occurring in each group.

insulin glargine 100 U/mL (Lantus) versus insulin lispro (Humalog)

In an open-label, multicenter study, 418 patients with T2DM inadequately controlled with oral hypoglycemic agents were randomized to receive either insulin glargine 100 U/mL administered once daily (n=205) or insulin lispro administered 3 times daily (n=210).[305] The primary efficacy endpoint was the change in HbA1c from baseline to endpoint (week 44). There was no significant difference between the 2 treatment groups relative to mean reduction in HbA1c. The percentage of patients that reached HbA1c ≤ 7% was 57% in the glargine group and 69% in the lispro group. However, the mean change in fasting blood glucose was significantly greater in the insulin glargine group (-4.3 mmol/L) compared to the insulin lispro group (-1.8 mmol/L; p<0.0001). Patients treated with insulin glargine were also shown to have greater reductions in nocturnal blood glucose compared with patients treated with insulin lispro (-3.3 versus -2.6 mmol/L; p=0.0041). Hypoglycemic episodes occurred at a rate of 5.2 events per patient per year for insulin glargine and 24 events per patient per year for insulin lispro (p<0.001). There was no significant difference in mean weight gain between the 2 treatment groups.

insulin glargine 100 U/mL (Lantus) versus biphasic insulin lispro (Humalog Mix)

Patients with T2DM (n=374) were randomly assigned to insulin lispro mix 50/50 three times daily with meals or insulin glargine 100 U/mL at bedtime plus mealtime insulin lispro in a 24-week, multicenter, open-label, noninferiority trial.[306] Investigators could replace insulin lispro mix 50/50 with 75/25 at the evening meal if the fasting plasma glucose target was unachievable. At week 24, HbA1c was lower with insulin glargine (6.78% versus 6.95%; p=0.021), but HbA1c was reduced significantly from baseline for both therapies (p<0.0001). Noninferiority of insulin lispro mix to insulin glargine was not demonstrated based on the prespecified noninferiority margin of 0.3%. The percentages of patients achieving target HbA1c varied depending on the specific target; statistically significant differences did occur in favor of insulin glargine at HbA1c < 7% and HbA1c < 6.5%. Rates of hypoglycemia were similar for both groups.

insulin glargine-yfgn 100 U/mL (Semglee) versus insulin glargine 100 U/mL (Lantus)

Insulin glargine-yfgn was approved through an abbreviated approval pathway (505[b][2]).[307] FDA approval was based on clinical trials that included patients with T1DM or T2DM and on the safety and effectiveness data for Lantus.[308] Two multicenter, open-label, randomized, parallel-group trials compared the glucose lowering effect of the same once-daily doses of insulin glargine-yfgn and insulin glargine.[309,310] INSTRIDE-1 (n=558) included patients with T1DM who were also on insulin lispro. At week 24, treatment with insulin glargine-yfgn was similar to the comparator based on the mean change in HbA1c over 24 weeks of treatment; the least square mean change in HbA1c from baseline to week 24 was 0.14% with insulin glargine-yfgn and 0.11% with insulin glargine. INSTRIDE-2 (n=560) enrolled patients with T2DM. Both products were administered in combination with oral antidiabetic drugs. At week 24, treatment with insulin glargine-yfgn was found to be non-inferior to insulin glargine based on a difference in reduction in HbA1c from baseline between the 2 product of 0.06 (95% CI, -0.098 to 0.218). In addition, both trials demonstrated that the incidence of total and cross-reactive anti-drug antibodies was comparable between the products.[311]

insulin glargine 300 U/mL (Toujeo) versus insulin degludec (Tresiba)

BRIGHT, a 24-week, multicenter, open-label, active-controlled, 2-arm, parallel-group, noninferiority study, compared insulin glargine 300 U/mL (n=466) to insulin degludec 100 U/mL (n=463) in insulin-naive patients with uncontrolled T2DM.[312] Both agents were titrated to a fasting self-monitored plasma glucose of 80 to 100 mg/dL. Noninferiority of insulin glargine 300 U//mL compared to insulin degludec was demonstrated (least squares mean difference, 20.05% [95% CI, 20.15 to 0.05]; p<0.0001) based on change in HbA1c from baseline to 24 weeks. The incidence of hypoglycemia, defined as blood glucose ≤ 70 mg/dL, was comparable between the groups; however, during the active titration period (0 to 12 weeks), both the incidence and rate of anytime (24-h) confirmed hypoglycemia were lower with insulin glargine 300 U/mL (66.5% versus 69%; OR, 0.88 [95% CI, 0.66 to 1.17]).

The 12-week, randomized, active-controlled, open-label InRange study compared CGM-based time in range (TIR) between insulin glargine 300 U/mL (n=172) and insulin degludec 100 U/mL (n=171) in adult patients with T1DM.[313] Patients who were eligible for inclusion had an HbA1c ≥ 7% and ≤ 10% and had been receiving prior treatment with a stable basal/bolus insulin regimen. The primary objective of the study was to show non-inferiority of insulin glargine 300 U/mL versus insulin degludec 100 U/mL with regard to glycemic control, which was assessed through the primary endpoint of percentage TIR ≥ 70 mg/dL to ≤ 180 mg/dL at week 12 using blinded CGM. Non-inferiority of insulin glargine 300 U/mL compared to insulin degludec 100 U/mL was shown for the primary endpoint; mean estimates for TIR at week 12 were 52.74% (95% CI, 51.06% to 54.42%) and 55.09% (95% CI, 53.34% to 56.84%), respectively, for a mean difference of 3.16% (95% CI, 0.88% to 5.44%; non-inferiority p=0.0067).

insulin glulisine (Apidra) versus regular human insulin

Patients with T1DM (n=860) received daily insulin glargine 100 U/mL and were randomized to either insulin glulisine injected within 15 minutes before or immediately after meals or regular human insulin, injected 30 to 45 minutes before meals in an open-label, controlled, multicenter, parallel-group, 12-week study.[314] Changes in mean HbA1c were -0.26%, -0.11%, and -0.13% in the pre-meal insulin glulisine, post-meal insulin glulisine, and regular insulin groups, respectively. The reduction in HbA1c was greater for the pre-meal insulin glulisine group in comparison with the regular insulin group (p=0.02) and the post-meal insulin glulisine group (p=0.006); no significant difference was found between post-meal insulin glulisine versus regular insulin. Overall, blood glucose profiles were similar in all 3 treatment groups but were significantly lower for pre-meal insulin glulisine post-breakfast and post-dinner measurements. Severe hypoglycemic episodes were comparable for all groups. Body weight increased (0.3 kg) in the regular insulin and pre-meal insulin glulisine groups; however, weight decreased in the post-meal insulin glulisine group (-0.3 kg; p=0.03).

Patients with T2DM who had received at least 6 months of continuous insulin therapy were randomized in a multinational, controlled, open-label, parallel group, 26-week study.[315] Patients (n=890) received NPH insulin twice daily and either insulin glulisine or regular insulin at least twice daily. There were no differences in HbA1c reductions (insulin glulisine: -0.32%; regular insulin: -0.35%; p=0.57). Insulin glulisine lowered plasma glucose significantly more versus regular insulin at 2 hours (14.14 mmol/L versus 15.28 mmol/L; p=0.0025). Nocturnal hypoglycemia from the fourth month to the end of treatment was less frequent with insulin glulisine versus regular insulin (9.1% versus 14.5%; p=0.029).

insulin glulisine (Apidra) versus insulin lispro (Humalog)

The objective of the multinational, multicenter, controlled, open-label, randomized, parallel-group study was to compare the efficacy and safety of insulin glulisine to that of insulin lispro in adults diagnosed with T1DM.[316] Of the 683 patients randomized, 672 received treatment. Over the 26-week study, a similar reduction in mean HbA1c occurred in both groups (adjusted mean change from baseline, -0.14% in both groups). The basal insulin dose was relatively unchanged from baseline in the insulin glulisine group but increased in the insulin lispro group (0.12 units versus 1.82 units, respectively; p=0.0001). There was no relevant difference between the 2 groups in the reporting of symptomatic hypoglycemia (overall, nocturnal, or severe).

In an effort to compare the safety and efficacy of insulin glulisine to that of insulin lispro in children and adolescents with T1DM, 572 patients aged ≥ 4 years were randomized to receive either insulin glulisine or insulin lispro, administered subcutaneously within 15 minutes before a meal, in an open-label, active-controlled, noninferiority trial.[317] During this 26-week study, patients also received insulin glargine 100 U/mL (administered once daily in the evening) or NPH insulin (administered once in the morning and once in the evening). There were no significant differences observed between the 2 treatment groups with respect to glycemic control.

insulin lispro (Admelog)

Admelog was approved through an abbreviated approval pathway (505[b][2]). FDA approval was based on 2 phase 3 trials with Admelog and on the safety and effectiveness data for Humalog (insulin lispro injection).[318] In two 26-week, open-label, phase 3 trials, Admelog was non-inferior to another insulin lispro U-100 product (including a non-US-approved insulin lispro U-100) in patients with T1DM (n=507) and patients with T2DM (n=505).[319] In both trials, insulin lispro products were given in combination with insulin glargine. The adjusted mean difference in change from baseline in HbA1c was 0.06% in both the T1DM and the T2DM studies (95% CI, -0.086 to 0.201 for T1DM; 95% CI, -0.209 to 0.091 for T2DM).

insulin lispro (Humalog) versus regular human insulin

In a 5.5-month randomized, open-label, parallel study of 148 patients with T2DM receiving either insulin lispro (n=70) or regular human insulin (n=78), 8-point blood glucose profiles and HbA1c measurements were collected at baseline, 1.5, 3.5, and 5.5 months.[320] Two-hour post-breakfast and 2-hour post-supper blood glucose levels were significantly lower for insulin lispro than for regular human insulin at the end point (p=0.02 in both cases). HbA1c improved from 10.5% (insulin lispro) and 10.3% (regular human insulin) to 8% in each treatment arm. Hypoglycemia rates were similar during the day with a trend towards a reduced incidence in the night hours with insulin lispro (0.08 episodes/month versus 0.16 episodes/month; p=0.057).

insulin lispro-aabc (Lyumjev)

The approval of insulin lispro-aabc was based on two, 26-week studies in adults with either T1DM (PRONTO-T1D; n=1,222) or T2DM (PRONTO-T2D; n=673).[321] In PRONTO-T1D, patients were randomized 4:4:3, in combination with either insulin glargine or insulin degludec, to blinded mealtime (0 to 2 min prior to the meal) insulin lispro-aabc, blinded mealtime insulin lispro (Humalog), or open-label postmeal (20 minutes after meal start) insulin lispro-aabc. At week 26, mealtime and postmeal insulin lispro-aabc met the prespecified noninferiority margin in HbA1c reduction (0.4%) when compared to mealtime insulin lispro. In all groups, insulin doses were similar at baseline and at 26 weeks. In PRONTO-T2D, patients who were on ≥ 3 oral antidiabetic agents, basal insulin and ≥ 1 prandial insulin, or premixed insulin with ≥ 2 injections daily were randomized 1:1, in combination with either insulin glargine or insulin degludec, to blinded mealtime (0 to 2 min prior to the meal) insulin lispro-aabc or insulin lispro (Humalog). At week 26, mealtime insulin lispro-aabc met the prespecified noninferiority margin in HbA1c reduction (0.4%) when compared to mealtime insulin lispro. In both groups, insulin doses were similar at baseline and at 26 weeks.

Insulin lispro-aabc was approved for pediatric use based on data from the randomized, active-controlled PRONTO-Peds trial (NCT03740919).[322] In this 26-week study, 716 pediatric patients with T1DM who were ≥ 1 year of age were randomized in a 2:2:1 ratio to either blinded mealtime insulin lispro-aabc (n=280) or insulin lispro (n=298), injected 0 to 2 minutes before meals; or open-label post-meal insulin lispro-aabc (n=138) injected up to 20 minutes after the start of meals. All patients in the study also received basal insulin, with a 4-week lead-in period to optimize the dose. The mean patient age was 12 years (range, 3 to 17 years), and the mean HbA1c at baseline was 7.8%. The primary endpoint was change in HbA1c from baseline after 26 weeks, with a noninferiority margin of 0.4%. Treatment with both mealtime and post-meal insulin lispro-aabc produced a mean change in HbA1c that demonstrated non-inferiority to mealtime insulin lispro, with an estimated treatment difference of -0.02% (95% CI, -0.17 to 0.13) for mealtime insulin lispro-aabc and an estimated treatment difference of -0.02% (95% CI, -0.2 to 0.17) for post-meal insulin lispro-aabc. The rate and incidence of hypoglycemia were similar between all groups, however, more participants experienced injection site reactions with mealtime insulin lispro-aabc (7.9%) versus post-meal insulin lispro-aabc (2.9%) and insulin lispro (2.7%).

insulin glargine 300 U/mL (Toujeo) versus insulin glargine 100 U/mL (Lantus)

EDITION 4: In a 26-week, open-label study, 546 adults with T1DM were randomized to basal-bolus treatment with insulin glargine 300 U/mL or 100 U/mL administered once daily in the morning (time period covering from pre-breakfast until pre-lunch) or in the evening (time period defined as prior to the evening meal until at bedtime).[323] A mealtime insulin analog was administered before each meal. At week 26, treatment with insulin glargine 300 U/mL provided a similar reduction in HbA1c as insulin glargine 100 U/mL (-0.4% versus -0.44%, respectively) and met the pre-specified noninferiority margin of 0.4%. Patients treated with insulin glargine 300 U/mL used 17.5% more basal insulin than patients treated with insulin glargine 100 U/mL. There were no clinically important differences in glycemic control when insulin glargine 300 U/mL was administered once daily in the morning or in the evening. Hypoglycemia was similar between the groups, except for during the first 8 weeks, when nocturnal confirmed or severe hypoglycemia was lower with insulin glargine 300 U/mL (rate ratio, 0.69 [95% CI, 0.53 to 0.91]).[324] There were no clinically important differences in body weight between treatment groups.

EDITION 1: In a 26-week, open-label study, 804 adults with T2DM were randomized to a once-daily treatment in the evening with insulin glargine 300 U/mL or 100 U/mL. Patients also received mealtime insulin analogs with or without metformin.[325,326] At week 26, insulin glargine 300 U/mL provided a mean reduction in HbA1c that met the pre-specified noninferiority margin of 0.4% compared to insulin glargine 100 U/mL. Patients treated with insulin glargine 300 U/mL used 11% more basal insulin compared to those treated with insulin glargine 100 U/mL. A lower percentage of patients experienced ≥ 1 confirmed (≤ 70 mg/dl) or severe hypoglycemic event with the 300 U/mL concentration than the 100 U/mL concentration at any time of day (86% versus 92%; relative risk [RR], 0.94 [95% CI, 0.89 to 0.99]) and during the night (54% versus 65%; RR, 0.84 [95% CI, 0.75 to 0.94]), although the annualized rates of such hypoglycemic events were similar. There were no clinically important differences in body weight between treatment groups.

In two, 26-week, open-label studies, 1,670 adults with T2DM were randomized to either insulin glargine 300 U/mL or 100 U/mL once daily in combination with non-insulin anti-diabetic drugs.[327] At the time of randomization, 808 patients were treated with basal insulin for more than 6 months (EDITION 2) and 862 patients were insulin-naïve (EDITION 3). At week 26, treatment with insulin glargine 300 U/mL provided a mean reduction in HbA1c that met the pre-specified noninferiority margin of 0.4% compared to insulin glargine 100 U/mL. A lower percentage of patients experienced nocturnal hypoglycemia in the 300 U/mL groups than in the 100 U/mL groups (EDITION 2: RR, 0.86 [95% CI, 0.73 to 1.01]; EDITION 3: RR, 0.76 [95% CI, 0.59 to 0.99]).[328,329] When annualized, the EDITION 2 study reported a 37% relative reduction in nocturnal confirmed or severe hypoglycemic events with glargine 300 U/mL versus 100 U/mL, while the EDITION 3 study reported similar event rates in the 2 groups. Patients treated with insulin glargine 300 U/mL used 12% (EDITION 2) and 15% (EDITION 3) more basal insulin than patients treated with insulin glargine 100 U/mL. There were no clinically important differences in body weight between treatment groups.

SENIOR, an open-label, 2-arm, parallel-group, randomized, multicenter phase 3b trial that included 1,014 patients (mean age, 71 years) with T2DM, compared insulin glargine 300 U/mL and insulin glargine 100 U/mL.[330] At 26 weeks, the reduction in HbA1c from baseline was similar in both groups in the overall populations (least squares mean difference, 0.02% [95% CI, -0.092 to 0.129]) and in the subgroup of patients ≥ 75 years of age (least squares mean difference, -0.11% [95% CI, -0.33 to 0.106]). Confirmed or severe hypoglycemia also occurred at similar rates in each group. In patients ≥ 75 years of age, significantly lower annualized rates of documented symptomatic hypoglycemia (≤ 70 mg/dL) were reported with insulin glargine 300 U/mL (1.12 versus 2.71, respectively; rate ratio, 0.45 [95% CI, 0.25 to 0.83]).

A 26-week, randomized, open-label, trial compared basal-bolus doses of insulin glargine 300 U/mL and insulin glargine 100 U/mL in 463 pediatric patients ages 6 to 17 years with T1DM.[331] Study drug was administered once daily in the morning or evening and a mealtime insulin analogue was administered before each meal. At week 26, insulin glargine 300 U/mL met the prespecified noninferiority margin (0.3%) based on difference in HbA1c reduction from baseline compared to insulin glargine 100 U/mL (difference, 0.02% [95% CI, -0.16 to 0.2]). Common adverse reactions in pediatrics treated with insulin glargine 300 U/mL were similar as seen in adults. In patients treated with insulin glargine 300 U/mL, the incidence of severe hypoglycemia was 6% and the incidence of hypoglycemia accompanied by a self-monitored or plasma glucose < 54 mg/dL regardless of symptoms was 80.3%.

Inhalation insulin

insulin inhalation powder (Afrezza) versus insulin aspart (Novolog)

A 24-week open-label, active-controlled study enrolled patients with inadequately controlled T1DM to evaluate the glucose lowering effect of mealtime insulin inhalation powder used in combination with a basal insulin.[332] During a 4-week run-in period, subjects were converted to mealtime insulin aspart using a 1:1 unit conversion and titrated their basal insulin dosage to achieve a fasting plasma glucose (FPG) < 120 mg/dL and ≥ 100 mg/dL (and not to exceed 180 mg/dL for eligibility). All subjects remained on their prior basal insulin (NPH, glargine 100 U/mL, or detemir) throughout the study. After the run-in period, 344 patients were randomized 1:1 to insulin inhalation powder or insulin aspart administered at each meal of the day. During the first 12 weeks, mealtime and basal insulin doses were titrated to pre-specified glycemic goals, after which doses remained relatively unchanged and adjusted only for safety or change in patients' clinical status such as infection. Supplemental insulin doses were allowed in the inhaled insulin group. At week 24, the mean daily doses for inhaled insulin increased by 30.7 units (equivalent to approximately 7.7 units SC insulin) and for insulin aspart by 1.6 units. The mean daily basal insulin dose was also higher in the inhaled insulin group than the insulin aspart group, 37.1 units versus 31.6 units, respectively. At week 24, treatment with basal insulin plus mealtime inhaled insulin provided less HbA1c reduction than insulin aspart (-0.21 versus -0.4%, respectively; difference, -0.19% [95% CI, 0.02 to 0.36). The mean reduction provided by basal insulin plus inhaled insulin narrowly met the pre-specified noninferiority margin of 0.4%. A greater proportion of patients in the insulin aspart group achieved the target HbA1c ≤ 7% (30.7% versus 18.3%; p=0.0158). Patients treated with insulin inhalation powder experienced a mean decrease in weight of 0.39 kg, while those treated with insulin aspart showed a mean increase of 0.93 kg. Severe hypoglycemia was experienced in 18.4% of subjects on inhaled insulin and 29.2% of those on insulin aspart; the incidence of mild to moderate hypoglycemia was similar between the groups (96% and 99.6%, respectively). The most common respiratory adverse reaction was cough, which was reported in 31.6% of subjects in the inhaled insulin group and 2.3% for the insulin aspart group. Cough was generally mild and intermittent, but led to study discontinuation in 5.7% of patients that received inhaled insulin and 0% subjects on insulin aspart.

In a 52-week, open-label trial, 539 patients with T1DM were randomized to insulin glargine 100 U/mL (basal) plus either insulin inhalation powder or insulin aspart.[333] Dose titration was permitted during the entire trial based on pre-meal and postprandial blood glucose levels. This trial did not meet its primary efficacy endpoint of noninferiority margin of 0.4% for insulin inhalation powder compared with insulin aspart. At week 52 mean change in HbA1c was -0.13% and -0.37% for insulin inhalation powder and insulin aspart, respectively (difference, 0.24 [95% CI, 0.08 to 0.404]). A similar proportion of patients achieved HbA1c ≤ 7% in both groups (16.3% versus 16%, respectively). Patients treated with insulin inhalation powder reported a mean decrease in weight of 0.5 kg, while those treated with insulin aspart showed a mean increase of 1.4 kg. Incidence of hypoglycemia was reported in 0.08 events/subject-month for the inhaled insulin group and 0.1 events/subject-month for the insulin aspart group.

A 24-week double-blind, placebo-controlled trial, enrolled adults with T2DM inadequately controlled on optimal or maximally tolerated doses of metformin monotherapy, or at least 2 oral antidiabetic agents.[334] Following a 6-week run-in period, 353 patients were randomized 1:1 to add-on therapy with insulin inhalation powder or an inhaled placebo powder. Insulin doses were titrated for the first 12 weeks and remained stable thereafter. Oral antidiabetic doses remained unchanged. Open-label rescue therapy (insulin glargine 100 U/mL or glimepiride) in addition to the study treatment was allowed in patients who experienced persistent or worsening hyperglycemia greater than pre-specified thresholds. At week 24, the insulin group reported statistically significantly greater mean reduction in HbA1c compared to the placebo group (0.82% versus 0.42%; p<0.0001). A greater proportion of patients in the insulin group achieved the target HbA1c ≤ 7% (32.2% versus 15.3%, respectively; p=0.0005). Patients in the insulin group experienced a mean increase in weight of 0.5 kg, while those in the placebo group reported a mean decrease of 1.1 kg. Severe hypoglycemia was reported in 5.7% of patients on inhaled insulin and 1.7% of those who received placebo. Cough was reported in 24% of the active treatment group and 20% of the placebo group.

insulin inhalation powder (Afrezza) plus insulin glargine 100 U/mL (Lantus) versus human insulin 70/30

A 52-week, open-label trial randomized 618 patients with T2DM who had been receiving SC insulin therapy to a basal/bolus regimen with insulin glargine 100 U/mL plus insulin inhalation powder or to a twice daily regimen with 70/30 biphasic insulin.[335] For patients assigned to insulin glargine plus inhaled insulin, half of the total daily pre-randomization insulin dose was replaced with mealtime inhaled insulin and the remaining was replaced by basal insulin glargine. Dose titration was permitted throughout the study. At week 52, mean change in HbA1c were -0.59% and -0.71% for insulin glargine/inhaled insulin and biphasic insulin, respectively. Noninferiority (margin 0.4%) of inhaled insulin plus basal insulin was demonstrated compared to biphasic insulin (difference, 0.12% [95% CI, -0.05 to 0.29]). A greater proportion of patients in the biphasic insulin group achieved the target HbA1c ≤ 7% (26.8% versus 22.1%, respectively; p=0.28). A lower incidence of severe hypoglycemia, defined as blood glucose < 37 mg/dL, was reported with inhaled insulin/insulin glargine than biphasic insulin (4.3% versus 10%, respectively; p<0.01). Patients in the inhaled insulin/insulin glargine group experienced a mean increase in weight of 0.9 kg and those in the biphasic insulin group reported a mean increase of 2.5 kg.

META-ANALYSES

A systematic review of 45 studies was performed to compare premixed insulin analogs with any other antidiabetic agents for the treatment of T2DM in adults.[336] The outcomes examined included fasting glucose, postprandial glucose, HbA1c, and weight gain. Mortality data are scant. Of the 45 studies, 43 were randomized controlled trials. The studies included a total of 14,603 patients with a mean age of 59 years, a median HbA1c of 8.7%, and a mean body mass index (BMI) of 29.4 kg/m^2. When compared with long-acting insulin analogs, premixed insulin analogs were found to be more effective in reducing postprandial glucose levels (pooled difference, -27.9 mg/dL [95% CI, -34.3 to -21.5]) and HbA1c (pooled difference, -0.39% [95% CI, -0.5 to -0.3]). However, premixed insulin analogs were found to be less effective than long-acting insulin analogs in reducing fasting glucose levels (pooled difference, 12 mg/dL [95% CI, 6 to 18.1]). Premixed insulin analogs were also associated with an increased incidence of hypoglycemia (OR, 2; CI, 1.3 to 3) and weight gain (pooled difference, 2 kg [95% CI, 1.1 to 3 kg]) compared with long-acting insulins. Premixed insulin analogs were similar to premixed human insulin in decreasing fasting glucose levels, HbA1c levels, and the incidence of hypoglycemia but were more effective in decreasing postprandial glucose levels (mean difference, 219.2 mg/dL [95% CI, 225.9 to 212.5]). Compared to other non-insulin anti-diabetic agents, premixed insulin analogs were more effective in decreasing fasting glucose levels, postprandial glucose levels and HbA1c levels, but were associated with a higher incidence of hypoglycemia.

Four studies were included in a meta-analysis that compared efficacy and hypoglycemia occurrence of once-daily insulin glargine U-100 with NPH insulin in T2DM insulin-naïve patients (n=2,091) who were also on oral antidiabetic drugs (OAD).[337] Mean HbA1c and FPG reductions and proportion of patients that achieved HbA1c < 7% were similar with both insulin products, regardless of concurrent OAD therapy. Rates of overall and nocturnal hypoglycemia were lower for insulin glargine than insulin NPH (overall relative risk [RR], 0.93 [95% CI, 0.87 to 1; p=0.41]; nocturnal RR, 0.73 [95% CI, 0.65 to 0.83]; p<0.001). Weight gain was higher with insulin glargine, as was the insulin dosage after 24 week of therapy.

A total of 13 randomized, 24-week, controlled trials (n=5,401) were included a meta-analysis comparing premixed insulin lispro and insulin glargine in patients with T2DM.[338] Insulin lispro was favored over insulin glargine in HbA1c reduction (parallel trials: weighted mean difference [WMD], -0.18% [95% CI, -0.31 to -0.06]; p=0.004; crossover trials: WMD, 0.37% [95% CI, -0.51 to -0.23]; p<0.00001). Insulin lispro led to more weight gain compared to insulin glargine (parallel trials: WMD, 0.64 kg [95% CI, 0.14 to 1.15]; p=0.01; crossover trials: WMD, 0.74 kg [95% CI, 0.19 to 1.29]; p=0.009). Insulin lispro was also associated with a higher risk of hypoglycemia than insulin glargine (parallel trials: OR, 1.2 [95% CI, 1.06 to 1.36]; p=0.005; crossover trials: OR, 2.24 [95% CI, 1.45 to 3.46]; p=0.0003).

Another meta-analysis included 18 trials (n=16,791) that compared safety and efficacy of insulin degludec with insulin glargine in patients with T1DM or T2DM.[339] The HbA1c was slightly higher with insulin degludec compared to insulin glargine; however, this was not clinically significant (estimated treatment difference, 0.03 [95% CI, 0 to 0.06]; p=0.06]. There was a significant reduction in confirmed hypoglycemia rate with insulin degludec was at the maintenance treatment period (estimated rate ratio [ERR], 0.81 [95% CI, 0.72 to 0.92]; p=0.001). The differences in the rates of hypoglycemia were more evident during the nocturnal period and maintenance periods and in T2DM patients than those with T1DM. The incidence of severe hypoglycemia in T2DM was lower with insulin degludec (ERR, 0.65 [95% CI, 0.52 to 0.89]; p=0.005), but this was not the case in patients with T1DM. The rate of adverse events, including total mortality and cardiovascular events, was not significantly different between the 2 treatment strategies.

Eleven systematic reviews containing randomized controlled trials (dated through October 2016) were identified to compare the efficacy of the long-acting insulin analogs (e.g., insulin glargine or insulin detemir) to NPH insulin for T1DM.[340] The reviews were comprised of 7 original systematic reviews, 4 with meta-analysis, 2 indirect comparisons, and 2 complete health technology assessment studies. There was a statistically significant reduction in HbA1c (mean difference from baseline to study end) with the long-acting insulin analogues compared to NPH insulin (95% CI, -0.23 to -0.12; I^2=99.7%). The meta-analysis revealed a statistically significant difference between the insulin analogue and NPH insulin (RR, 0.95 [95% CI 0.91 to 0.99]; I^2=97.5%) for hypoglycemia. Of the studies that reported severe hypoglycemia, no statistically significant difference between long-acting insulin analogues and NPH insulin was shown.

SUMMARY

Human insulin products (Humulin and Novolin), produced by recombinant DNA technology, contain the exact same insulin amino acids and have the same action as endogenous insulin. Depending on the composition of the product, the onset, peak, and duration of activity can vary, but the effects of these products on HbA1c, fasting plasma glucose, and hypoglycemia are very similar.

Human analog insulins include insulin aspart (Fiasp, Novolog, generic), insulin glulisine (Apidra), insulin lispro (Admelog, Humalog), and insulin lispro-aabc (Lyumjev), which are injectable insulin products that have a faster onset of activity and shorter duration of action than human insulin. Insulin aspart and insulin lispro have been shown to decrease HbA1c (by an additional 0.1% to 0.2%), the incidence of hypoglycemia episodes (by approximately 20%), nocturnal hypoglycemic episodes (by 25% to 50%), and fasting plasma glucose levels compared to human insulins. Insulin glulisine studies show an additional decrease in HbA1c of about 0.1% as well. All of these products may be administered with a meal rather than the 30 to 60 minutes prior to a meal for regular human insulin. Insulin aspart vials and cartridges are latex-free, and the solution contains less metacresol than insulin lispro or insulin lispro-aabc, as does insulin glulisine. All of the rapid-acting insulins are approved for use in pediatric patients as well as for use in external insulin pumps. All are also available in cartridge and/or pen delivery systems.

The biphasic injectable insulins (Humalog Mix 50/50 and 75/25, Novolog Mix 70/30, and human insulin 70/30) combine both a fast-acting and a long-acting insulin. Their purpose is to decrease the number of injections needed per day. Both insulin lispro and insulin aspart combinations have a faster onset of activity and shorter duration of action than biphasic human insulin. Insulin glulisine is not available in such a combination.

Insulin degludec (Tresiba), insulin detemir (Levemir), insulin glargine 100 U/mL (Basaglar, Lantus), insulin glargine-yfgn (Semglee), and insulin glargine 300 U/mL (Toujeo) have changes in the insulin amino acid sequence. They produce a longer duration of action with minimal peak effect and are used as basal insulins. These agents may be used in patients with T1DM as basal insulin and in combination with oral antidiabetic medications in patients with T2DM. Each agent consistently controls glycemic levels better than insulin NPH, with less hypoglycemia. Compared to human insulin, these injectable agents decrease episodes of hypoglycemia by 25% to 50%, decrease nocturnal hypoglycemic episodes by 25% to 33%, and generally result in lower fasting plasma glucose levels. Effects on HbA1c are comparable with human insulin. Insulin U-500 displays a delayed onset and longer duration of action and characteristics more in-line with an intermediate-acting (NPH) insulin.

In December 2016 and June 2020, Basaglar and Semglee (both insulin glargine 100 U/mL), respectively, were approved as *follow-on* products for Lantus. In December 2017, Sanofi-Aventis's Admelog (insulin lispro 100 U/mL), a *follow-on* to Humalog 100 U/mL, was also approved. These products, considered to be *follow-on* products of their corresponding reference products, were approved as drugs under the Food, Drug and Cosmetic (FD&C) Act 505(b)(2) pathway. Effective March 23, 2020, all insulin products previously approved under this pathway are now considered to be biologics under section 351 of the Public Health Service Act (PHSA). This transition allows insulin products to receive competition through the biosimilar pathway, which also allows biosimilar products to receive additional designation as an *interchangeable* biosimilar. Substitution of an interchangeable biosimilar product for the reference product without the intervention of the prescriber at the pharmacy, depending on state substitution laws, is allowed. In June 2020, insulin lispro-aabc (Lyumjev) became the first commercially available insulin in the United States (US) that was approved under section 351(a) of the Public Health Service Act. In July 2021, insulin glargine-yfgn (Semglee) became the first product in the US to receive a determination of interchangeability for its reference product insulin glargine (Lantus). Commercial availability has been transitioned from insulin glargine U-100 (Semglee) to insulin glargine-yfgn, and insulin glargine U-100 (Semglee) has been phased out of the US market. Authorized generics are available for insulin aspart (Novolog) and insulin lispro (Humalog) and may also be substituted for their corresponding brand reference product, since they are identical to the brand product.

Insulin inhalation powder (Afrezza) provides an alternative dosage form to prandial (mealtime) insulin and should be prescribed with injectable basal insulin for T1DM and injectable basal insulin or oral antidiabetic agents for patients with T2DM. The inhaled dosage form could be an option for adults with diabetes in whom the injectable administration is a barrier to insulin therapy. Insulin inhalation powder is contraindicated in patients with chronic lung disease due to the increased risk of bronchospasm. The long-term pulmonary safety of insulin inhalation is unknown.

REFERENCES

1 Afrezza [package insert]. Danbury, CT; Mannkind Corporation; February 2023.
2 Fiasp [package insert]. Plainsboro, NJ; Novo Nordisk; September 2022.
3 Novolog [package insert]. Princeton, NJ; Novo Nordisk; October 2021.
4 Apidra [package insert]. Bridgewater, NJ; Sanofi-Aventis; November 2022.
5 Admelog [package insert]. Bridgewater, NJ; Sanofi-Aventis; December 2020.
6 Humalog [package insert]. Indianapolis, IN; Eli Lilly; November 2019.
7 Insulin Lispro [package insert]. Indianapolis, IN; Eli Lilly; February 2020.
8 Lyumjev [package insert]. Indianapolis, IN; Eli Lilly; October 2022.
9 Humulin R U-100 [package insert]. Indianapolis, IN; Eli Lilly; June 2022.
10 Humulin R U-500 [package insert]. Indianapolis, IN; Eli Lilly; June 2022.
11 Novolin R [package insert]. Plainsboro, NJ; Novo Nordisk; November 2022.
12 Humulin N [package insert]. Indianapolis, IN; Eli Lilly; June 2022.
13 Novolin N [package insert]. Plainsboro, NJ; Novo Nordisk; November 2022.
14 Tresiba [package insert]. Plainsboro, NJ; Novo Nordisk; July 2022.
15 Levemir [package insert]. Princeton, NJ; Novo Nordisk; December 2022.
16 Basaglar [package insert]. Indianapolis, IN; Eli Lilly; July 2021.
17 Lantus [package insert]. Bridgewater, NJ; Sanofi-Aventis; June 2022.
18 Semglee [package insert]. Morgantown, WV; Mylan Specialties; October 2022.
19 Toujeo [package insert]. Bridgewater, NJ; Sanofi-Aventis; August 2022.
20 Semglee [package insert]. Morgantown, WV; Mylan Specialties; October 2022.
21 Novolog Mix 70/30 [package insert]. Princeton, NJ; Novo Nordisk; April 2021.
22 Humalog Mix 75/25 [package insert]. Indianapolis, IN; Eli Lilly; November 2019.
23 Humalog Mix 50/50 [package insert]. Indianapolis, IN; Eli Lilly; November 2019.
24 Humulin 70/30 [package insert]. Indianapolis, IN; Eli Lilly; June 2022.
25 Novolin 70/30 [package insert]. Princeton, NJ; Novo Nordisk; November 2022.
26 Myxredlin [package insert]. Rosemont, IL; Baxter; June 2020.
27 Center for Drug Evaluation and Research. Application number 208157Orig1s000. Summary Review. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/208157Orig1s000SumR.pdf. Accessed February 3, 2023.
28 Diabetes Statistics. Available at: https://www.diabetes.org/resources/statistics. Accessed February 2, 2023.
29 Skyler JS. Glucose control in type 2 diabetes mellitus. Ann Intern Med. 1997; 127: 837-839.
30 World Health Organization. Classification of diabetes mellitus. 2019. Available at: https://www.who.int/publications. Accessed February 2, 2023.
31 Chung WK, Erion K, Florez JC, et al. Precision medicine in diabetes: a Consensus Report from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2020; 63:1671–1693. DOI: 10.1007/s00125-020-05181-w. Available at: https://diabetesjournals.org/care. Accessed February 2, 2023.
32 Precision Medicine in Diabetes: The Road Ahead. February 9, 2021. Available at: https://www.emjreviews.com/innovations/article/precision-medicine-in-diabetes-the-road-ahead/. Accessed February 2, 2023.
33 American Diabetes Association. Precision medicine in diabetes initiative. Available at: https://professional.diabetes.org/content-page/precision-medicine-diabetes-initiative-0. Accessed February 2, 2023.
34 Holt RIG, DeVries JH, Hess-Fischl A, et al. The management of type 1 diabetes in adults. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Consensus Report. Diabetologia. 2021; 64:2609–2652. DOI: 10.1007/s00125-021-05568-3. Available at: https://diabetesjournals.org/care. Accessed February 2, 2023.
35 Blonde L, Umpierrez GE, Reddy, SS, et al. American Association of Clinical Endocrinology clinical practice guidelines for developing a diabetes mellitus comprehensive care plan – 2022 update. Endocrine Practice. 2022; 28(10): 923-1094. DOI: 10.1016/j.eprac.2022.08.002. Available at: https://pro.aace.com/resources?keys=&field_disease_state_content_t_value%5BGuidelines%5D=Guidelines. Accessed February 2, 2023.
36 American Diabetes Association. Classification and diagnosis of diabetes: Standards of Medical Care in Diabetes-2023. Diabetes Care. 2023;46(Suppl 1):S19–S40. DOI: 10.2337/dc23-S002. Available at: https://professional.diabetes.org/content-page/practice-guidelines-resources. Accessed February 2, 2023.
37 American Diabetes Association. Pharmacologic approaches to glycemic treatment: Standards of Care in Diabetes – 2023. Diabetes Care. 2023; 46(Supp 1):S140-S157. DOI: 10.2337/dc23-S009. Available at: https://professional.diabetes.org/content-page/practice-guidelines-resources. Accessed February 2, 2023.

38 Qaseen A, Wilt TJ, Kansagara D, et al. Hemoglobin A1c targets for glycemic control with pharmacologic therapy for nonpregnant adults with type 2 diabetes mellitus: A guidance statement update from the American College of Physicians. 2018. Ann Intern Med. 2018. Published online. DOI: 10.7326/M17-0939. Available at: https://www.acponline.org/clinical-information/guidelines. Accessed February 2, 2023.
39 American Diabetes Association Glycemic targets: Standards of Medical Care in Diabetes – 2023. Diabetes Care 2023;46(Supplement_1):S97–S110. DOI: 10.2337/dc23-S006. Available at: https://professional.diabetes.org/content-page/practice-guidelines-resources. Accessed February 2, 2023.
40 American Diabetes Association. Children and adolescents – Standards of Medical Care in Diabetes -2023. Diabetes Care. 2023; 46 (Suppl 1): S208-S231. DOI: 10.2337/dc23-S014. Available at: https://professional.diabetes.org/content-page/practice-guidelines-resources. Accessed February 2, 2023.
41 American Diabetes Association. Older adults – Standards of Medical Care in Diabetes – 2023. Diabetes Care. 2023; 46 (Suppl 1):S216-S229. DOI: 10.2337/dc23-S013. Available at: https://professional.diabetes.org/content-page/practice-guidelines-resources. Accessed February 2, 2023.
42 American Diabetes Association. Management of diabetes in pregnancy - Standards of Medical Care in Diabetes -2023. Diabetes Care. 2023; 46 (Suppl 1): S254-S266. DOI: 10.2337/dc23-S015. Available at: https://professional.diabetes.org/content-page/practice-guidelines-resources. Accessed February 2, 2023.
43 American Diabetes Association: Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes-2023. Diabetes Care. 2023; 46 (Suppl 1): S140-S157. DOI: 10.2337/dc23-S009. Available at: https://professional.diabetes.org/content-page/practice-guidelines-resources. Accessed February 3, 2023.
44 Management of diabetes in pregnancy: Standards of Medical Care in Diabetes-2023. Diabetes Care. 2023;46(Suppl. 1):S254–S266. DOI: 10.2337/dc23-S015. Available at: https://professional.diabetes.org/content-page/practice-guidelines-resources. Accessed February 3, 2023.
45 American Diabetes Association. Children and adolescents: Standards of Medical Care in Diabetes-2023. Diabetes Care. 2023;46(Suppl 1):S1208-S231. DOI: 10.2337/dc23-S014. Available at: https://professional.diabetes.org/content-page/practice-guidelines-resources. Accessed February 3, 2023.
46 Davies MJ, Aroda BS, Collins RA, et al. Management of hyperglycemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2022;45(2753-2786. Available at: https://www.easd.org/guidelines/statements-and-guidelines.html. Accessed February 3, 2023.
47 Blonde L, Umpierrez GE, Reddy SS, et al. American Association of Clinical Endocrinology clinical practice guideline: developing a diabetes mellitus comprehensive care plan – 2022 update. Endocrine Practice. 2022; 28:923-1049. Available at: https://pro.aace.com/disease-state-resources/diabetes/guidelines. Accessed February 3, 2023.
48 Blonde L, Umpierrez GE, Reddy SS, et al. American Association of Clinical Endocrinology clinical practice guideline: developing a diabetes mellitus comprehensive care plan – 2022 update. Endocrine Practice. 2022; 28:923-1049. Available at: https://pro.aace.com/disease-state-resources/diabetes/guidelines. Accessed February 3, 2023.
49 Garber AJ, Handelsman Y, Grunberger G, et al. AACE/ACE comprehensive type 2 diabetes management algorithm 2020. Available at: https://www.aace.com/disease-state-resources/diabetes/guidelines. Accessed February 3, 2023.
50 American Association of Clinical Endocrinology. Comprehensive type 2 diabetes management algorithm (2020) – executive summary. Available at: https://pro.aace.com/disease-state-resources/diabetes/clinical-practice-guidelines-treatment-algorithms/comprehensive. Accessed February 3, 2023.
51 McCall AL, Lieb DC, Gianchandani R, et al. Management of individuals with diabetes at high risk for hypoglycemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2022. DOI: 10.1210/clinem/dgac596. Available at: https://www.endocrine.org/clinical-practice-guidelines. Accessed February 3, 2023.
52 World Health Organization. Guidelines on second- and third-line medicines and type of insulin for the control of blood glucose levels in non-pregnant adults with diabetes mellitus – 2018. Available at: https://www.who.int/publications/i?healthtopics=17f23e6d-2c9a-4f9e-9a08-0151693e0d0a&publishingoffices-hidden=true. Accessed February 3, 2023.
53 Roglic G, Norris SL. Medicines for treatment intensification in type 2 diabetes and type 1 diabetes in low-recourse settings: synopsis of the World Health Organization Guidelines on second- and third-line medicines and type of insulin for the control of blood glucose levels in nonpregnant adults with diabetes mellitus. Ann Intern Med. 2018; 169(6):394-397. DOI: 10.7326/M18-1149.
54 World Health Organization. HEARTS-D. Diagnosis and Management of Type 2 Diabetes. 2020. Available at: https://www.who.int/publications/i/item/hearts-technical-package. Accessed February 3, 2023.
55 Koren D, Levitsky L. Type 2 diabetes mellitus in childhood and adolescents. Pediatr Rev. 2021; 42(4): 167-179. DOI: 10.1542/pir.2019-0236. Available at: https://publications.aap.org/pediatricsinreview/article-abstract/42/4/167/180698/Type-2-Diabetes-Mellitus-in-Childhood-and?redirectedFrom=fulltext. Accessed March 2, 2023.
56 LeRoith D, Biessels GJ, Braithwaite SS, et al. Treatment of diabetes in older adults guideline resources. J Clin Endocrinol Metab. 2019; 104 (5): 1520–1574. DOI:10.1210/jc.2019-00198. Available at: https://www.endocrine.org/clinical-practice-guidelines. Accessed February 3, 2023.
57 White J, Goldman J. Biosimilar and follow-on insulin: The ins, outs, and interchangeability. J Pharm Technol. 2019; 35(1): 25-35. DOI: 10.1177/8755122518802268.
58 FDA Statement: Statement from FDA Commissioner Scott Gottlieb, M.D., on new actions advancing the agency's biosimilars policy framework. December 11, 2018. Available at: https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-new-actions-advancing-agencys-biosimilars-policy. Accessed February 3, 2023.
59 FDA Guidance Document: The "Deemed to be a License" provision of the BPCI Act: Questions and Answers. March 2020. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/deemed-be-license-provision-bpci-act-questions-and-answers. Accessed February 3, 2023.
60 Biosimilars Guidance. Updated October 5, 2021. Available at: https://www.fda.gov/vaccines-blood-biologics/general-biologics-guidances/biosimilars-guidances. Accessed February 3, 2023.
61 FDA Statement: Statement from FDA Commissioner Scott Gottlieb, M.D., on new actions advancing the agency's biosimilars policy framework. Updated December 11, 2018. Available at: https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-new-actions-advancing-agencys-biosimilars-policy. Accessed February 3, 2023.
62 U.S. Food and Drug Administration. Biosimilar and interchangeable biologics: more treatment choices. Current as of October 12, 2021. Available at: https://www.fda.gov/consumers/consumer-updates/biosimilar-and-interchangeable-biologics-more-treatment-choices. Accessed February 3, 2023.
63 U.S. Food and Drug Administration. Biosimilar and interchangeable biologics: more treatment choices. Current as of October 12, 2021. Available at: https://www.fda.gov/consumers/consumer-updates/biosimilar-and-interchangeable-biologics-more-treatment-choices. Accessed February 3, 2023.

64 Lyumjev. FDA approval letter. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/761109Orig1s000ltr_replacement.pdf. Accessed February 3, 2023.
65 FDA Approves First Interchangeable Biosimilar Insulin Product for Treatment of Diabetes. July 28, 2021. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-first-interchangeable-biosimilar-insulin-product-treatment-diabetes. Accessed February 3, 2023.
66 Viatris and Biocon Biologics Announce Launch of Interchangeable Semglee (insulin glargine-yfgn) Injection and Insulin Glargine (insulin glargine-yfgn) Injection. November 16, 2021. https://newsroom.viatris.com/2021-11-16-Viatris-and-Biocon-Biologics-Announce-Launch-of-Interchangeable-SEMGLEE-R-insulin-glargine-yfgn-Injection-and-Insulin-Glargine-insulin-glargine-yfgn-Injection#:~:text=SEMGLEE%20(insulin%20glargine%2Dyfgn),of%20the%202021%20calendar%20year. Accessed February 3, 2023.
67 Schuit FC, Huypens P, Heimberg H, et al. Glucose sensing in pancreatic β-cells. Diabetes. 2001; 50(1): 1-11. DOI: 10.2337/diabetes.50.1.1
68 Humulin R U-100 [package insert]. Indianapolis, IN; Eli Lilly; June 2022.
69 Afrezza [package insert]. Danbury, CT; Mannkind Corporation; February 2023.
70 Humulin 70/30 [package insert]. Indianapolis, IN; Eli Lilly; June 2022.
71 Fiasp [package insert]. Plainsboro, NJ; Novo Nordisk; September 2022.
72 Novolin R [package insert]. Plainsboro, NJ; Novo Nordisk; November 2022.
73 Insulin (class). Micromedex. Available at: https://www.micromedexsolutions.com/home/dispatch. Accessed February 3, 2023.
74 Afrezza [package insert]. Danbury, CT; Mannkind Corporation; February 2023.
75 Novolog [package insert]. Princeton, NJ; Novo Nordisk; October 2021.
76 Apidra [package insert]. Bridgewater, NJ; Sanofi-Aventis; November 2022.
77 Admelog [package insert]. Bridgewater, NJ; Sanofi-Aventis; December 2020.
78 Available at: https://www.micromedexsolutions.com/. Accessed February 3, 2023.
79 Lyumjev [package insert]. Indianapolis, IN; Eli Lilly; October 2022.
80 Humalog [package insert]. Indianapolis, IN; Eli Lilly; November 2019.
81 Novolog Mix 70/30 [package insert]. Princeton, NJ; Novo Nordisk; April 2021.
82 Humalog Mix 75/25 [package insert]. Indianapolis, IN; Eli Lilly; November 2019.
83 Humalog Mix 50/50 [package insert]. Indianapolis, IN; Eli Lilly; November 2019.
84 Humulin 70/30 [package insert]. Indianapolis, IN; Eli Lilly; June 2022.
85 Novolin [package insert]. Princeton, NJ; Novo Nordisk; March 2013.
86 Humulin R U-100 [package insert]. Indianapolis, IN; Eli Lilly; June 2022.
87 Humulin R U-500 [package insert]. Indianapolis, IN; Eli Lilly; June 2022.
88 Clinical Pharmacology. Available at: https://www.clinicalkey.com/pharmacology/. Accessed February 3, 2023.
89 Humulin 70/30 [package insert]. Indianapolis, IN; Eli Lilly; June 2022.
90 Novolin R [package insert]. Plainsboro, NJ; Novo Nordisk; November 2022.
91 Humulin N [package insert]. Indianapolis, IN; Eli Lilly; June 2022.
92 Novolin N [package insert]. Plainsboro, NJ; Novo Nordisk; November 2022.
93 Tresiba [package insert]. Plainsboro, NJ; Novo Nordisk; July 2022.
94 Levemir [package insert]. Princeton, NJ; Novo Nordisk; December 2022.
95 Basaglar [package insert]. Indianapolis, IN; Eli Lilly; July 2021.
96 Semglee [package insert]. Morgantown, WV; Mylan Specialties; October 2022.
97 Lantus [package insert]. Bridgewater, NJ; Sanofi-Aventis; June 2022.
98 Toujeo [package insert]. Bridgewater, NJ; Sanofi-Aventis; August 2022.
99 Novolin 70/30 [package insert]. Princeton, NJ; Novo Nordisk; November 2022.
100 Plank J, Bodenlenz M, Sinner F, et al. A double-blind, randomized, dose-response study investigating the pharmacodynamic and pharmacokinetic properties of the long-acting insulin analog detemir. Diabetes Care. 2005; 28(5): 1107-12. DOI: 10.2337/diacare.28.5.1107.
101 Shiramoto M, Eto T, Irie S, et al. Single-dose new insulin glargine 300 U/mL provides prolonged stable glycaemic control in Japanese and European people with type 1 diabetes. Diabetes Obes Metab. 2015; 17(3): 254-60. DOI: 10.1111/dom.12415.
102 Fiasp. Pharmacokinetics. Clinical Pharmacology. Revised April 21, 2021. Available at: https://www.clinicalkey.com/pharmacology/. Accessed February 3, 2023.
103 Garber AJ, Handelsman Y, Grunberger G, et al. AACE/ACE comprehensive type 2 diabetes management algorithm 2020. Available at: https://pro.aace.com/resources?keys=&field_disease_state_content_t_value%5BGuidelines%5D=Guidelines. Accessed February 3, 2023.
104 American Diabetes Association: Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes-2023. Diabetes Care. 2023; 46 (Suppl 1): S140-S157. DOI: 10.2337/dc23-S009. Available at: https://professional.diabetes.org/content-page/practice-guidelines-resources. Accessed February 3, 2023.
105 Afrezza [package insert]. Danbury, CT; Mannkind Corporation; February 2023.
106 Fiasp [package insert]. Plainsboro, NJ; Novo Nordisk; September 2022.
107 Novolog [package insert]. Princeton, NJ; Novo Nordisk; October 2021.
108 Apidra [package insert]. Bridgewater, NJ; Sanofi-Aventis; November 2022.
109 Admelog [package insert]. Bridgewater, NJ; Sanofi-Aventis; December 2020.
110 Lyumjev [package insert]. Indianapolis, IN; Eli Lilly; October 2022.
111 Humalog [package insert]. Indianapolis, IN; Eli Lilly; November 2019.
112 Insulin Lispro [package insert]. Indianapolis, IN; Eli Lilly; February 2020.
113 Humulin R U-500 [package insert]. Indianapolis, IN; Eli Lilly; June 2022.
114 Humulin R U-100 [package insert]. Indianapolis, IN; Eli Lilly; June 2022.
115 Novolin R [package insert]. Plainsboro, NJ; Novo Nordisk; November 2022.
116 Humulin N [package insert]. Indianapolis, IN; Eli Lilly; June 2022.
117 Novolin N [package insert]. Plainsboro, NJ; Novo Nordisk; November 2022.

118 Tresiba [package insert]. Plainsboro, NJ; Novo Nordisk; July 2022.
119 Levemir [package insert]. Princeton, NJ; Novo Nordisk; December 2022.
120 Basaglar [package insert]. Indianapolis, IN; Eli Lilly; July 2021.
121 Lantus [package insert]. Bridgewater, NJ; Sanofi-Aventis; June 2022.
122 Semglee [package insert]. Morgantown, WV; Mylan Specialties; October 2022.
123 Toujeo [package insert]. Bridgewater, NJ; Sanofi-Aventis; August 2022.
124 Novolog Mix 70/30 [package insert]. Princeton, NJ; Novo Nordisk; April 2021.
125 Humalog Mix 75/25 [package insert]. Indianapolis, IN; Eli Lilly; November 2019.
126 Humalog Mix 50/50 [package insert]. Indianapolis, IN; Eli Lilly; November 2019.
127 Humulin 70/30 [package insert]. Indianapolis, IN; Eli Lilly; June 2022.
128 Novolin 70/30 [package insert]. Princeton, NJ; Novo Nordisk; November 2022.
129 FDA Drug Safety Communication: FDA requires label warnings to prohibit sharing of multi-dose diabetes pen devices among patients. February 26, 2018. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm435271.htm. Accessed March 2, 2023.
130 FDA advises health care professionals and patients about insulin pen packaging and dispensing. October 13, 2020. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-health-care-professionals-and-patients-about-insulin-pen-packaging-and-dispensing. Accessed February 3, 2023.
131 FDA Safety Communication. FDA warns against the use of devices for diabetes management not authorized for sale in the United States: FDA Safety Communication. May 17, 2019. Available at: https://www.fda.gov/news-events/press-announcements/fda-warns-against-use-unauthorized-devices-diabetes-management. Accessed February 3, 2023.
132 Afrezza [package insert]. Danbury, CT; Mannkind Corporation; February 2023.
133 Fiasp [package insert]. Plainsboro, NJ; Novo Nordisk; September 2022.
134 Novolog [package insert]. Princeton, NJ; Novo Nordisk; October 2021.
135 Apidra [package insert]. Bridgewater, NJ; Sanofi-Aventis; November 2022.
136 Admelog [package insert]. Bridgewater, NJ; Sanofi-Aventis; December 2020.
137 Lyumjev [package insert]. Indianapolis, IN; Eli Lilly; October 2022.
138 Humalog [package insert]. Indianapolis, IN; Eli Lilly; November 2019.
139 Insulin Lispro [package insert]. Indianapolis, IN; Eli Lilly; February 2020.
140 Humulin R U-100 [package insert]. Indianapolis, IN; Eli Lilly; June 2022.
141 Humulin R U-500 [package insert]. Indianapolis, IN; Eli Lilly; June 2022.
142 Novolin R [package insert]. Plainsboro, NJ; Novo Nordisk; November 2022.
143 Humulin N [package insert]. Indianapolis, IN; Eli Lilly; June 2022.
144 Novolin N [package insert]. Plainsboro, NJ; Novo Nordisk; November 2022.
145 Tresiba [package insert]. Plainsboro, NJ; Novo Nordisk; July 2022.
146 Levemir [package insert]. Princeton, NJ; Novo Nordisk; December 2022.
147 Basaglar [package insert]. Indianapolis, IN; Eli Lilly; July 2021.
148 Lantus [package insert]. Bridgewater, NJ; Sanofi-Aventis; June 2022.
149 Semglee [package insert]. Morgantown, WV; Mylan Specialties; October 2022.
150 Toujeo [package insert]. Bridgewater, NJ; Sanofi-Aventis; August 2022.
151 Novolog Mix 70/30 [package insert]. Princeton, NJ; Novo Nordisk; April 2021.
152 Humalog Mix 75/25 [package insert]. Indianapolis, IN; Eli Lilly; November 2019.
153 Humalog Mix 50/50 [package insert]. Indianapolis, IN; Eli Lilly; November 2019.
154 Humulin 70/30 [package insert]. Indianapolis, IN; Eli Lilly; June 2022.
155 Novolin 70/30 [package insert]. Princeton, NJ; Novo Nordisk; November 2022.
156 Afrezza [package insert]. Danbury, CT; Mannkind Corporation; February 2023.
157 Fiasp [package insert]. Plainsboro, NJ; Novo Nordisk; September 2022.
158 Novolog [package insert]. Princeton, NJ; Novo Nordisk; October 2021.
159 Apidra [package insert]. Bridgewater, NJ; Sanofi-Aventis; November 2022.
160 Admelog [package insert]. Bridgewater, NJ; Sanofi-Aventis; December 2020.
161 Lyumjev [package insert]. Indianapolis, IN; Eli Lilly; October 2022.
162 Humalog [package insert]. Indianapolis, IN; Eli Lilly; November 2019.
163 Insulin Lispro [package insert]. Indianapolis, IN; Eli Lilly; February 2020.
164 Humulin R U-100 [package insert]. Indianapolis, IN; Eli Lilly; June 2022.
165 Humulin R U-500 [package insert]. Indianapolis, IN; Eli Lilly; June 2022.
166 Novolin R [package insert]. Plainsboro, NJ; Novo Nordisk; November 2022.
167 Humulin N [package insert]. Indianapolis, IN; Eli Lilly; June 2022.
168 Novolin N [package insert]. Plainsboro, NJ; Novo Nordisk; November 2022.
169 Tresiba [package insert]. Plainsboro, NJ; Novo Nordisk; July 2022.
170 Levemir [package insert]. Princeton, NJ; Novo Nordisk; December 2022.
171 Basaglar [package insert]. Indianapolis, IN; Eli Lilly; July 2021.
172 Lantus [package insert]. Bridgewater, NJ; Sanofi-Aventis; June 2022.
173 Semglee [package insert]. Morgantown, WV; Mylan Specialties; October 2022.
174 Toujeo [package insert]. Bridgewater, NJ; Sanofi-Aventis; August 2022.
175 Novolog Mix 70/30 [package insert]. Princeton, NJ; Novo Nordisk; April 2021.
176 Humalog Mix 75/25 [package insert]. Indianapolis, IN; Eli Lilly; November 2019.
177 Humalog Mix 50/50 [package insert]. Indianapolis, IN; Eli Lilly; November 2019.

178 Humulin 70/30 [package insert]. Indianapolis, IN; Eli Lilly; June 2022.
179 Novolin 70/30 [package insert]. Princeton, NJ; Novo Nordisk; November 2022.
180 The Medical Letter. Insulins for Type 2 Diabetes. May 6, 2019. Available at: https://secure.medicalletter.org/. Accessed February 3, 2023.
181 Afrezza [package insert]. Danbury, CT; Mannkind Corporation; February 2023.
182 Fiasp [package insert]. Plainsboro, NJ; Novo Nordisk; September 2022.
183 Novolog [package insert]. Princeton, NJ; Novo Nordisk; October 2021.
184 Apidra [package insert]. Bridgewater, NJ; Sanofi-Aventis; November 2022.
185 Admelog [package insert]. Bridgewater, NJ; Sanofi-Aventis; December 2020.
186 Lyumjev [package insert]. Indianapolis, IN; Eli Lilly; October 2022.
187 Humalog [package insert]. Indianapolis, IN; Eli Lilly; November 2019.
188 Insulin Lispro [package insert]. Indianapolis, IN; Eli Lilly; February 2020.
189 Humulin R U-100 [package insert]. Indianapolis, IN; Eli Lilly; June 2022.
190 Humulin R U-500 [package insert]. Indianapolis, IN; Eli Lilly; June 2022.
191 Novolin R [package insert]. Plainsboro, NJ; Novo Nordisk; November 2022.
192 Humulin N [package insert]. Indianapolis, IN; Eli Lilly; June 2022.
193 Novolin N [package insert]. Plainsboro, NJ; Novo Nordisk; November 2022.
194 Tresiba [package insert]. Plainsboro, NJ; Novo Nordisk; July 2022.
195 Levemir [package insert]. Princeton, NJ; Novo Nordisk; December 2022.
196 Basaglar [package insert]. Indianapolis, IN; Eli Lilly; July 2021.
197 Lantus [package insert]. Bridgewater, NJ; Sanofi-Aventis; June 2022.
198 Semglee [package insert]. Morgantown, WV; Mylan Specialties; October 2022.
199 Toujeo [package insert]. Bridgewater, NJ; Sanofi-Aventis; August 2022.
200 Novolog Mix 70/30 [package insert]. Princeton, NJ; Novo Nordisk; April 2021.
201 Humalog Mix 75/25 [package insert]. Indianapolis, IN; Eli Lilly; November 2019.
202 Humalog Mix 50/50 [package insert]. Indianapolis, IN; Eli Lilly; November 2019.
203 Humulin 70/30 [package insert]. Indianapolis, IN; Eli Lilly; June 2022.
204 Novolin 70/30 [package insert]. Princeton, NJ; Novo Nordisk; November 2022.
205 Afrezza [package insert]. Danbury, CT; Mannkind Corporation; February 2023.
206 Fiasp [package insert]. Plainsboro, NJ; Novo Nordisk; September 2022.
207 Novolog [package insert]. Princeton, NJ; Novo Nordisk; October 2021.
208 Apidra [package insert]. Bridgewater, NJ; Sanofi-Aventis; November 2022.
209 Admelog [package insert]. Bridgewater, NJ; Sanofi-Aventis; December 2020.
210 Lyumjev [package insert]. Indianapolis, IN; Eli Lilly; October 2022.
211 Humalog [package insert]. Indianapolis, IN; Eli Lilly; November 2019.
212 Insulin Lispro [package insert]. Indianapolis, IN; Eli Lilly; February 2020.
213 Humulin R U-100 [package insert]. Indianapolis, IN; Eli Lilly; June 2022.
214 Humulin R U-500 [package insert]. Indianapolis, IN; Eli Lilly; June 2022.
215 Novolin R [package insert]. Plainsboro, NJ; Novo Nordisk; November 2022.
216 Humulin N [package insert]. Indianapolis, IN; Eli Lilly; June 2022.
217 Novolin N [package insert]. Plainsboro, NJ; Novo Nordisk; November 2022.
218 Tresiba [package insert]. Plainsboro, NJ; Novo Nordisk; July 2022.
219 Levemir [package insert]. Princeton, NJ; Novo Nordisk; December 2022.
220 Basaglar [package insert]. Indianapolis, IN; Eli Lilly; July 2021.
221 Lantus [package insert]. Bridgewater, NJ; Sanofi-Aventis; June 2022.
222 Semglee [package insert]. Morgantown, WV; Mylan Specialties; October 2022.
223 Toujeo [package insert]. Bridgewater, NJ; Sanofi-Aventis; August 2022.
224 Novolog Mix 70/30 [package insert]. Princeton, NJ; Novo Nordisk; April 2021.
225 Humalog Mix 75/25 [package insert]. Indianapolis, IN; Eli Lilly; November 2019.
226 Humalog Mix 50/50 [package insert]. Indianapolis, IN; Eli Lilly; November 2019.
227 Humulin 70/30 [package insert]. Indianapolis, IN; Eli Lilly; June 2022.
228 Novolin 70/30 [package insert]. Princeton, NJ; Novo Nordisk; November 2022.
229 Novolin 70/30 [package insert]. Princeton, NJ; Novo Nordisk; November 2022.
230 Available at: https://www.mynovoinsulin.com/insulin-products/levemir/home.html. Accessed February 28, 2023.
231 FDA approves first dedicated syringe for U-500 insulin. July 13, 2016. Available at: http://www.medscape.com/viewarticle/866091. Accessed February 3, 2023.
232 Taking Novolog. Available at: http://www.rapidactinginsulin.com/novolog/using-novolog/insulin-delivery-options.html. Accessed March 2, 2023.
233 Tempo personalized diabetes management platform. Updated December 2022. Available at: https://www.lillytempo.com/. Accessed January 30, 2023.
234 Fiasp [package insert]. Plainsboro, NJ; Novo Nordisk; September 2022.
235 Russell-Jones D, Bode BW, De Block C, et al. Fast-acting insulin aspart improves glycemic control in basal-bolus treatment for type 1 diabetes: results of a 26-week multicenter, active-controlled, treat-to-target, randomized, parallel-group trial (onset 1). Diabetes Care. 2017; 40: 943–950. DOI: 10.2337/dc16-1771.
236 Fiasp [package insert]. Plainsboro, NJ; Novo Nordisk; September 2022.

237 Bowering K, Case C, Harvey J, et al. Faster aspart versus insulin aspart as part of a basal-bolus regimen in inadequately controlled type 2 diabetes: the onset 2 trial. Diabetes Care. 2017; 40(7): 951-957. DOI: 10.2337/dc16-1770.
238 Fiasp [package insert]. Plainsboro, NJ; Novo Nordisk; September 2022.
239 Tamas G, Marre M, Astorga R, et al. Glycaemic control in type 1 diabetic patients using optimised insulin aspart or human insulin in a randomised multinational study. Diabetes Res Clin Pract. 2001; 54(2): 105-114. DOI: 10.1016/s0168-8227(01)00262-5.
240 Home RD, Lindholm A, Riis A. Insulin aspart versus human insulin in the management of long-term blood glucose control in type 1 diabetes mellitus: a randomized controlled trial. Diabet Med. 2000; 17: 762-770. DOI: 10.1046/j.1464-5491.2000.00380.x.
241 Raskin P, Guthrie RA, Leiter L, et al. Use of insulin aspart, a fast-acting insulin analog, as the mealtime insulin in the management of patients with type 1 diabetes. Diabetes Care. 2000; 23(5): 583-588. DOI: 10.2337/diacare.23.5.583.
242 DeVries JH, Lindholm A, Jacobsen JL, et al. A randomized trial of insulin aspart with intensified basal NPH insulin supplementation in people with type 1 diabetes. Diabet Med. 2003; 20(4): 312-8. DOI: 10.1046/j.1464-5491.2003.00936.x.
243 Bott U, Ebrahim S, Hirschberger S, et al. Effect of the rapid-acting insulin analogue insulin aspart on quality of life and treatment satisfaction in patients with Type 1 diabetes. Diabet Med. 2003; 20(8): 626-634. DOI: 10.1046/j.1464-5491.2003.01010.x.
244 Heller SR, Colagiuri S, Vaaler S, et al. Hypoglycaemia with insulin aspart: a double-blind, randomised, crossover trial in subjects with type 1 diabetes. Diabet Med. 2004; 21(7): 769-775. DOI: 10.1111/j.1464-5491.2004.01244.x.
245 Abrahamian H, Ludvik B, Schernthaner G, et al. Improvement of glucose tolerance in type 2 diabetic patients: traditional versus modern insulin regimens (results from the Austrian Biaspart Study). Horm Metab Res. 2005; 37(11):684-689. DOI: 10.1055/s-2005-870579.
246 Mortensen H, Kocova M, Teng LY, et al. Biphasic insulin aspart versus human insulin in adolescents with type 1 diabetes on multiple daily insulin injections. Pediatr Diabetes. 2006; 7(1): 4-10. DOI: 10.1111/j.1399-543X.2006.00138.x.
247 Bretzel RG, Arnolds S, Medding J, et al. A direct efficacy and safety comparison of insulin aspart, human soluble insulin, and human premix insulin (70/30) in patients with type 2 diabetes. Diabetes Care. 2004; 27(5): 1023-1027. DOI: 10.2337/diacare.27.5.1023.
248 Christiansen JS, Vaz JA, Metelko Z, et al. Twice daily biphasic insulin aspart improves postprandial glycaemic control more effectively than twice daily NPH insulin, with low risk of hypoglycaemia, in patients with type 2 diabetes. Diabetes Obes Metab. 2003; 5(6): 446-454. DOI: 10.1046/j.1463-1326.2003.00300.x.
249 Niskanen L, Jensen LE, Rastam J, et al. Randomized, multinational, open-label, 2-period, crossover comparison of biphasic insulin aspart 30 and biphasic insulin lispro 25 and pen devices in adult patients with type 2 diabetes mellitus. Clin Ther. 2004; 26(4): 531-540. DOI: 10.1016/s0149-2918(04)90055-0.
250 Tresiba [package insert]. Plainsboro, NJ; Novo Nordisk; July 2022.
251 Davies M, Sasaki T, Gross JL, et al. Comparison of insulin degludec with insulin detemir in type 1 diabetes: a 1-year treat-to-target trial. Diabetes Obes Metab. 2016; 18(1): 96-9. DOI: 10.1111/dom.12573.
252 Tresiba [package insert]. Plainsboro, NJ; Novo Nordisk; July 2022.
253 Tresiba [package insert]. Plainsboro, NJ; Novo Nordisk; July 2022.
254 Tresiba [package insert]. Plainsboro, NJ; Novo Nordisk; July 2022.
255 Center for Drug Evaluation and Research. Application number 203313Orig1s000. Tresiba. FDA briefing document. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/203313Orig1s000_203314Orig1s000MedR.pdf. Accessed February 3, 2023.
256 Tresiba [package insert]. Plainsboro, NJ; Novo Nordisk; July 2022.
257 Center for Drug Evaluation and Research. Application number 203313Orig1s000. Tresiba. FDA briefing document. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/203313Orig1s000_203314Orig1s000MedR.pdf. Accessed February 3, 2023.
258 Tresiba [package insert]. Plainsboro, NJ; Novo Nordisk; July 2022.
259 Center for Drug Evaluation and Research. Application number 203313Orig1s000. Tresiba. FDA briefing document. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/203313Orig1s000_203314Orig1s000MedR.pdf. Accessed February 3, 2023.
260 Tresiba [package insert]. Plainsboro, NJ; Novo Nordisk; July 2022.
261 Center for Drug Evaluation and Research. Application number 203313Orig1s000. Tresiba. FDA briefing document. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/203313Orig1s000_203314Orig1s000MedR.pdf. Accessed February 3, 2023.
262 Tresiba [package insert]. Plainsboro, NJ; Novo Nordisk; July 2022.
263 Center for Drug Evaluation and Research. Application number 203313Orig1s000. Tresiba. FDA briefing document. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/203313Orig1s000_203314Orig1s000MedR.pdf. Accessed February 3, 2023.
264 Lane W, Bailey TS, Gerety G, et al. Effect of insulin degludec vs insulin glargine U100 on hypoglycemia in patients with type 1 diabetes: The SWITCH 1 randomized clinical trial. JAMA. 2017; 318(1): 33-44. DOI: 10.1001/jama.2017.7115.
265 Wysham C, Bhargava A, Chaykin L, et al. Effect of insulin degludec vs insulin glargine U100 on hypoglycemia in patients with type 2 diabetes: The SWITCH 2 randomized clinical trial. JAMA. 2017; 318(1):45-56. DOI: 10.1001/jama.2017.7117.
266 Goldenberg RM, Aroda VR, Billings LK, et al. 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 hypo glycaemia. Diabetes Obes Metab. 2021;23:2572–2581. DOI: 10.1111/dom.14504.
267 Marso SP, McGuire DK, Zinman B, et al. Design of DEVOTE (trial comparing cardiovascular safety of insulin degludec vs insulin glargine in patients with type 2 diabetes at high risk of cardiovascular events – DEVOTE 1. Am Heart J. 2016; 179: 175-83. DOI: 10.1016/j.ahj.2016.06.004.
268 Russell-Jones D, Simpson R, Hylleberg B, et al. Effects of QD insulin detemir or neutral protamine Hagedorn on blood glucose control in patients with type I diabetes mellitus using a basal-bolus regimen. Clin Ther. 2004; 26(5): 724-736. DOI: 10.1016/s0149-2918(04)90072-0.
269 Robertson KJ, Schoenle E, Gucev Z, et al. Insulin detemir compared with NPH insulin in children and adolescents with type 1 diabetes. Diabet Med. 2007; 24(1): 27-34. DOI: 10.1111/j.1464-5491.2007.02024.x.
270 Thalange N, Bereket A, Larsen J, et al. Treatment with insulin detemir or NPH insulin in children aged 2-5 yr with type 1 diabetes mellitus. Pediatr Diabetes. 2011; 12(7): 632-41. DOI: 10.1111/j.1399-5448.2010.00750.x.
271 Levemir [package insert]. Princeton, NJ; Novo Nordisk; December 2022.
272 Vellanki P, Umpierrez G. Detemir is non-inferior to NPH insulin in women with pregestational type 2 diabetes and gestational diabetes mellitus. Am J Obstet Gynecol. 2015; 213: 426.e1–7. DOI: 10.1136/ebmed-2015-110309.
273 Philis-Tsimikas A, Charpentier G, Clauson P, et al. Comparison of once-daily insulin detemir with NPH insulin added to a regimen of oral antidiabetic drugs in poorly controlled type 2 diabetes. Clin Ther. 2006; 28(10): 1569-1581. DOI: 10.1016/j.clinthera.2006.10.020.

274 Hermansen K, Davies M, Derezinski T, et al. A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naive people with type 2 diabetes. Diabetes Care. 2006; 29(6): 1269-1274. DOI: 10.2337/dc05-1365.
275 Herrera KM, Rosenn BM, Foroutan J, et al. Randomized controlled trial of insulin detemir versus NPH for the treatment of pregnant women with diabetes. Am J Obstet Gynecol. 2015; 213(3): 426.e1-7. DOI: 10.1016/j.ajog.2015.06.010.
276 Holman RR, Thorne KI, Farmer AJ, et al. Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. N Engl J Med. 2007; 357(17): 1716-30.
277 Vague P, Selam JL, Skeie S, et al. Insulin detemir is associated with more predictable glycemic control and reduced risk of hypoglycemia than NPH insulin in patients with type 1 diabetes on a basal-bolus regimen with premeal insulin aspart. Diabetes Care. 2003; 26(3): 590-596. DOI: 10.2337/diacare.26.3.590.
278 Home P, Bartley P, Russell-Jones D, et al. Insulin detemir offers improved glycemic control compared with NPH insulin in people with type 1 diabetes: a randomized clinical trial. Diabetes Care. 2004; 27(5): 1081-1087. DOI: 10.2337/diacare.27.5.1081.
279 Haak T, Tiengo A, Draeger E, et al. Lower within-subject variability of fasting blood glucose and reduced weight gain with insulin detemir compared to NPH insulin in patients with type 2 diabetes. Diabetes Obes Metab. 2005; 7(1): 56-64. DOI: 10.1111/j.1463-1326.2004.00373.x.
280 Pieber TR, Draeger E, Kristensen A, et al. Comparison of three multiple injection regimens for type 1 diabetes: morning plus dinner or bedtime administration of insulin detemir versus morning plus bedtime NPH insulin. Diabet Med. 2005; 22(7): 850-857. DOI: 10.1111/j.1464-5491.2005.01545.x.
281 Hermansen K, Fontaine P, Kukolja KK, et al. Insulin analogues (insulin detemir and insulin aspart) versus traditional human insulins (NPH insulin and regular human insulin) in basal-bolus therapy for patients with type 1 diabetes. Diabetologia. 2004; 47(4): 622-629. DOI: 10.1007/s00125-004-1365-z.
282 Raslova K, Bogoev M, Raz I, et al. Insulin detemir and insulin aspart: a promising basal-bolus regimen for type 2 diabetes. Diabetes Res Clin Pract. 2004; 66(2): 193-201. DOI: 10.1016/j.diabres.2004.03.003.
283 FDA approves Basaglar, the first “follow-on” insulin glargine product to treat diabetes. December 16, 2015. https://wayback.archive-it.org/7993/20170722061458/https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm477734.htm. Accessed February 3, 2023.
284 Basaglar [package insert]. Indianapolis, IN; Eli Lilly; July 2021.
285 A Study in Adults With Type 1 Diabetes (ELEMENT 1). Available at: https://clinicaltrials.gov/ct2/show/record/NCT01421147?term=NCT01421147&draw=2&rank=1. Accessed February 3, 2023.
286 Basaglar [package insert]. Indianapolis, IN; Eli Lilly; July 2021.
287 A Study of LY2963016 compared to Lantus in adult participants with type 2 diabetes mellitus (ELEMENT 5). Available at: https://clinicaltrials.gov/ct2/show/results/NCT02302716?term=LY2963016&draw=3. Accessed February 3, 2023.
288 Raskin P. A 16-week comparison of the novel insulin analog insulin glargine (HOE 901) and NPH human insulin used with insulin lispro in patients with type 1 diabetes. Diabetes Care. 2000; 23(11): 1666-1671. DOI: 10.2337/diacare.23.11.1666.
289 Ratner RE, Hirsch IB, Neifing JL, et al. Less hypoglycemia with insulin glargine in intensive insulin therapy for type 1 diabetes. U.S. Study Group of Insulin Glargine in Type 1 Diabetes. Diabetes Care. 2000; 23(5): 639-643. DOI: 10.2337/diacare.23.5.639.
290 Hershon KS et al. Once-daily insulin glargine compared with twice-daily NPH insulin in patients with type 1 diabetes. Endocr Pract. 2004; 10(1): 10-17. DOI: 10.4158/EP.10.1.10.
291 Fulcher GR, Gilbert RE, Yue DK. Glargine is superior to neutral protamine Hagedorn for improving glycated haemoglobin and fasting blood glucose levels during intensive insulin therapy. Intern Med J. 2005; 35(9):536-542. DOI: 10.1111/j.1445-5994.2005.00902.x.
292 Schober E, Schoenle E, Van Dyk J, et al. Comparative trial between insulin glargine and NPH insulin in children and adolescents with type 1 diabetes mellitus. J Pediatr Endocrinol Metab. 2002; 15(4):369-376. DOI: 10.2337/diacare.24.11.2005.
293 Riddle MC, Rosenstock J, Gerich J, et al. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care. 2003; 26(11): 3080-3086. DOI: 10.2337/diacare.26.11.3080.
294 Rosenstock J, Schwartz SL, Clark CM Jr, et al. Basal insulin therapy in type 2 diabetes: 28-week comparison of insulin glargine (HOE 901) and NPH insulin. Diabetes Care. 2001; 24(4): 631-636. DOI: 10.2337/diacare.24.4.631.
295 Fritsche A, Schweitzer MA, Haring HU. Glimepiride combined with morning insulin glargine, bedtime neutral protamine Hagedorn insulin, or bedtime insulin glargine in patients with type 2 diabetes. A randomized, controlled trial. Ann Intern Med. 2003; 138(12): 952-959. DOI: 10.2337/dc21-1606.
296 Massi Benedetti M, Humburg E, Dressler A, et al. A one-year, randomised, multicentre trial comparing insulin glargine with NPH insulin in combination with oral agents in patients with type 2 diabetes. Horm Metab Res. 2003; 35(3): 189-196. DOI: 10.1055/s-2003-39080.
297 Eliaschewitz FG, Calvo C, Valbuena H, et al. Therapy in type 2 diabetes: insulin glargine versus NPH insulin both in combination with glimepiride. Arch Med Res. 2006; 37(4): 495-501. DOI: 10.1016/j.arcmed.2005.10.015.
298 Janka HU, Plewe G, Riddle MC, et al. Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial insulin therapy for type 2 diabetes. Diabetes Care. 2005; 28(2): 254-259. DOI: 10.2337/diacare.28.2.254.
299 Heller S, Koenen C, Bode B. Comparison of insulin detemir and insulin glargine in a basal-bolus regimen, with insulin aspart as the mealtime insulin, in patients with type 1 diabetes: a 52-week, multinational, randomized, open-label, parallel-group, treat-to-target noninferiority trial. Clin Ther. 2009. 31(10): 2086-97. DOI: 10.1016/j.clinthera.2009.10.006.
300 Swinnen S, Dain M, Aronson R, et al. A 24-week, randomized, treat-to-target trial comparing initiation of insulin glargine once-daily with insulin detemir twice-daily in patients with type 2 diabetes inadequately controlled on oral glucose-lowering drugs. Diabetes Care. 2010; 33(6): 1176-1178. DOI: 10.2337/dc09-2294.
301 Pieber TR, Treichel HC, Hompesch B, et al. Comparison of insulin detemir and insulin glargine in subjects with type 1 diabetes using intensive insulin therapy. Diabet Med. 2007; 24(6): 635-642. DOI: 10.1111/j.1464-5491.2007.02113.x.
302 Raskin P, Allen E, Hollander P, et al. Initiating insulin therapy in type 2 diabetes: A comparison of biphasic and basal insulin analogs. Diabetes Care. 2005; 28(2): 260-265. DOI: 10.2337/diacare.28.2.260.
303 Kann PH, Wascher T, Zackova V, et al. Starting insulin therapy in type 2 diabetes: twice-daily biphasic insulin aspart 30 plus metformin versus once-daily insulin glargine plus glimepiride. Exp Clin Endocrinol Diabetes. 2006; 114(9): 527-532. DOI: 10.1055/s-2006-949655.
304 Strojek K, Bebakar WM, Khutsoane DT, et al. Once-daily initiation with biphasic insulin aspart 30 versus insulin glargine in patients with type 2 diabetes inadequately controlled with oral drugs: an open-label, multinational, RCT. Curr Med Res Opin. 2009; 25(12): 2887-94. DOI: 10.1185/03007990903354674.
305 Bretzel RG, Nuber U, Landgraf W, et al. Once-daily basal insulin glargine versus thrice-daily prandial insulin lispro in people with type 2 diabetes on oral hypoglycaemic agents (APOLLO): an open randomized controlled trial. Lancet. 2008; 371(9618): 1073-84. DOI: 10.1016/S0140-6736(08)60485-7.

306 Rosenstock J, Ahmann AJ, Colon G, et al. Advancing insulin therapy in type 2 diabetes previously treated with glargine plus oral agents: prandial premixed (insulin lispro protamine suspension/lispro) versus basal/bolus (glargine/lispro) therapy. Diabetes Care. 2008; 31(1): 20-25. DOI: 10.2337/dc07-1122.
307 FDA approval letter. Semglee. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/210605Orig1s000ltr.pdf. Accessed February 3, 2023.
308 Semglee [package insert]. Morgantown, WV; Mylan Specialties; October 2022.
309 Non-inferiority study to compare the efficacy and safety of Mylan's insulin glargine with Lantus® in type 1 diabetes mellitus patients (INSTRIDE 1). Available at: https://clinicaltrials.gov/ct2/show/record/NCT02227862. Accessed February 3, 2023.
310 Non-inferiority study to compare the efficacy and safety of Mylan's insulin glargine with Lantus® in type 2 diabetes mellitus patients (INSTRIDE 2) (INSTRIDE 2). Available at: https://clinicaltrials.gov/ct2/show/NCT02227875?term=Mylan%27s+Insulin+Glargine&draw=2&rank=1. Accessed February 3, 2023.
311 Sun B, Sengupta N, Rao A, et a. Similar immunogenicity profiles between the proposed biosimilar MYL-1501D and reference insulin glargine in patients with diabetes mellitus: the phase 3 INSTRIDE 1 and INSTRIDE 2 studies. BMC Endocr Disord. 2021;21(1):129. DOI: 10.1186/s12902-021-00797-4.
312 Rosenstock J, Cheng A, Ritzel R, et al. More similarities than differences testing insulin glargine 300 Units/mL versus insulin degludec 100 Units/mL in insulin-naive type 2 diabetes: The randomized head-to-head BRIGHT trial. Diabetes Care. 2018; 41: 2147–2154. DOI: 10.2337/dc18-0559.
313 Battelino T, Danne T, Edelman SV, et al. Continuous glucose monitoring-based time-in-range using insulin glargine 300 units/mL versus insulin degludec 100 units/mL in type 1 diabetes: the head-to-head randomized controlled InRange trial. Diabetes Obes Metab. 2023. 25(2):545-555. DOI: 10.1111/dom.14898.
314 Garg SK, Rosenstock J, Ways K. Optimized Basal-bolus insulin regimens in type 1 diabetes: insulin glulisine versus regular human insulin in combination with Basal insulin glargine. Endocr Pract. 2005; 11(1): 11-17. DOI: 10.4158/EP.11.1.11.
315 Rayman G, Profozic V, Middle M. Insulin glulisine imparts effective glycaemic control in patients with type 2 diabetes. Diabetes Res Clin Pract. 2007; 76(2): 304-312. DOI: 10.1016/j.diabres.2006.09.006.
316 Dreyer M, Prager R, Robinson A, et al. Efficacy and safety of insulin glulisine in patients with type 1 diabetes. Horm Metab Res. 2005; 37(11): 702-707. DOI: 10.1055/s-2005-870584.
317 Apidra [package insert]. Bridgewater, NJ; Sanofi-Aventis; November 2022.
318 FDA approval letter. Admelog. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2017/209196Orig1s000ltr.pdf. Accessed February 3, 2023.
319 Admelog [package insert]. Bridgewater, NJ; Sanofi-Aventis; December 2020
320 Ross SA, Zinman B, Campos RV, et al. A comparative study of insulin lispro and human regular insulin in patients with type 2 diabetes mellitus and secondary failure of oral hypoglycemic agents. Clin Invest Med. 2001; 24(6): 292-8.
321 Lyumjev [package insert]. Indianapolis, IN; Eli Lilly; October 2022.
322 Wadwa RP, Laffel LM, Franco DR, et al. Efficacy and safety of ultra-rapid lispro versus lispro in children and adolescents with type 1 diabetes: the PRONTO-Peds trial. Diabetes Obes Metab. 2023. 25(1):89-97. DOI: 10.1111/dom.14849.
323 Toujeo [package insert]. Bridgewater, NJ; Sanofi-Aventis. December 2020.
324 Home PD, Bergenstal RM, Bolli GB, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 1 diabetes: a randomized, phase 3a, open-label clinical trial (EDITION 4). Diabetes Care. 2015; 38(12): 2217-25. DOI: 10.2337/dc15-0249.
325 Toujeo [package insert]. Bridgewater, NJ; Sanofi-Aventis. December 2020.
326 Riddle MC, Yki-Järvinen H, Bolli GB, et al. One-year sustained glycaemic control and less hypoglycaemia with new insulin glargine 300 U/ml compared with 100 U/ml in people with type 2 diabetes using basal plus meal-time insulin: the EDITION 1 12-month randomized trial, including 6-month extension. Diabetes Obes Metab. 2015; 17(9): 835-42. DOI: 10.1111/dom.
327 Toujeo [package insert]. Bridgewater, NJ; Sanofi-Aventis. December 2020.
328 Yki-Jarvinen H, Bergenstal RM, Bolli GB, et al. Glycaemic control and hypoglycaemia with new insulin glargine 300 U/ml versus insulin glargine 100 U/ml in people with type 2 diabetes using basal insulin and oral antihyperglycaemic drugs: the EDITION 2 randomized 12-month trial including 6-month extension. Diabetes Obes Metab. 2015; 17(12): 1142-9. DOI: 10.1111/dom.
329 Bollli GB, Riddle MC, Bergenstal RM, et al. New insulin glargine 300 U/ml compared with glargine 100 U/ml in insulin-naïve people with type 2 diabetes on oral glucose-lowering drugs: a randomized controlled trial (EDITION 3). Diabetes Obes Metab. 2015; 17(4): 386–394. DOI: 10.1111/dom.12438.
330 Ritzel R, Harris SB, Baron H, et al. A randomized controlled trial comparing efficacy and safety of insulin glargine 300 Units/mL versus 100 Units/mL in older people with type 2 diabetes: results from the SENIOR study. Diabetes Care. 2018; 41(8): 1672-1680. DOI: 10.2337/dc18-0168.
331 Toujeo [package insert]. Bridgewater, NJ; Sanofi-Aventis; November 2019.
332 Afrezza [package insert]. Danbury, CT; Mannkind Corporation; February 2023.
333 Afrezza [package insert]. Danbury, CT; Mannkind Corporation; February 2023.
334 Afrezza [package insert]. Danbury, CT; Mannkind Corporation; February 2023.
335 Afrezza [package insert]. Danbury, CT; Mannkind Corporation; February 2023.
336 Qayyum R, Bolen S, Maruthur N, et al. Systematic review: comparative effectiveness and safety of premixed insulin analogues in type 2 diabetes. Ann Intern Med. 2008; 149. DOI: 10.7326/0003-4819-149-8-200810210-00242.
337 Owens DR, Traylor L, Mullins P, Landgraf W. Patient-level meta-analysis of efficacy and hypoglycaemia in people with type 2 diabetes initiating insulin glargine 100 U/mL or neutral protamine Hagedorn insulin analysed according to concomitant oral antidiabetes therapy. Diabetes Res Clin Pract. 2017; 124: 57-65. DOI: 10.1016/j.diabres.2016.10.022.
338 Sun D, Zhang X, Hou XX. Effects of insulin treatment with glargine or premixed insulin lispro programs in type 2 diabetes mellitus patients: A meta-analysis of randomized clinical trials. Diabetes Technol Ther. 2018; 20(9): 622-627. DOI: 10.1089/dia.2018.0132.
339 Zhang XW, Zhang XL, Xu B, Kang LN. Comparative safety and efficacy of insulin degludec with insulin glargine in type 2 and type 1 diabetes: a meta-analysis of randomized controlled trials. Acta Diabetol. 2018; 55(5): 429-441. DOI: 10.1007/s00592-018-1107-1.
340 Laranjeira FO, de Andrade KRC, Figueiredo ACMG, et al. Long-acting insulin analogues for type 1 diabetes: An overview of systematic reviews and meta-analysis of randomized controlled trials. PLoS ONE.13(4): e0194801. DOI: 10.1371/journal.pone.0194801.