

Therapeutic Class Overview

Insulin and Combination Agents

INTRODUCTION

- Diabetes mellitus is defined as a group of metabolic disorders characterized by hyperglycemia that result from defects in the secretion and action of insulin (*American Diabetes Association [ADA] 2021[a]*).
- The classification of diabetes includes four clinical classes: 1) Type 1 diabetes (T1DM) which results from beta-cell (β -cell) destruction, usually leading to absolute insulin deficiency; 2) Type 2 diabetes (T2DM) which results from a progressive insulin secretory defect on the background of insulin resistance; 3) Other specific types of diabetes due to other causes, e.g., genetic defects in β -cell function, genetic defects in insulin action, diseases of the exocrine pancreas (such as cystic fibrosis), and drug- or chemical-induced (such as in the treatment of HIV/AIDS or after organ transplantation; and 4) Gestational diabetes mellitus (diabetes diagnosed during pregnancy that is not clearly overt diabetes) (*ADA 2021[b]*).
- In 2018, an estimated 34.2 million people, or 10.5%, of the United States (US) population had diabetes mellitus, with 7.3 million estimated to be undiagnosed (*Centers for Disease Control and Prevention [CDC] 2020*).
- The insulin products are approved for use in the management of both T1DM and T2DM. Other pharmacologic options for T2DM include sulfonylureas, biguanides, thiazolidinediones, meglitinides, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) agonists, amylinomimetics, sodium-glucose cotransporter 2 (SGLT2) inhibitors, and combination products.
- Insulin is used as replacement therapy in patients with diabetes, replacing deficient endogenous insulin and temporarily restoring the ability of the body to properly utilize carbohydrates, fats, and proteins. Insulin is secreted by the β -cells in the pancreas and lowers blood glucose by facilitating peripheral glucose uptake into cells and by inhibiting gluconeogenesis in the liver. In addition to its glycemic effects, insulin has anabolic properties, enhancing protein synthesis, inhibiting lipolysis in adipocytes, and stimulating lipogenesis (*Powers 2018*).
- The first insulin products were derived from animal sources, primarily pork and beef; however, they are no longer available in the US. These older products have been replaced with human insulin and insulin analogs. Human insulin is biosynthesized utilizing recombinant deoxyribonucleic acid (DNA) with strains of *Escherichia coli* or *Saccharomyces cerevisiae* (baker's yeast) and is structurally identical to endogenous insulin. Insulin analogs are also derived from recombinant DNA technology. They are structurally different from human insulin but have comparable glucose-lowering effects. The insulin analogs differ in the addition, deletion, or substitution of amino acids on the B chain (*Powers 2018*). Insulin analogs available today include insulin aspart, insulin degludec, insulin detemir, insulin glargine, insulin glulisine, and insulin lispro. The primary differences between commercially available insulin products revolve around pharmacodynamic and pharmacokinetic properties, particularly onset and duration of action. Individual insulin products are often classified into categories based on their onset and duration of action.
 - Bolus insulin products, also known as rapid- or short-acting insulin, include insulin aspart, insulin glulisine, insulin lispro, and certain human insulins. Unique formulations within this category include a rapid-acting, human insulin inhalation powder, and a higher strength of rapid-acting insulin lispro that provides 200 units (U) per milliliter (U-200). In September 2017, Fiasp (insulin aspart) was approved (*Drugs@FDA 2021*). Fiasp is a new formulation of Novolog that contains niacinamide. Niacinamide helps to increase the speed of initial insulin absorption, resulting in an onset of appearance in the blood in an estimated 2.5 minutes. Additionally, in December 2017, Admelog (insulin lispro) was the first short-acting insulin approved as a "follow-on" product through the Food and Drug Administration's (FDA) abbreviated 505(b)(2) pathway (*FDA news release 2017*). A novel formulation of insulin lispro, Lyumjev (insulin lispro-aabc) was also approved in June 2020 (*Drugs@FDA 2021*). Lyumjev is a new formulation of Humalog with a quicker onset; appearance in the blood occurs approximately 1 minute after injection of Lyumjev (*Eli Lilly press release 2020, Lyumjev prescribing information 2020*).
 - Basal insulin products, also known as intermediate- or long-acting insulin, include neutral protamine Hagedorn (NPH) isophane, insulin degludec, insulin detemir, and insulin glargine. Unique products within this category include a formulation of insulin glargine that provides 300 U of insulin glargine per mL and enables patients to utilize a higher dose in one injection (U-300). Additionally, Basaglar and Semglee (insulin glargine) were FDA approved via new drug applications (NDAs) under the 505(b)(2) pathway. As of March 2020, the NDA for Semglee was automatically

deemed to be a biologic licensing application (BLA) via section 351(a) via the Biologics Price Competition and Innovation Act (*Fierce Biotech FDA press release 2015, Drugs@FDA 2021, Hagen 2020*).

- Insulin therapy is usually administered by subcutaneous (SC) injection, which allows for prolonged absorption and less pain compared to intramuscular (IM) injection. Humalog, Humalog Kwikpen, Novolog, Novolog PenFil, Novolog FlexPen, Novolog Mix 70/30, and Novolog Mix FlexPen 70/30 have authorized generics, while the rest of the insulin products do not have a generic (*Lilly 2019[a], Lilly 2019[b], Novo Nordisk 2019*). Of note, insulin products are available by prescription, as well as over-the-counter (OTC) (short- and intermediate-acting products only).
- This review will focus on the insulin preparations and combination insulin/GLP-1 agonist products outlined in Table 1 for their respective FDA-approved indications.
- Medispan Class: Antidiabetics, Insulin

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Rapid-Acting Insulins	
Admelog, Admelog SoloStar (insulin lispro)	-
Afrezza (insulin human) inhalation powder	-
Apidra, Apidra SoloStar (insulin glulisine)	-
Fiasp, Fiasp FlexTouch, Fiasp PenFill (insulin aspart)	-
Humalog, Humalog KwikPen, Humalog Junior KwikPen, Humalog Tempo Pen (insulin lispro)	✓ *
Lyumjev (insulin lispro-aabc)	-
Novolog, Novolog PenFill, Novolog FlexPen (insulin aspart)	✓ †
Short-Acting Insulins	
Humulin R (insulin, regular, human recombinant)	-
Humulin R U-500, Humulin R U-500 KwikPen (insulin, regular, human recombinant)	-
Novolin R, Novolin R FlexPen, Novolin R ReliOn (insulin, regular, human recombinant)	-
Intermediate-Acting Insulins	
Humulin N, Humulin N Kwikpen (insulin, NPH human recombinant isophane)	-
Novolin N, Novolin N FlexPen, Novolin N ReliOn (insulin, NPH human recombinant isophane)	-
Long-Acting Insulins	
Basaglar (insulin glargine)	-
Lantus, Lantus SoloStar (insulin glargine)	-
Levemir, Levemir FlexTouch (insulin detemir)	-
Semglee (insulin glargine)	-
Toujeo SoloStar, Toujeo Max SoloStar (insulin glargine U-300)	-
Tresiba, Tresiba FlexTouch (insulin degludec)	-
Combination Insulins, Rapid-Acting and Intermediate-Acting	
Humalog Mix 50/50, Humalog Mix 50/50 KwikPen (50% insulin lispro protamine/50% insulin lispro)	-
Humalog Mix 75/25, Humalog Mix 75/25 KwikPen (75% insulin lispro protamine/25% insulin lispro)	-
Novolog Mix 70/30, Novolog Mix 70/30 FlexPen, Novolog 70/30 PenFill (70% insulin aspart protamine/30% insulin aspart)	✓ †
Combination Insulins, Short-Acting and Intermediate-Acting	
Humulin 70/30, Humulin 70/30 KwikPen (70% NPH, human insulin isophane/30% regular human insulin)	-

Drug	Generic Availability
Novolin 70/30, Novolin 70/30 ReliOn, Novolin 70/30 FlexPen (70% NPH, human insulin isophane/30% regular human insulin)	-
Combination, Long-Acting Insulin and GLP-1 Receptor Agonist	
Soliqua 100/33 (insulin glargine/lixisenatide)	-
Xultophy 100/3.6 (insulin degludec/liraglutide)	-

*Eli Lilly launched an authorized generic of Humalog (vial and KwikPen) through its subsidiary, ImClone Systems (*Lilly 2019[a], Lilly 2019[b]*).

†Novo Nordisk launched an authorized generic of Novolog (vial, Penfil, and FlexPen) and Novolog Mix (vial and FlexPen) through its affiliate, Novo Nordisk Pharma Inc (*Novo Nordisk 2019*).

(*Drugs@FDA 2021, Purple Book: Database of Licensed Biological Products 2021*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications – Insulins

Product	Control of hyperglycemia in patients with diabetes mellitus	Improve glycemic control in adults with diabetes mellitus	Improve glycemic control in adults and children with diabetes mellitus
Rapid-Acting Insulins			
Admelog (insulin lispro)			✓ **
Afrezza (insulin human)		✓ §	
Apidra (insulin glulisine)			✓ #
Fiasp (insulin aspart)			✓
Humalog (insulin lispro)			✓
Lyumjev (insulin lispro-aabc)		✓ #	
Novolog (insulin aspart)			✓
Short-Acting Insulins			
Humulin R (insulin, regular, human recombinant)			✓ ¥
Novolin R (insulin, regular, human recombinant)			✓
Intermediate-Acting Insulins			
Humulin N (insulin, NPH human recombinant isophane)			✓
Novolin N (insulin, NPH human recombinant isophane)			✓
Long-Acting Insulins			
Basaglar (insulin glargine)			✓ ‡
Lantus (insulin glargine)			✓ ‡
Levemir (insulin detemir)			✓ †
Semglee (insulin glargine)			✓ ††¶
Toujeo (insulin glargine U-300)			✓ †¶
Tresiba (insulin degludec)			✓
Combination Insulins, Rapid-Acting and Intermediate-Acting			
Humalog Mix 50/50 Humalog Mix 75/25 (insulin lispro protamine/insulin lispro)	✓		
Novolog Mix 70/30 (insulin aspart protamine/insulin aspart)		✓	
Combination Insulins, Short-Acting and Intermediate-Acting			

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Product	Control of hyperglycemia in patients with diabetes mellitus	Improve glycemic control in adults with diabetes mellitus	Improve glycemic control in adults and children with diabetes mellitus
Humulin 70/30 (NPH, human insulin isophane/regular human insulin)		✓	
Novolin 70/30 (NPH, human insulin isophane/regular human insulin)			✓

*Indicated for patients ≥ 3 years of age for T1DM and adults with T2DM.

† Limitations of use: Not recommended for treating diabetic ketoacidosis. Use intravenous, rapid-acting or short-acting insulin instead.

‡ Not indicated for children with T2DM.

§ Limitations of use: Must use with a long-acting insulin in patients with T1DM. Not recommended for treating diabetic ketoacidosis. Not recommended in patients who smoke.

|| Indicated for patients 1 year of age and older with diabetes mellitus; the U-100 vial is recommended for pediatric patients requiring < 5 units daily.

¶ Indicated for patients 6 years and older with diabetes mellitus.

#Should generally be used in regimens with an intermediate or long-acting insulin.

¥ Humulin R U-500 is useful for the treatment of insulin-resistant patients with diabetes requiring daily doses of more than 200 units.

(Prescribing information: [Admelog 2020](#), [Afrezza 2018](#), [Apidra 2020](#), [Basaglar 2019](#), [Fiasp 2019](#), [Humalog 2019](#), [Humalog Mix 50/50 2019](#), [Humalog Mix 75/25 2019](#), [Humulin 70/30 2019](#), [Humulin N 2019](#), [Humulin R U-100 2019](#), [Humulin R U-500 2019](#), [Lantus 2019](#), [Levemir 2020](#), [Lyumjev 2020](#), [Novolin 70/30 2019](#), [Novolin N 2019](#), [Novolin R 2019](#), [Novolog 2019](#), [Novolog Mix 70/30 2019](#), [Semglee 2020](#), [Toujeo 2020](#), [Tresiba 2019](#))

Table 3. Food and Drug Administration Approved Indications – Insulins and GLP-1 Receptor Agonists

Indication	Soliqua (insulin glargine/ lixisenatide)	Xultophy (insulin degludec/ liraglutide)
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM	✓	✓
Limitations of Use		
Not recommended as first-line therapy for patients inadequately controlled on diet and exercise.	--	✓
Has not been studied in patients with a history of unexplained pancreatitis. Other antidiabetic therapies should be considered in patients with a history of pancreatitis.	✓	--
Not recommended for use in combination with any other product containing another GLP-1 receptor agonist.	✓	✓
Not for treatment of T1DM or diabetic ketoacidosis.	✓	✓
Not recommended for use in patients with gastroparesis.	✓	--
Has not been studied in combination with prandial insulin.	✓	✓

(Prescribing information: [Soliqua 2020](#), [Xultophy 2019](#))

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Rapid- and Short-Acting Insulins

- Clinical trials conducted with the newer insulin analogs have shown that they are at least as effective as the older insulin formulations. A number of comparative effectiveness reviews revealed that both insulin aspart and insulin lispro produced comparable lowering of glycosylated hemoglobin (HbA1c) in patients with T2DM compared to regular insulin (*Fullerton et al 2018, Plank et al 2005*). In patients with T1DM, insulin lispro and insulin aspart produced small, but significant differences in lowering HbA1c compared to regular insulin. Clinical trials comparing insulin glulisine to regular insulin demonstrated similar results, with at least comparable decreases in HbA1c and a few trials reporting a significantly greater decrease in HbA1c when compared to regular insulin in patients with T1DM and T2DM (*Dailey et al 2004, Garg et al 2005, Melo et al 2019, Nørgaard et al 2018, Rayman et al 2007, Seufert et al 2021*).
- The rapid-acting analogs have demonstrated a more favorable post-prandial glycemic profile compared to regular insulin in patients with T1DM or T2DM (*Anderson et al 1997a, Chen et al 2006, Dailey et al 2004, Melo et al 2019, Nørgaard et al 2018, Raskin et al 2000, Vignati et al 1997*). Most trials reported comparable rates of hypoglycemia between rapid-acting insulin analogs and regular insulin (*Anderson et al 1997b, Bretzel et al 2004, Chen et al 2006, Colquitt et al 2003, Dailey et al 2004, Fairchild et al 2000, Fullerton et al 2016, Fullerton et al 2018, Garg et al 2005, Home et al 2006, McSorley et al 2002, Mortensen et al 2006, Plank et al 2005, Raskin et al 2000, Vignati et al 1997*). One large trial of patients with T1DM reported a 12% lower incidence of hypoglycemia with insulin lispro compared to regular insulin ($p < 0.001$) (*Anderson et al 1997a*). In another trial, a significantly lower frequency of nocturnal hypoglycemia was reported in patients with T2DM patients with insulin glulisine compared to regular insulin (9.1% vs 14.5%; $p = 0.029$) (*Rayman et al 2007*). A meta-analysis (MA) comparing rapid-acting agents with regular insulin in patients with T1DM found that rapid-acting agents are associated with less total hypoglycemic episodes (risk ratio [RR], 0.93; 95% confidence interval [CI], 0.87 to 0.99), nocturnal hypoglycemia (RR, 0.55; 95% CI, 0.40 to 0.76), and severe hypoglycemia (RR, 0.68; 95% CI, 0.60 to 0.77), and lower post-prandial glucose (PPG) (mean difference [MD], -19.44 mg/dL; 95% CI, -21.49 to -17.39) and HbA1c (MD, -0.13%; 95% CI, -0.16 to -0.10) (*Melo et al 2019*). In contrast, in a Cochrane review comparing rapid-acting insulins with regular insulin in adult, non-pregnant patients with T2DM, no clear significant differences were found between the groups for all-cause mortality or hypoglycemia events (*Fullerton et al 2018*).
- Afrezza was evaluated in both T1DM and T2DM patients; in a 24-week open-label (OL), active-controlled (AC), non-inferiority trial, patients with T1DM on basal insulin were randomized to receive prandial Afrezza or insulin aspart. Afrezza met the prespecified non-inferiority margin of 0.4% reduction of HbA1c from baseline, but reductions were significantly less with Afrezza compared to insulin aspart and fewer Afrezza patients achieved a HbA1c target of $< 7\%$ (*Bode et al 2015*). T2DM patients inadequately controlled on oral antidiabetic agents (OADs) were randomized to receive Afrezza or placebo in a double-blind (DB) trial. At week 24, treatment with Afrezza provided a statistically significantly greater mean reduction in HbA1c than placebo (*Rosenstock et al 2015[a]*). Afrezza was also compared to insulin lispro in a 16-week randomized-controlled trial (RCT) including 138 patients with T1DM. Afrezza met the prespecified non-inferiority margin of 0.4% reduction of HbA1c from baseline. PPG 90 minutes after a meal was significantly lower with Afrezza vs insulin lispro but the between-group difference diminished thereafter (*McGill et al 2021*). A 24-week RCT that included adults with T2DM receiving basal insulin compared prandial Afrezza to insulin aspart. Both Afrezza and insulin aspart groups experienced reductions in mean HbA1c to 7.9% and 7.7%, respectively, from a baseline mean of 8.9% to 9% across groups; the predefined equivalency margin of 0.4% for the mean treatment difference was not met (*Hoogwerf et al 2021*).
- Fiasp was evaluated in the Onset clinical trial program. Onset 1 was a 26-week, Phase 3, AC, RCT that compared Fiasp (mealtime and post meal) to Novolog in patients with T1DM. Both mealtime and post meal Fiasp were demonstrated to be non-inferior to Novolog in change in HbA1c (Estimated treatment difference [ETD], -0.15; $p < 0.0001$; ETD, 0.04%; $p < 0.0001$, respectively) (*Russell-Jones et al 2017*). Onset 2 was a 26-week, Phase 3, DB, AC, RCT in T2DM patients on insulin and OADs. Patients were randomized to receive mealtime Fiasp ($n = 345$) or Novolog ($n = 344$). Fiasp demonstrated non-inferiority to Novolog in HbA1c lowering (ETD, -0.02%; $p < 0.0001$) (*Bowering et al 2017*). Onset 3 was an 18-week, Phase 3, OL, RCT in T2DM patients inadequately controlled on basal insulin and OADs. Patients were randomized to receive mealtime Fiasp + basal insulin ($n = 116$), or basal insulin alone ($n = 120$). The addition of Fiasp to basal insulin demonstrated superior HbA1c lowering from baseline (ETD, -0.94%; $p < 0.0001$ for superiority) and significantly more patients achieved an HbA1c $< 7.0\%$ (60.3% vs 18.3%; OR, 9.31; $p < 0.0001$); however, with the addition of Fiasp, there was an increase in the frequency of severe or blood glucose-confirmed hypoglycemic episodes (RR, 8.24; $p < 0.0001$) and modest weight gain (*Rodbard et al 2017[b]*). Onset 9 was a 16-week RCT in adults with T2DM inadequately controlled on a basal-bolus insulin regimen. Patients were randomized to receive mealtime Fiasp + insulin degludec with or without metformin ($n = 546$) or Novolog + insulin degludec with or without metformin ($n = 545$).

Change in HbA1c in Fiasp-treated patients was found to be non-inferior to Novolog-treated patients (ETD, -0.04%; 95% CI, -0.11 to 0.03). Fiasp demonstrated superior reduction in 1-hour PPG increment vs Novolog ($p = 0.001$), but differences at 2, 3, and 4 hours were not significant between groups. Treatment-emergent severe hypoglycemia or blood glucose confirmed hypoglycemia was significantly lower with Fiasp vs Novolog (estimated treatment ratio, 0.81; 95% CI, 0.68 to 0.97) (*Lane et al 2020*).

- In 2020, Fiasp's indication was expanded to include children with diabetes based on results from the Onset 7 Trial (*Bode et al 2019*). This trial demonstrated non-inferiority of Fiasp to Novolog in 519 patients 1 to 17 years of age with T1DM. The estimated change from baseline to week 26 in HbA1c at meal time was -0.17% (95% CI, -0.30 to -0.03) and post meal it was 0.13% (95% CI, -0.01 to 0.26); the change from baseline in HbA1c at meal time was statistically significant between groups in favor of Fiasp.
- The safety and efficacy of Admelog, the first "follow-on" rapid-acting insulin, were evaluated in two 26-week, Phase 3, OL, parallel group, RCTs in both T1DM (N = 506) (SORELLA 1; *Garg et al 2017*) and T2DM (N = 505) patients (SORELLA 2; *Derwahl et al 2018*). Patients were randomized to receive Admelog or its reference product, Humalog. Change in HbA1c in Admelog-treated patients was found to be non-inferior in both trials (SORELLA 1: least squares mean difference [LSMD], 0.06%; 95% CI, -0.084 to 0.197; SORELLA 2: LSMD, -0.07%; 95% CI, -0.215 to 0.067). Rates of hypoglycemia were similar between the treatment arms in both trials.
- The safety and efficacy of Lyumjev were evaluated in two 26-week, Phase 3, DB/OL, PG, RCTs in both T1DM (N = 1222) (PRONTO-T1D) and T2DM (N = 673) patients (PRONTO-T2D). Patients were randomized to receive Lyumjev or Humalog. The change in HbA1c for Lyumjev-treated patients was found to be noninferior in both trials (PRONTO-T1D: mealtime Lyumjev: ETD, -0.08%; 95% CI, -0.16 to 0.00; $p = 0.06$ for noninferiority; post meal Lyumjev: ETD, +0.13%; 95% CI, 0.04 to 0.22; $p = 0.003$ for noninferiority; PRONTO-T2D: mealtime Lyumjev: ETD, 0.06%; 95% CI, -0.05 to 0.16; noninferiority). Lyumjev significantly lowered PPG 1- and 2-hours post dose compared to Humalog. Rates of hypoglycemia were similar between the treatment arms in both trials (*Blevins et al 2020, Klaff et al 2020*).
- Head-to-head trials of rapid-acting analogs suggest comparable effectiveness in terms of decreasing HbA1c, achieving similar self-monitored glucose profiles, rates of hypoglycemia, and achieving glycemic goals in patients with T1DM (*Dreyer et al 2005, Philotheou et al 2011, Van Ban et al 2011*).

Long-Acting Insulins

- While not consistently demonstrated, data suggest that long-acting insulin analogs are superior to isophane (NPH) insulin in decreasing HbA1c, as well as the incidence of hypoglycemia in adults, adolescents, and children with T1DM and T2DM as demonstrated by the results of several active-comparator trials and MAs (*Bartley et al 2008, Bazzano et al 2008, Buse et al 2009, Chase et al 2008, Danne et al 2013, De Leeuw et al 2005, Fritsche et al 2003, Garber et al 2007, Haak et al 2005, Heller et al 2009, Hermansen et al 2004, Hermansen et al 2006, Herwig et al 2007, Home et al 2004, Kølendorf et al 2006, Lee et al 2012, Montañana et al 2008, Pan et al 2007, Pieber et al 2005, Philis-Tsimikas et al 2006, Raslová et al 2007, Ratner et al 2000, Riddle et al 2003, Robertson et al 2007, Rosenstock et al 2005, Russell-Jones et al 2004, Schober et al 2002, Semlitsch et al 2020, Siegmund et al 2007, Standl et al 2004, Tan et al 2004, Tricco et al 2014, Vague et al 2003, Yenigun et al 2009, Yki-Järvinen et al 2000, Yki-Järvinen et al 2006*).
- The safety and efficacy of the long-acting analog Toujeo (insulin glargine U-300) have been compared to that of Lantus (insulin glargine U-100) in OL, randomized, AC, parallel studies of up to 26 weeks in patients with T1DM and T2DM. The reductions in HbA1c and fasting plasma glucose (FPG) with Toujeo were found to be similar to that of Lantus, including patients aged ≥ 65 years (*Home et al 2018, Bolli et al 2015, Home et al 2015, Riddle et al 2014[b], Ritzel et al 2018, Yki-Järvinen et al 2014*).
- A 2018 MA comparing Toujeo with Lantus in patients with T1DM and T2DM found that Toujeo was associated with a reduced risk of nocturnal hypoglycemia (RR, 0.81; 95% CI, 0.69 to 0.95) and a slight benefit in HbA1c reduction (effect size, -0.08; 95% CI, -0.14 to -0.01) (*Diez-Fernandez et al 2019*).
- Tresiba (insulin degludec) was evaluated in more than 5,600 T1DM and T2DM patients throughout 9 pivotal studies and 5 extension studies (BEGIN clinical program).
 - In 8 of the pivotal trials, Tresiba was non-inferior to Lantus (insulin glargine U-100) or Levemir (insulin detemir) in lowering HbA1c from baseline, with similar rates of hypoglycemia; in 5 trials, the rate of nocturnal hypoglycemia was significantly lower with Tresiba compared to Lantus or Levemir (*Davies et al 2014, Garber et al 2012, Gough et al 2013, Heller et al 2012, Mathieu et al 2013, Meneghini et al 2013[a], Onishi et al 2013, Zinman et al 2012*). It is noteworthy that 2 of the 8 Tresiba trials resulted in a nominally lower reduction in HbA1c for Tresiba compared to the active comparator basal insulin agents (*Davies et al 2014, Heller et al 2012*). The HbA1c and hypoglycemia trends

were also observed in the published extension trials (*Bode et al 2013, Davies et al 2016, Hollander et al 2015, Rodbard et al 2013*). In the ninth pivotal trial, Tresiba lowered HbA1c significantly more than oral sitagliptin 100 mg once daily in patients with T2DM who were receiving 1 or 2 concomitant background OAD agents (treatment difference, -0.43; 95% CI, -0.61 to -0.24; $p < 0.001$), but there were significantly more episodes of overall confirmed hypoglycemia ($p < 0.0001$) (*Phillis-Tsimikas et al 2013*).

- Across the BEGIN trials, a consistently increased risk of major adverse cardiovascular events (MACE) was observed with Tresiba. At the request of an FDA Advisory Committee, Novo Nordisk conducted a pre-specified MA of MACE, which included a pooled analysis of 8,068 patients from 16 Phase 3 trials conducted for Tresiba monotherapy and insulin degludec/insulin aspart (Ryzodeg). According to the 2012 analysis, there was a consistent trend towards harm in the pooled insulin degludec groups compared to active comparators (hazard ratio [HR], 1.67; 95% CI, 1.01 to 2.75). Additional post-hoc analyses consistently trended towards harm regardless of endpoint, effect measure, analysis method, and subgroup analyses (*FDA Briefing Document 2012, Novo Nordisk Briefing Document 2012*).
- The large, DB, active-comparator DEVOTE trial was subsequently initiated to prospectively and rigorously compare the cardiovascular (CV) safety of Tresiba to Lantus in patients with T2DM at high risk for CV events. The primary composite endpoint of death from CV causes, nonfatal myocardial infarction (MI), or nonfatal stroke occurred in 8.5% of the Tresiba group and 9.3% of the Lantus group (HR, 0.91; 95% CI, 0.78 to 1.06; $p < 0.001$ for non-inferiority), confirming non-inferiority of Tresiba to Lantus in terms of CV safety. Tresiba also demonstrated statistically significantly lower rates of severe hypoglycemia (odds ratio [OR] for severe hypoglycemic events, 0.73; 95% CI, 0.60 to 0.89; $p < 0.001$ for superiority) (*Marso et al 2017*).
- The efficacy of Tresiba vs Lantus in reducing the rate of symptomatic hypoglycemic episodes in patients with T1DM and T2DM was examined in the SWITCH 1 and SWITCH 2 trials, respectively. These 65-week, DB, crossover trials enrolled patients with hypoglycemia risk factors to receive Tresiba or Lantus. In both trials, Tresiba was found to cause fewer symptomatic hypoglycemic episodes (SWITCH 1: estimated rate ratio [ERR], 0.89; $p < 0.001$; SWITCH 2: ERR, 0.70; $p < 0.001$) and nocturnal hypoglycemic episodes (SWITCH 1: ERR, 0.64; $p < 0.001$; SWITCH 2: ERR, 0.58; $p < 0.001$) during the maintenance period than Lantus (*Lane et al 2017, Wysham et al 2017*).
- A MA of 18 trials with 16,791 patients compared the safety and efficacy of Tresiba to Lantus, and similarly found that Tresiba was associated with a significant reduction in risk for all confirmed hypoglycemia during the maintenance treatment period (ERR, 0.81; 95% CI, 0.72 to 0.92; $p=0.001$), nocturnal confirmed hypoglycemia during the entire (ERR, 0.71; 95% CI, 0.63 to 0.80; $p,0.001$) and maintenance treatment periods (ERR, 0.65; 95% CI, 0.59 to 0.71; $p,0.001$), and a significantly lower FPG level (ETD, -0.28 mmol/L; 95% CI, -0.44 to -0.11 mmol/L; $p=0.001$). Tresiba was found to reduce the incidence of severe hypoglycemia in patients with T2D, but not T1D (*Zhang et al 2018*).
- A MA of 15 trials with 16,694 patients that compared Tresiba to Lantus found that Tresiba was associated with improved mean reduction in FPG (weighted mean difference, -5.2 mg/dL; 95% CI, -7.34 to -3.07; $p < 0.00001$) and less nocturnal hypoglycemia (RR, 0.81; 95% CI, 0.75 to 0.88; $p < 0.0001$). However, fewer patients achieved HbA1c $\leq 7\%$ with Tresiba compared with Lantus (RR, 0.92; 95% CI, 0.86 to 0.98; $p = 0.01$). The MA showed no statistically significant differences between Tresiba and Lantus for HbA1c reduction, body weight gain, and serious adverse events (AEs) (*Zhou et al 2019*).
- Additionally, Tresiba was evaluated for safety and efficacy in pediatric patients (ages 1 to 17) (N = 350) with T1DM in a 26-week, randomized, OL trial. Tresiba was non-inferior to Lantus with a difference in HbA1c reduction from baseline of 0.15% (95% CI, -0.03 to 0.33%) between the groups (pre-specified non-inferiority margin, 0.4%) (*Tresiba prescribing information 2019*).
- The safety and efficacy of Basaglar (insulin glargine U-100) compared to Lantus (insulin glargine U-100) were evaluated in 2 pivotal studies enrolling 534 and 744 patients with T1DM (ELEMENT 1 trial) and T2DM (ELEMENT 2 trial), respectively. Both trials were multicenter (MC), parallel group, RCTs; ELEMENT 1 was OL and ELEMENT 2 was DB. Both trials were conducted over 24 weeks; however, ELEMENT 1 also included a 28-week comparative safety extension period. Mealtime insulin lispro was administered 3 times daily in both groups within the ELEMENT 1 trial. The use of an OAD medication was permitted in conjunction with insulin treatment within the ELEMENT 2 trial. The primary efficacy endpoint tested the non-inferiority of agents by the reduction in HbA1c from baseline to 24 weeks. In both ELEMENT 1 and ELEMENT 2, Basaglar and Lantus had similar and significant ($p < 0.001$) within-group decreases in HbA1c values from baseline. Basaglar met non-inferiority criteria compared to Lantus for change in HbA1c from baseline to 24 weeks in both trials (ELEMENT 1: -0.35% vs -0.46%, respectively; LSMD, 0.108%; 95% CI, -0.002 to 0.219; $p > 0.05$; ELEMENT 2: -1.29% vs -1.34%, respectively; LSMD, 0.052%; 95% CI, -0.07 to 0.175; $p > 0.05$). There were no statistically significant differences between treatment groups for the rate of each category of hypoglycemia (total,

nocturnal, severe) at 24 or 52 weeks in ELEMENT 1 and at 24 weeks in ELEMENT 2 ($p > 0.05$ for all treatment comparisons). No significant differences between treatment groups were seen for change from baseline in body weight (ELEMENT 1, week 24 and 52: both $p > 0.05$; ELEMENT 2, week 24: $p > 0.05$) (Blevins et al 2015, Rosenstock et al 2015[b]). Basaglar has also been compared to Lantus when used in combination with OADs in patients with T2DM. ELEMENT 5 was a 24-week trial and included predominately Asian (48%) and White (46%) patients. Basaglar met non-inferiority criteria compared to Lantus for change in HbA1c from baseline to 24 weeks (-1.25% vs -1.22%; LSMD, -0.04%; 95% CI, -0.22 to 0.15). Other 24-week efficacy and safety outcomes were similar between groups (Pollom et al 2019).

- The safety and efficacy of Semglee and reference insulin glargine were compared in 2 OL RCTs enrolling 558 (INSTRIDE 1; Blevins et al 2018) and 127 (INSTRIDE 3) patients with T1DM. In both trials, patients also received mealtime insulin lispro. INSTRIDE 1 demonstrated non-inferiority of Semglee to reference insulin glargine for LSMD in change in HbA1c from baseline to week 24 (0.03%; standard error [SE], 0.046; 95% CI, -0.066 to 0.117), as did INSTRIDE 3 from baseline to week 36 (LSMD, 0.01%; 95% CI, -0.08 to 0.101). The safety profile of products did not significantly differ in either trial. Semglee was also compared to reference insulin glargine in 560 patients with T2DM in an OL RCT (INSTRIDE 2). This trial included patients who were insulin-naïve and insulin-non-naïve receiving OADs. Semglee was non-inferior to the reference insulin glargine for LSMD in change in HbA1c from baseline to week 24 (0.06%; 95% CI, -0.10 to 0.22). The safety profile was also similar between products in this trial; (Blevins et al 2019, Blevins et al 2020[a]).
- At this time, there is a lack of substantial head-to-head data demonstrating the superiority of one long-acting insulin analog over another. When comparing the long-acting insulin analogs head-to-head, several trials have demonstrated non-inferiority among the products when used in the management of T1DM and as add-on therapy in patients with T2DM (Heller et al 2009, Hollander et al 2008, Pieber et al 2007, Raskin et al 2009, Rosenstock et al 2008, Swinnen et al 2010).
 - In one head-to-head trial of Lantus and metformin vs Levemir and metformin, Lantus had greater HbA1c lowering, but Levemir demonstrated less weight gain and hypoglycemia (Meneghini et al 2013[b]).
 - A 2011 Cochrane review (included 4 trials; N = 2250) concluded that Lantus and Levemir are equally effective in achieving and maintaining glycemic control (HbA1c). The review also found no differences in overall, nocturnal, and severe hypoglycemic events (Swinnen et al 2011). A 2018 MA similarly found no differences in HbA1c reduction between insulin degludec, detemir, or glargine in T1DM and T2DM patients, but the incidence of hypoglycemia was less with degludec as compared to glargine (nocturnal hypoglycemia; T1DM: RR, 0.68; 95% CI, 0.56 to 0.81; T2DM: RR, 0.73; 95% CI, 0.65 to 0.82) (Holmes et al 2019).
 - To further inform the differences between basal insulin agents, a network meta-analysis (NMA) (included 41 trials, of which 25 trials included patients on basal-oral therapy; N = 15,746) evaluated the safety and efficacy of Toujeo (insulin glargine U-300) vs other basal insulin therapies in the treatment of T2DM. The authors found that the change in HbA1c was comparable between Toujeo and Levemir (difference, -0.08; 95% credible interval [CrI], -0.4 to 0.24) and Tresiba (difference, -0.12; CrI, -0.42 to 0.2). Additionally, there were no differences in nocturnal or documented symptomatic hypoglycemic events (Freemantle et al 2016).
 - The safety of Tresiba was compared to Toujeo in the 2019 CONCLUDE trial that included 1609 patients with T2DM. In this trial, the rate of overall symptomatic hypoglycemia, the primary endpoint, was similar between Tresiba and Toujeo (RR, 0.88; 95% CI, 0.73 to 1.06). However, the rates of nocturnal symptomatic hypoglycemia and severe hypoglycemia (both of which were exploratory endpoints) were lower with Tresiba vs Toujeo (RR, 0.63; 95% CI, 0.48 to 0.84 and RR, 0.20; 95% CI, 0.07 to 0.57, respectively) (Philis-Tsimikas et al 2020).
- In 2019, Toujeo's indication was expanded to include children with diabetes mellitus as young as 6 years of age based on results of the EDITION JUNIOR trial. In this study, Toujeo demonstrated non-inferiority to Lantus for the primary endpoint of change in HbA1c from baseline to week 26 (mean reduction, 0.4% in both groups; 95% CI, -0.17 to 0.18) with comparable numbers of patients experiencing ≥ 1 episode of hypoglycemia (Danne et al 2019).

Combination Insulins

- A direct comparative trial evaluating 2 types of premixed biphasic insulin (insulin lispro 50/50 and insulin aspart 70/30) demonstrated similar results in terms of reducing HbA1c (Domeki et al 2014). Another trial comparing biphasic insulin to basal plus prandial insulin in T2DM demonstrated that basal plus prandial insulin therapy was slightly more effective than premixed insulin with less hypoglycemia (Riddle et al 2014[a]).

Other Evidence

- A systematic review (SR) that included 11 studies and compared the efficacy and safety of biosimilar insulins (Basaglar and Admelog) to their reference products found comparable pharmacokinetic and/or pharmacodynamic parameters, clinical efficacy and immunogenicity, and AEs between the biosimilar agents and their reference products (*Tieu et al 2018*). Similar conclusions were made in a 2020 SR (*Ampudia-Blasco 2020*).
- Insulin therapies have been compared to GLP-1 agonists with mixed study results. A study comparing glycemic control with Lantus vs exenatide demonstrated that better glycemic control was sustained with exenatide (*Diamant et al 2012*). Other studies have demonstrated that GLP-1 agonists are statistically non-inferior to Lantus for change in HbA1c (*Inagaki et al 2012, Weissman et al 2014*). Studies comparing the addition of GLP-1 agonists to Lantus were found to be non-inferior to the addition of thrice daily insulin lispro to Lantus (*Diamant et al 2014, Rosenstock et al 2014, Rosenstock et al 2020*).
- In terms of clinical outcomes, the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) have demonstrated that intensive glycemic control with insulin significantly reduces the rate of onset and progression of diabetic complications when compared to standard therapy (DCCT 1993, UKPDS 1998). Neither trial indicated the specific insulin formulations utilized; however, in the UKPDS, the risk reduction in microvascular complications was related more toward tight glycemic control rather than to one specific therapy (UKPDS, 1998).

Combination Products: Long-Acting Insulin and GLP-1 Receptor Agonist

- A 2017 SR and MA evaluated the efficacy and safety of insulin degludec/liraglutide vs insulin glargine/lixisenatide treatment in T2DM (*Cai et al 2017*). The analysis included 8 trials. The absolute HbA1c change relative to baseline with insulin glargine/lixisenatide was -1.50% and -1.89% with insulin degludec/liraglutide; comparisons between the groups revealed no significant differences. Additionally, there was no significant difference between the groups with regard to body weight changes.

Soliqua (insulin glargine/lixisenatide)

- The efficacy and safety of insulin glargine/lixisenatide were evaluated over 30 weeks in 2 Phase 3, AC, OL, RCTs, titled the LIXILAN trials:
 - T2DM patients uncontrolled on basal insulin:
 - The LIXILAN-L trial was a 2-treatment arm study in 731 T2DM patients. At baseline, patients were receiving basal insulin for at least 6 months at stable daily doses \pm OADs. Patients who had an insulin glargine daily dose of 20 to 50 U were randomized to either insulin glargine/lixisenatide 100/33 (n = 366) or insulin glargine 100 U/mL (n = 365). The maximum dose of insulin glargine allowed in the trial was 60 U for both groups. For the primary endpoint, HbA1c reduction after 30 weeks of treatment, the LSMD between insulin glargine/lixisenatide and insulin glargine was statistically significant favoring combination therapy over monotherapy (LSMD, -0.5%; 95% CI, -0.6 to -0.4; p < 0.0001) (*Aroda et al 2016, FDA briefing document [Soliqua] 2016, FDA summary review [Soliqua] 2016*).
 - A 2020 MA including 8 RCTs (N = 3828) compared insulin glargine/lixisenatide to other treatment intensification strategies in people whose T2DM was inadequately controlled (*Home et al 2020*). The estimated difference in HbA1c reduction with insulin glargine/lixisenatide vs premixed insulin, three times daily mealtime insulin + basal insulin, and once daily mealtime insulin + basal insulin was -0.50 %-units (95% CI, -0.93 to -0.06), -0.35 %-units (-95% CI, -0.89 to 0.13) and -0.68 %-units (95% CI, -1.18 to -0.17), respectively. Safety was similar or improved with insulin glargine/lixisenatide vs other insulin regimens.
 - Comparative data vs GLP-1 receptor agonists: The LIXILAN-O trial was a 3-treatment arm study in 1167 patients with T2DM who were inadequately controlled on metformin \pm OADs. Patients who met HbA1c goals based on prior therapy were then randomized to either insulin glargine/lixisenatide 100/33 (n = 468), insulin glargine 100 U/mL (n = 466), or lixisenatide (n = 233). The maximum dose of insulin glargine allowed in the trial was 60 U. For the primary endpoint, insulin glargine/lixisenatide required a non-inferior HbA1c reduction over 30 weeks compared to insulin glargine (non-inferiority upper margin of 0.3%). After 30 weeks of treatment, the LSMD in HbA1c reduction met non-inferiority compared to insulin glargine (LSMD, -0.3%; 95% CI, -0.4 to -0.2; p < 0.0001) and also demonstrated superiority for the endpoint (p < 0.0001). At week 30, the LSMD in HbA1c reduction between insulin glargine/lixisenatide and lixisenatide was also statistically significant (LSMD, -0.8%; 95% CI, -0.9 to -0.7; p < 0.0001) (*Rosenstock et al 2016, FDA briefing document [Soliqua] 2016, FDA summary review [Soliqua] 2016*).

- Weight and hypoglycemic events: Treatment with insulin glargine/lixisenatide was associated with mean weight losses of up to 0.7 kg from baseline across the aforementioned trials. Hypoglycemic rates were comparable for insulin glargine/lixisenatide and insulin glargine; however, fewer lixisenatide-treated patients experienced documented symptomatic hypoglycemic events compared to insulin glargine/lixisenatide (6.4% vs 25.6%, respectively) (Aroda *et al* 2016, Rosenstock *et al* 2016, FDA summary review [Soliqua] 2016).

Xultophy (insulin degludec/liraglutide)

- The efficacy and safety of insulin degludec/liraglutide were evaluated over 26 weeks in 9 Phase 3, parallel-group, AC, RCTs, titled the DUAL trials (Xultophy dossier 2016).
 - T2DM patients uncontrolled on basal insulin and/or OADs:
 - The DUAL I trial was a 3-treatment arm, OL study in 1,663 T2DM patients that compared fixed-dose combination of insulin degludec/liraglutide (n = 834) to insulin degludec (n = 414) and liraglutide (n = 415) components. Prior to randomization, patients were receiving metformin ± pioglitazone. The HbA1c reduction from baseline after 26 weeks of treatment was -1.8% for fixed-dose combination insulin degludec/liraglutide, -1.4% for insulin degludec, and -1.2% for liraglutide. The ETD for HbA1c showed that the fixed-dose combination insulin degludec/liraglutide is non-inferior to insulin degludec (ETD, -0.47%; 95% CI, -0.58 to -0.36; p < 0.0001) and superior to liraglutide (ETD, -0.64%; 95% CI, -0.75 to -0.53, p < 0.0001) (Gough *et al* 2014).
 - The DUAL II trial was a 2-treatment arm, DB study in 413 T2DM patients that compared insulin degludec/liraglutide (n = 207) to insulin degludec (n = 206). Prior to randomization, uncontrolled patients were receiving basal insulin (20 to 40 U) and metformin ± OADs. The maximum dose of insulin degludec allowed in the trial was 50 U, and the maximum allowed dose of liraglutide was 1.8 mg. HbA1c reduction from baseline after 26 weeks of treatment, the primary endpoint, was 1.9% for insulin degludec/liraglutide and 0.9% for insulin degludec. The ETD for HbA1c statistically favored combination injectable therapy over monotherapy (ETD, -1.1%; 95% CI, -1.3 to -0.8; p < 0.0001) (Buse *et al* 2014).
 - The DUAL IV trial was a DB study in 435 T2DM patients that compared insulin degludec/liraglutide (n = 289) to placebo (n = 146). Prior to randomization, uncontrolled patients were receiving sulfonylurea ± metformin. The HbA1c reduction from baseline after 26 weeks of treatment was -1.5% for insulin degludec/liraglutide and -0.5% for placebo. The ETD for HbA1c statistically favored insulin degludec/liraglutide over placebo (ETD, -1.02%; 95% CI, -1.18 to -0.87; p < 0.001) (Rodbard *et al* 2017[a]).
 - The DUAL V trial was a 2-treatment arm, OL, non-inferiority study in 557 T2DM patients that compared insulin degludec/liraglutide (n = 278) to insulin glargine (n = 279) and metformin. Prior to randomization, uncontrolled patients were receiving insulin glargine (20 to 50 U) and metformin. The trial maximum dose of insulin degludec/liraglutide was 50 U of insulin degludec and 1.8 mg of liraglutide; there was no maximum dose for insulin glargine. For the primary endpoint, an upper bound of the 95% CI < 0.3% was required for non-inferiority, which was achieved. The HbA1c reduction from baseline after 26 weeks of treatment was -1.8% for insulin degludec/liraglutide and -1.1% for insulin glargine. The ETD for HbA1c statistically favored combination injectable therapy over monotherapy (ETD, -0.59%; 95% CI, -0.74 to -0.45; p < 0.001 for non-inferiority) (Lingvay *et al* 2016).
 - The DUAL VI trial was a 32-week, OL, non-inferiority study in 420 T2DM patients that compared insulin degludec/liraglutide titrated once weekly (n = 210) to insulin degludec/liraglutide titrated twice weekly (n = 210). Prior to randomization, patients were receiving metformin ± pioglitazone. The mean HbA1c reduction from baseline after 32 weeks was -2% with once-weekly titration and -2% with twice-weekly titration. The ETD revealed a non-inferiority between the 2 treatment regimens (ETD, 0.12%; 95% CI, -0.04 to 0.28) (Harris *et al* 2017).
 - The DUAL VII trial was a 2-treatment, OL study in 506 T2DM patients that compared insulin degludec/liraglutide (n = 252) to insulin glargine + insulin aspart (n = 254). Prior to randomization, patients were receiving metformin and insulin glargine. The HbA1c reduction from baseline after 26 weeks of treatment was -1.5% for insulin degludec/liraglutide and -1.5% for insulin glargine with insulin aspart. The ETD revealed non-inferiority between the 2 treatments (ETD, -0.02%; 95% CI, -0.16 to 0.12) (Billings *et al* 2018).
 - The DUAL VIII trial was a 26-week, OL, randomized study in patients with T2DM that compared once daily insulin degludec/liraglutide (n=506) with insulin glargine (n=506) (Aroda *et al* 2019). Prior to randomization, patients were uncontrolled on stable doses of oral antidiabetic agents. Results demonstrated that patients who received insulin degludec/liraglutide had a longer time to initiation of therapy intensification (met when HbA1c was ≥ 7% at 2 consecutive visits after 26 weeks of treatment) compared to insulin glargine (>2 years vs 1 year).

- The DUAL IX trial was a 26-week, OL, randomized study that compared once daily insulin degludec/liraglutide (n=210) with insulin glargine (n=210) in patients with T2DM uncontrolled with SGLT2 inhibitors (*Philis-Tsimikas et al 2019*). The results of this study demonstrated that treatment with insulin degludec/liraglutide was non-inferior to insulin glargine with respect to the primary outcome of change in HbA1c from baseline to week 26 (-1.9% and -1.7%, respectively). In a confirmatory analysis, insulin degludec/liraglutide was also found superior to insulin glargine for the primary outcome with an ETD of -0.36% (95% CI, -0.50 to -0.21).
- T2DM patients uncontrolled on GLP-1 receptor agonists:
 - The DUAL III trial was a 2-treatment arm, OL study in 438 T2DM patients that compared insulin degludec/liraglutide (n = 292) to the currently administered maximum dose of GLP-1 receptor agonist (n = 146) and metformin ± OAD therapy. Prior to randomization, patients were receiving maximum doses of liraglutide once daily or exenatide twice daily, according to the local labeling, and metformin ± OADs. The trial maximum dose of insulin degludec/liraglutide was 50 U of insulin degludec and 1.8 mg of liraglutide. HbA1c reduction from baseline after 26 weeks of treatment, the primary endpoint, was 1.4% for insulin degludec/liraglutide and 0.3% for unchanged doses of GLP-1 receptor agonists. The ETD for HbA1c statistically favored combination injectable therapy over monotherapy (ETD, -0.94%; 95% CI, -1.1 to -0.8; p < 0.001) (*Linjawi et al 2017*).
- Weight and hypoglycemic events: Treatment with insulin degludec/liraglutide was associated with mean weight losses of up to 2.7 kg and weight gain of 2 kg from baseline across the aforementioned trials. Hypoglycemia rates with insulin degludec/liraglutide were comparable to insulin degludec. However, compared to GLP-1 receptor agonists, the estimated rate ratio (ERR) was 25.36 (95% CI, 10.63 to 60.51; p < 0.001), demonstrating a statistically significantly higher rate of hypoglycemic episodes in the insulin degludec/liraglutide group vs the GLP-1 receptor agonist group. Conversely, the ERR favored insulin degludec/liraglutide over insulin glargine with a statistically significantly higher rate of hypoglycemic episodes in the insulin glargine group (ERR, 0.43; 95% CI, 0.3 to 0.61; p < 0.001) (*Buse et al 2014, Lingvay et al 2016, Linjawi et al 2017, Xultophy dossier 2016*).

Cardiovascular (CV) outcomes

- A number of key CV studies have been conducted with insulin glargine, insulin degludec, liraglutide, and lixisenatide; of these, only liraglutide has demonstrated CV-positive outcomes. Studies with adequate power have not been conducted with the long-acting insulin and GLP-1 receptor agonist combination products.
 - The ORIGIN trial was a randomized trial without blinding conducted in 12,612 patients with CV risk factors plus impaired fasting glucose, impaired glucose tolerance, or T2DM. Patients were randomized to receive insulin glargine or standard of care therapy, which included continuing their pre-existing glycemic control regimen. CV risk factors at baseline included previous MI, stroke, angina, or revascularization. After a median 6.2 year follow-up, no significant difference in the co-primary outcomes of nonfatal MI, nonfatal stroke, or death from CV causes, and these events plus revascularization or hospitalization for heart failure (HF), were observed. The rates of incident CV outcomes were similar in the insulin glargine and standard care groups: 2.94 and 2.85 per 100 person-years, respectively, for the first co-primary outcome (HR, 1.02; 95% CI, 0.94 to 1.11; p = 0.63) and 5.52 and 5.28 per 100 person-years, respectively, for the second co-primary outcome (HR, 1.04; 95% CI, 0.97 to 1.11; p = 0.27) (*Gerstein et al 2012*).
 - ELIXA, a MC, DB, randomized, placebo-controlled (PC) trial (N = 6068) was conducted to evaluate the long-term effects of lixisenatide vs placebo on CV outcomes in patients with T2DM who had a recent acute coronary syndrome event within 180 days of screening. The primary endpoint was a composite of the first occurrence of any of the following: death from CV causes, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina. The median follow-up was 25 months. It was found that the primary endpoint event occurred in 13.4% of patients in the lixisenatide group and 13.2% in the placebo group (HR, 1.02; 95% CI, 0.89 to 1.17), which demonstrated non-inferiority of lixisenatide to placebo (p < 0.001), but did not demonstrate superiority (p = 0.81). The rates of the individual CV components of the primary endpoint were similar between the lixisenatide and placebo groups (*Pfeffer et al 2015*).
 - LEADER, a MC, DB, randomized, PC trial (N = 9340) was conducted to evaluate the long-term effects of liraglutide vs placebo on CV outcomes in patients with T2DM and high CV risk. The median follow-up was 3.8 years. It was found that the primary composite outcome (CV death, nonfatal MI, or nonfatal stroke) occurred in fewer patients in the liraglutide group (13%) vs the placebo group (14.9%) (HR, 0.87; 95% CI, 0.78 to 0.97; p < 0.001 for non-inferiority; p = 0.01 for superiority). Mortality from CV causes was lower in the liraglutide group (4.7%) vs the placebo group (6%) (HR, 0.78; 95% CI, 0.66 to 0.93; p = 0.007). Additionally, the rate of death from any cause was lower in the liraglutide group (8.2%) vs the placebo group (9.6%) (HR, 0.85; 95% CI, 0.74 to 0.97; p = 0.02). The rates of nonfatal MI,

nonfatal stroke, and hospitalization for heart failure were nonsignificantly lower in the liraglutide group than in the placebo group (*Marso et al 2016*).

- A MA of 26 studies (n = 24,348) demonstrated that insulin did not significantly increase the risk of all-cause and CV mortality, acute MI, or stroke in patients with T2DM. Insulin did significantly increase the risk of severe hypoglycemia vs other antidiabetic regimens (RR, 2.98; 95% CI, 2.47 to 3.61) (*Rados et al 2021*).

CLINICAL GUIDELINES

T1DM Overview

- Insulin is the mainstay of therapy for adult and pediatric patients with T1DM. Current guidelines recommend that most people with T1DM be treated with multiple daily injections (3 to 4 injections per day of basal and prandial insulin) or continuous subcutaneous insulin infusion. Either multiple daily injections or a continuous infusion can be considered, with some recent data demonstrating modest advantages with pump therapy such as increased HbA1c lowering and reduced severe hypoglycemia rates. In addition, the guidelines suggest that most people with T1DM should use insulin analogs to reduce hypoglycemia risk (*ADA 2021[b]*, *Chiang et al 2018*, *Garber et al 2020*).

T2DM Overview

- Professional society guidelines emphasize individualized therapy based upon patient- and drug-specific factors such as comorbidities, weight, hypoglycemia risk, propensity for AEs, drug interactions, and patient preferences (*ADA 2021[b]*, *Copeland et al 2013*, *Buse et al 2020*, *Garber et al 2020*).
- Metformin is recommended for first-line pharmacologic therapy in treatment-naïve patients with T2DM, unless the patient has contraindications or intolerance. SGLT2 inhibitors or GLP-1 receptor agonists should be considered for patients with established atherosclerotic CV disease (ASCVD), high ASCVD risk, HF, or chronic kidney disease (CKD), independent of HbA1c. Metformin is considered the drug of choice for children with T2DM (*ADA 2021[b]*, *Buse et al 2020*, *Copeland et al 2013*, *Das et al 2020*, *Garber et al 2020*, *KDIGO 2020*, *Rangaswami et al 2020*).
- Consideration should be given to initiating insulin therapy (with or without other agents) at the outset of treatment in newly diagnosed patients with markedly symptomatic and/or elevated blood glucose levels or HbA1c (*ADA 2021[b]*, *Buse et al 2020*, *Garber et al 2020*). Insulin therapy is usually started once patients are not achieving glycemic goals with noninsulin therapies. Guidelines suggest that an insulin treatment program be designed specifically for an individual patient, to match the supply of insulin to his or her dietary/exercise habits and prevailing glucose trends, as revealed through self-monitoring. Anticipated glucose-lowering effects should be balanced with the convenience of the regimen in the context of an individual's specific therapy goals.

Guidelines relevant to clinical decision making for insulin products in patients with diabetes are summarized below.

• ADA: Standards of Medical Care in Diabetes – 2021 (*ADA 2021[b]*)

◦ Pharmacological therapy for T2DM:

- Metformin (if not contraindicated and if tolerated) is the preferred initial pharmacological agent for T2DM (level A; refer to guideline for description of levels of evidence).
- Metformin should be continued when used in combination with other agents, including insulin, if not contraindicated and if tolerated (level A).
- Early combination therapy can be considered in some patients at treatment initiation to extend the time to treatment failure (level A).
- Early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when HbA1c levels (> 10%) or blood glucose levels (> 300 mg/dL) are very high (level E).
- A patient-centered approach should be used to guide the choice of pharmacologic therapy. Considerations include comorbidities (ASCVD, HF, CKD), hypoglycemia risk, impact on weight, cost, risk for side effects, and patient preferences (level E).
- In patients with T2DM and established ASCVD or indicators of high risk, established kidney disease, or HF, SGLT2 inhibitors or GLP-1 receptor agonists with demonstrated CVD benefit are recommended as part of the antihyperglycemic regimen, independent of HbA1c (level A).
- In patients with T2DM who need greater glucose lowering than can be obtained with oral agents, GLP-1 receptor agonists are preferred to insulin when possible (level B).

- A basal insulin/GLP-1 agonist combination can be considered when first intensifying therapy to injectable products in patients with HbA1c > 10% and/or if the patient is above the target HbA1c by $\geq 1.5\%$ to 2%. The combination can also be considered in patients who require additional control after the addition of a GLP-1 agonist in the intensification algorithm.
- Intensification of treatment for patients with T2DM not meeting treatment goals should not be delayed (level B).
- The medication regimen and medication-taking behavior should be reevaluated at regular intervals (every 3 to 6 months) and adjusted as needed to incorporate specific factors that impact treatment choice (level E).
- For patients with indicators of high-risk or established ASCVD, CKD, or HF, SGLT2 inhibitors or GLP-1 receptor agonists with proven benefit should be considered independently of baseline HbA1c or individualized HbA1c target.
 - If ASCVD predominates, a GLP-1 receptor agonist with proven CVD benefit is preferred. Alternatively, an SGLT2 inhibitor with proven CVD benefit is recommended if eGFR is adequate.
 - If HF or CKD predominates, an SGLT2 inhibitor with evidence of reducing HF and/or CKD in CV outcome trials is preferred if eGFR is adequate. If SGLT2 inhibitors are contraindicated, not tolerated, or if eGFR is not adequate, a GLP-1 receptor agonist with proven CVD benefit should be added.

Table 4. 2021 ADA Factors to Consider for Antihyperglycemic Therapies in T2DM

Class*	Efficacy	Hypoglycemia	Weight	ASCVD	HF	Route	DKD Progression
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Oral	Neutral
SGLT2i	Intermediate	No	Loss	Benefit: empagliflozin [†] , canagliflozin	Benefit: empagliflozin [†] , canagliflozin, dapagliflozin [‡]	Oral	Benefit: canagliflozin [§] , empagliflozin, dapagliflozin
GLP-1ra	High	No	Loss	Benefit: dulaglutide [†] , liraglutide [†] , semaglutide [†] Neutral: exenatide once weekly, lixisenatide	Neutral	SQ, oral	Benefit (driven by albuminuria outcomes): liraglutide, semaglutide, dulaglutide
DPP-4i	Intermediate	No	Neutral	Neutral	Potential risk: saxagliptin	Oral	Neutral
TZD	High	No	Gain	Potential benefit: pioglitazone	Increased risk	Oral	Neutral
SFU (2nd generation)	High	Yes	Gain	Neutral	Neutral	Oral	Neutral
Insulin	Highest	Yes	Gain	Neutral	Neutral	SQ	Neutral

Abbreviations: ASCVD = atherosclerotic cardiovascular disease; DKD = diabetic kidney disease; DPP-4i = dipeptidyl peptidase 4 inhibitor; GLP-1ra = glucagon-like peptide-1 receptor agonist; HF = heart failure; SFU = sulfonylurea; SGLT2i = sodium-glucose cotransporter-2 inhibitor; SQ = subcutaneous; T2DM = type 2 diabetes mellitus; TZD = thiazolidinediones

* Other antidiabetic drugs not shown in above table (eg, inhaled insulin, alpha-glucosidase inhibitors (AGIs), colesevelam, bromocriptine, and pramlintide) may be tried in specific situations; however, considerations include modest efficacy in T2DM, frequency of administration, potential for drug interactions, cost, and/or side effects.

[†] FDA approved for CVD benefit

[‡] FDA approved for HF indication

[§] FDA approved for CKD indication

- **American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) - Consensus Statement on the Comprehensive Type 2 Diabetes Management Algorithm (Garber et al 2020)**
 - The choice of diabetes therapies must be individualized based on attributes specific to both patients and the medications themselves. Medication attributes include antihyperglycemic efficacy, mechanism of action, risk of inducing hypoglycemia, risk of weight gain, other AEs, tolerability, ease of use, likely adherence, cost, and safety or risk reduction in heart, kidney, or liver disease. Patient-specific considerations include initial HbA1c, duration of T2DM, and obesity status.
 - The choice of therapy depends on the individual patient's cardiac, cerebrovascular, and renal status.
 - Combination therapy is usually required and should involve agents with complementary mechanisms of action.
 - The therapeutic regimen should be as simple as possible to optimize adherence.
 - For patients with recent-onset T2DM or mild hyperglycemia (HbA1c < 7.5%), lifestyle therapy plus antihyperglycemic monotherapy (preferably with metformin) is recommended.
 - For patients with established or high ASCVD risk, stage 3 CKD, or HF with reduced ejection fraction, an SGLT2 inhibitor or long-acting GLP-1 receptor agonist with proven efficacy is recommended independent of glycemic control.
 - Other acceptable alternatives to metformin as initial therapy include DPP-4 inhibitors and TZDs. Alpha-glucosidase inhibitors, SFUs, and meglitinides may also be appropriate as monotherapy for select patients.
 - Patients are unlikely to achieve glycemic targets with a third oral antihyperglycemic agent if their HbA1c level is > 8% or in those with long-standing disease. A GLP-1 agent may be considered, but many patients will eventually require insulin. Basal (long-acting) insulin is recommended for those who are symptomatic with an entry HbA1c > 9.0%. Basal insulin analogs are preferred over NPH. If an intensified regimen is needed, the addition of a GLP-1 agonist, SGLT2 inhibitor, or DPP-4 inhibitor can be considered. The combination of basal insulin with a GLP-1 receptor agonist may offer greater efficacy than the oral agents. Prandial (rapid-acting) insulin prior to meals can be considered when the total daily dose of basal insulin exceeds 0.5 U/kg.
 - Newer basal insulin formulations (glargine U-300, and degludec U-100 and U-200) have more prolonged and stable pharmacokinetic and pharmacodynamic characteristics than glargine U-100 and detemir. RCTs have reported equivalent glycemic control and lower rates of severe or confirmed hypoglycemia, particularly nocturnal hypoglycemia, compared to glargine U-100 and detemir insulin; however, no recommendation for specific insulin products is given.
- **2019 Update to: Management of Hyperglycemia in Type 2 Diabetes, 2018: A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) (Buse et al, 2020)**
 - In the 2020 update to the ADA standards of medical care in diabetes, the pharmacologic treatment of T2DM was significantly changed to align with the ADA-EASD consensus report. Additional recommendations from the ADA-EASD report with regard to insulin therapy are as follows:
 - For patients with established ASCVD or CKD, insulin therapies with demonstrated CV disease safety (degludec and glargine U-100) should be considered.
 - For patients with hypoglycemia issues, a basal insulin with lower risk of hypoglycemia should be considered (risk of hypoglycemia: degludec/glargine U-300 < glargine U-100/detemir < NPH).
- **Endocrine Society: Guideline for Treatment of Diabetes in Older Adults (LeRoith et al 2019)**
 - Glycemic management strategies must be adjusted to the individual needs of older patients. Specific factors regarding certain drug classes are particularly important for older patients with diabetes, especially those with CKD and heart disease.
 - In T2DM patients ≥ 65 years of age, metformin is recommended as the initial oral medication chosen for glycemic management in addition to lifestyle management (unless the patient has significantly impaired kidney function or gastrointestinal intolerance).
 - Patients who are not able to achieve glycemic targets with metformin and lifestyle changes can receive add-on therapy with oral or injectable agents and/or insulin.
 - GLP-1 receptor agonists and SGLT2 inhibitors should be prescribed early, given their beneficial CV outcomes.
 - SFUs and meglitinides should be avoided and insulin should be used sparingly to reduce the risk of hypoglycemia.

- The addition of a long-acting insulin may be the initial step to control fasting glucose. Insulin degludec and insulin glargine U-300 may cause less hypoglycemia compared to insulin glargine U-100. Older adults typically have more postprandial hyperglycemia rather than fasting hyperglycemia. Therefore, adding a premeal insulin may be more optimal than titrating a long-acting basal insulin in certain cases.
- Glycemic treatment regimens should be kept as simple as possible.

SAFETY SUMMARY

Insulins

- **Contraindications:**
 - Insulins are contraindicated during episodes of hypoglycemia and with hypersensitivity to any ingredient of the product.
 - In addition, Afrezza is also contraindicated in patients with chronic lung disease, such as asthma or chronic obstructive pulmonary disease (COPD), because of the risk of acute bronchospasm.
- **Boxed Warnings:**
 - Afrezza has a boxed warning for the risk of acute bronchospasm in patients with chronic lung disease. Before initiating Afrezza, a detailed medical history, physical examination, and spirometry should be performed to identify potential lung disease in all patients.
- **Warnings/Precautions:**
 - Insulin pens must never be shared between patients, even if the needle is changed. Patients using insulin vials must never reuse or share needles or syringes with another person. Sharing poses a risk for transmission of blood-borne pathogens.
 - Changes in insulin regimen, including insulin manufacturer, type, strength, injection site, or method of administration, may affect glycemic control and lead to hypoglycemia or hyperglycemia. Frequent glucose monitoring and close medical supervision is recommended when making changes to a patient's insulin regimen.
 - Frequent glucose monitoring and insulin dose reduction may be required in patients with renal or hepatic impairment.
 - All insulins can cause hypokalemia, which if untreated, may result in respiratory paralysis, ventricular arrhythmia, and death.
 - Long-term use of insulin can cause lipodystrophy at the site of repeated insulin injections.
 - Accidental mix-ups between basal insulin products and other insulins, particularly rapid-acting insulins, have been reported. To avoid medication errors, patients should be instructed to always check the insulin label before each injection.
 - Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products. If hypersensitivity reactions occur, the insulin product should be discontinued.
 - Administration of Humulin R U-500 in syringes other than U-500 insulin syringes has resulted in dosing errors. Patients should be prescribed U-500 syringes for use with Humulin R U-500 vials. The prescribed dose should always be expressed in units of insulin.
 - Afrezza has additional respiratory-related warnings and precautions associated with its use including acute bronchospasm in patients with chronic lung disease, decline in pulmonary function, and lung cancer.
- **AEs:**
 - Hypoglycemia is the most commonly observed AE. Hypoglycemia can impair concentration ability and reaction time which may place an individual and others at risk in situations where these abilities are important. Severe hypoglycemia can cause seizures, may be life-threatening, or cause death. Self-monitoring of blood glucose plays an essential role in the prevention and management of hypoglycemia.
 - Weight gain, sodium retention and edema, and injection site reactions can occur.
 - Additional AEs observed with the inhaled insulin, Afrezza, include cough, throat pain or irritation, headache, diarrhea, productive cough, fatigue, nausea, decreased pulmonary function test, bronchitis, and urinary tract infection.
- **Drug Interactions:**
 - β -blockers, clonidine, guanethidine, and reserpine may mask hypoglycemic reactions.
 - Thiazolidinediones can cause dose-related fluid retention, particularly when used in combination with insulin.
 - Refer to the prescribing information for all drugs that can increase or reduce the glucose-lowering ability of insulin.

Combination, Long-Acting Insulin and GLP-1 Receptor Agonist

- **Contraindications:**
 - Both combination agents are contraindicated in patients with hypersensitivity to any component of the products and during episodes of hypoglycemia.
 - Xultophy (insulin degludec/liraglutide) is also contraindicated in and has a boxed warning for patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
- **Warnings/Precautions:**
 - Warnings and precautions are consistent with each individual agent and include pancreatitis, serious hypersensitivity reactions/allergic reactions, hypoglycemia or hyperglycemia, the potential for overdose due to medication errors, acute kidney injury, hypokalemia, and the potential for fluid retention and heart failure with use of thiazolidinediones. Prefilled pens should never be shared between patients (even if the needle is changed) due to the risk of transmission of blood-borne pathogens.
 - Additional warnings and precautions for Soliqua include immunogenicity risks associated with the development of antibodies to insulin glargine and lixisenatide resulting in a loss of glycemic control and a lack of clinical studies showing macrovascular risk reduction. Additional warnings for Xultophy include a potential increased risk for acute gallbladder disease.
- **AEs:**
 - The most common AEs reported with these agents include nausea, nasopharyngitis, diarrhea, headache, and upper respiratory tract infection.
 - Additional common AEs include hypoglycemia and allergic reactions with Soliqua and increased lipase with Xultophy.
- **Drug Interactions:**
 - The GLP-1 receptor agonist components may cause delayed gastric emptying of oral medications. Certain medications may require administration 1 hour before (ie, antibiotics, acetaminophen, oral contraceptives, or other medications dependent on threshold concentrations for efficacy) or 11 hours after (ie, oral contraceptives) administration of the GLP-1 receptor agonist.
 - Monitor use closely when administered concomitantly with other medications that may affect glucose metabolism.
 - Antiadrenergic medications (ie, beta blockers, clonidine, guanethidine, and reserpine) may mask the signs and symptoms of hypoglycemia.
- Lixisenatide and liraglutide slow gastric emptying. Patients with gastroparesis were excluded from trials; therefore, agents are generally not recommended in cases of severe gastroparesis.

DOSING AND ADMINISTRATION

- Injection sites should be rotated within the same region (abdomen, thigh or upper arm) from one injection to the next to reduce the risk of lipodystrophy.
- Dose adjustments in patients with renal and/or hepatic dysfunction may be required with the insulin products.
- In elderly patients, caution should be taken with initial insulin dosing and subsequent dose changes to avoid hypoglycemic reactions.

Table 4. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency*	Comments
Rapid-Acting Insulins				
Admelog (insulin lispro)	100 U/mL: SoloStar pen, vial	SC, IV	Administer within 15 minutes before a meal or immediately after a meal. Use in a regimen with intermediate- or long-acting insulin when administered by SC injection.	Safety and efficacy in children < 3 years with T1DM and in children with T2DM have not been established. Use SoloStar pen with caution in patients with visual impairment who rely on audible clicks to dial their dose.

Drug	Available Formulations	Route	Usual Recommended Frequency*	Comments
Afrezza (insulin human)	Single-use cartridges: 4, 8, 12 units Available in cartons with a single dosage and in titration packs with multiple dosages	Inhalation	Generally given 3 times daily at the beginning of a meal.	Safety and efficacy in pediatric patients or in renal or hepatic dysfunction have not been established.
Apidra (insulin glulisine)	100 U/mL: SoloStar pen, vial	SC, IV	Administer within 15 minutes before a meal or within 20 minutes after starting a meal. Dose and frequency are individualized per patient needs. Use in a regimen with intermediate- or long-acting insulin when administered by SC injection.	Safety and efficacy in children < 4 years with T1DM or in children with T2DM have not been established. Use SoloStar pen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Fiasp (insulin aspart)	100 U/mL: FlexTouch pen, vial, PenFill cartridges	SC, IV	Administer at the start of a meal or within 20 minutes after starting a meal. Use in a regimen with intermediate- or long-acting insulin when administered by SC injection.	Use FlexTouch pen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Humalog (insulin lispro)	100 U/mL: cartridge, KwikPen, Junior KwikPen, Tempo Pen, vial 200 U/mL: KwikPen	SC, IV (U-100 only)	Administer within 15 minutes before a meal or immediately after a meal. Use in a regimen with intermediate- or long-acting insulin when administered by SC injection.	Safety and efficacy in children < 3 years with T1DM and in children with T2DM have not been established. Use KwikPen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Lyumjev (insulin lispro-aabc)	100 U/mL: cartridge, KwikPen, Junior KwikPen, Tempo Pen, vial 200 U/mL: KwikPen	SC, IV (U-100 only)	Administer at the start of the meal or within 20 minutes after starting the meal. Use in a regimen with intermediate- or long-acting insulin when administered by SC injection.	Safety and efficacy in children have not been established. Use prefilled pens with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Novolog (insulin aspart)	100 U/mL: cartridge (PenFill), FlexPen, Vial	SC, IV	Novolog: Should be injected immediately (within 5 to 10 minutes) before a meal.	Safety and efficacy in children < 2 years with T1DM and in children with T2DM have not been established.

Drug	Available Formulations	Route	Usual Recommended Frequency*	Comments
			Use in a regimen with intermediate- or long-acting insulin when administered by SC injection.	Use FlexPen and PenFill cartridges with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Short-Acting Insulins				
Humulin R (insulin, regular, human recombinant)	100 U/mL: cartridge, vial 500 U/mL KwikPen, vial	SC, IV (U-100 only)	When given SC, generally given 3 or more times daily before meals (within 30 minutes). U-500: Generally given 2 to 3 times daily before meals. U-100: Often used concomitantly with intermediate- or long-acting insulin when administered by SC injection.	U-500: well-controlled studies in children not available. Dosing in pediatric patients must be individualized. Dose conversion should not be performed when using the U-500 KwikPen or a U-500 insulin syringe. Only a U-500 insulin syringe should be used with the Humulin U-500 vial. Use KwikPen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Novolin R (insulin, regular, human recombinant)	100 U/mL: Vial	SC, IV	Administration should be followed by a meal within 30 minutes of administration. Often used in combination with intermediate- or long-acting insulin when administered by SC injection.	Safety and efficacy in children < 2 years with T1DM or in children with T2DM have not been established. Use in pumps is not recommended due to risk of precipitation.
Intermediate-Acting Insulins				
Humulin N (insulin, NPH, human recombinant isophane)	100 U/mL: KwikPen, vial	SC	Generally given in 1 to 2 injections per day 30 to 60 minutes before a meal or bedtime.	Has not been studied in children. Dosing in pediatric patients must be individualized. Use KwikPen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Novolin N (insulin, NPH, human recombinant isophane)	100 U/mL: Vial, Flexpen	SC	Generally given in 1 to 2 injections per day 30 to 60 minutes before a meal or bedtime.	
Long-Acting Insulins				
Basaglar (insulin glargine)	100 U/mL: KwikPen	SC	Daily May be administered at any time of day, but at same time every day.	Safety and efficacy in children < 6 years with T1DM and in children with T2DM have not been established.

Drug	Available Formulations	Route	Usual Recommended Frequency*	Comments
				Use with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Lantus (insulin glargine)	100 U/mL: SoloStar pen, vial	SC	Daily May be administered at any time of day, but at same time every day.	Safety and efficacy in children < 6 years with T1DM and in children with T2DM have not been established. Use SoloStar pen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Semglee (insulin glargine)	100 U/mL; prefilled pen, vial	SC	Daily May be administered at any time of day, but at same time every day.	Safety and efficacy in children < 6 years with T1DM and in children with T2DM have not been established. Use Semglee prefilled pen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Levemir (insulin detemir)	100 U/mL: FlexTouch pen, vial	SC	Daily to twice daily Once daily administration should be given with evening meal or at bedtime. Twice daily administration should be given in the morning and then 12 hours later with evening meal or at bedtime.	Safety and efficacy in children < 2 years with T1DM and in children with T2DM have not been established. Use FlexTouch pen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Toujeo (insulin glargine U-300)	300 U/mL: SoloStar pen, Max SoloStar pen	SC	Daily May be administered at any time of day, but at the same time every day.	To minimize the risk of hypoglycemia, the dose of Toujeo should be titrated no more frequently than every 3 to 4 days. The Toujeo Max SoloStar pen carries 900 U of Toujeo U-300 (twice as many as the regular SoloStar pen) and is recommended for patients that require at least 20 U per day Use with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Tresiba (insulin degludec)	100 U/mL: FlexTouch pen, vial	SC	Daily	Safety and efficacy in children < 1 year have not been

Drug	Available Formulations	Route	Usual Recommended Frequency*	Comments
	200 U/mL: FlexTouch pen		May be administered at any time of day (should be same time of day in pediatric patients).	<p>established (use in children \geq 1 year with T2DM is supported by evidence from adult T2DM studies).</p> <p>The recommended number of days between dose increases is 3 to 4 days.</p> <p>Pediatric patients requiring $<$ 5 units daily should use the U-100 vial.</p> <p>Use FlexTouch pen with caution in patients with visual impairment who rely on audible clicks to dial their dose.</p>
Combination Insulins, Rapid-Acting and Intermediate-Acting				
Humalog Mix 50/50 Humalog Mix 75/25 (insulin lispro protamine/insulin lispro)	100 U/mL: KwikPen, vial	SC	Administer within 15 minutes before meals. Typically dosed twice daily.	<p>Safety and efficacy in children have not been established.</p> <p>Use Humalog Mix KwikPen and Novolog Mix FlexPen with caution in patients with visual impairment who rely on audible clicks to dial their dose.</p>
Novolog Mix 70/30 (insulin aspart protamine/insulin aspart)	100 U/mL: cartridge, FlexPen, vial	SC	<p>Twice daily</p> <p>T1DM: administer within 15 minutes before meals T2DM: administer within 15 minutes before or after meal</p>	
Combination Insulins, Short-Acting and Intermediate-Acting				
Humulin 70/30 (NPH, human insulin isophane/regular human insulin)	100 U/mL: KwikPen, vial	SC	Twice daily 30 to 45 minutes before a meal	<p>Safety and efficacy in children have not been established.</p> <p>Use KwikPen with caution in patients with visual impairment who rely on audible clicks to dial their dose.</p>
Novolin 70/30 (NPH, human insulin isophane/regular human insulin)	100 U/mL: FlexPen, vial	SC	Twice daily 30 to 60 minutes before a meal	
Combination Products, Long-Acting Insulin and GLP-1 Receptor Agonist				
Soliqua 100/33 (insulin glargine/lixisenatide)	100 U/mL; 33 mcg/mL: SoloStar pen	SC	Once daily within the hour prior to the first meal of the day	<p>The pen delivers doses from 15 to 60 U of insulin glargine with each injection.</p> <p>Not recommended for use in end-stage renal disease (ESRD).</p>

Drug	Available Formulations	Route	Usual Recommended Frequency*	Comments
				Frequent BG monitoring and dose adjustment may be necessary in hepatic impairment.
Xultophy 100/3.6 (insulin degludec/liraglutide)	100 U/mL; 3.6 mg/mL: pen	SC	Once daily at the same time each day with or without food	The pen delivers doses from 10 to 50 U of insulin degludec with each injection. Has not been studied in patients with hepatic impairment or severe renal impairment. Use with caution in patients with visual impairment who rely on audible clicks to dial their dose.

Abbreviations: BG = blood glucose, IV = intravenous, SC = subcutaneous, T1DM = type 1 diabetes mellitus, T2DM = type 2 diabetes mellitus, U = unit
*Dose and frequency of insulin products should be individualized per patient needs.

See the current prescribing information for full details

(Clinical Pharmacology 2021)

CONCLUSION

Insulins

- The insulin products are approved for use in the management of both T1DM and T2DM. The primary differences between commercially available insulin products revolve around pharmacodynamic and pharmacokinetic properties, particularly onset and duration of action.
- Individual insulin products may fall into 1 of 4 categories: rapid-, short-, intermediate-, or long-acting insulins. Insulin therapy is usually administered by SC injection, which allows for prolonged absorption and less pain compared to IM injection. Humalog, Humalog Kwikpen, Novolog, Novolog PenFil, Novolog FlexPen, Novolog Mix 70/30, and Novolog Mix FlexPen 70/30 have authorized generics or products that contain the same insulin (*Lilly 2019[a]*, *Lilly 2019[b]*, *Novo Nordisk 2019*).
- Safety profiles of the injectable rapid-acting insulins are comparable, with the exception of Afrezza, a rapid-acting inhaled insulin. The inhalation route offers a less invasive alternative route of administration and improved convenience of administration compared with injectable rapid-acting insulins. Afrezza has a boxed warning for bronchospasm and is contraindicated in patients with chronic lung disease. Due to this different route of administration, the most common AEs associated with Afrezza in clinical trials were hypoglycemia, cough, and throat pain or irritation.
- The safety and efficacy of insulin therapy in the management of diabetes are well established. Clinical trials have demonstrated that the newer rapid- and long-acting insulin analogs are as effective as regular and isophane (NPH) insulin in terms of glucose management. The data also suggest that long-acting insulin analogs are superior to NPH in decreasing HbA1c and are associated with a lower incidence of hypoglycemic events. Furthermore, head-to-head data do not consistently demonstrate the superiority of one rapid- or long-acting insulin analog over another.
- In terms of clinical outcomes, intensive glycemic control with insulin has been shown to significantly reduce the rate of onset and progression of diabetic complications when compared to standard therapy.
- Insulin is the mainstay of therapy for adult and pediatric patients with T1DM. Current guidelines recommend that most people with T1DM be treated with multiple daily injections (3 to 4 injections per day of basal and prandial insulin) or continuous subcutaneous insulin infusion. In addition, the guidelines suggest that most people with T1DM should use insulin analogs to reduce hypoglycemia risk (*ADA 2021[b]*, *Chiang 2018*).
- According to current clinical guidelines regarding the management of T2DM, consideration should be given to initiating insulin therapy (with or without other agents) at the outset of treatment in newly diagnosed patients with markedly

symptomatic and/or elevated blood glucose levels or HbA1c. Insulin therapy is usually started once patients are not achieving glycemic goals with noninsulin therapies (ADA 2021[b], Buse et al 2020, Garber et al 2020).

- Guidelines suggest that an insulin treatment program be designed specifically for an individual patient, to match the supply of insulin to his or her dietary/exercise habits and prevailing glucose trends, as revealed through self-monitoring. Anticipated glucose-lowering effects should be balanced with the convenience of the regimen in the context of an individual's specific therapy goals (ADA 2021[b], Buse et al 2020, Garber et al 2020).
- The ADA and EASD recommend that in most patients who require an injectable therapy a GLP-1 agonist should be the first choice, ahead of insulin. For patients with T2DM and established ASCVD, the level of evidence for MACE benefit is greatest for GLP-1 agonists. GLP-1 agonists are also suggested for patients without CVD but with indicators of high risk. Certain patient factors can influence the choice of insulin therapy and recommendations for certain products are made for those with ASCVD, CKD, and those with hypoglycemia issues (ADA 2021[b], Buse et al 2020).

Combination, Long-Acting Insulin and GLP-1 Receptor Agonist

- Insulin glargine/lixisenatide (Soliqua) and insulin degludec/liraglutide (Xultophy) are long-acting insulin and incretin-based antidiabetic combination therapies that are FDA-approved as adjunctive therapy to diet and exercise to improve glycemic control in adult T2DM patients.
- The medications are administered through a fixed ratio pen. Soliqua may be administered in doses of 15 to 60 U of insulin glargine and 5 to 20 mcg of lixisenatide, while Xultophy may be administered in doses of 10 to 50 U of insulin degludec and 0.36 to 1.3 mcg of liraglutide SC once daily depending on prior treatment and dosages. Individualized dosing is recommended based on metabolic needs, blood glucose monitoring, glycemic control, type of diabetes, and prior insulin use of the patient.
- These agents have been studied in combination with metformin, sulfonylureas, pioglitazone, and meglitinides. In studies, Soliqua demonstrated HbA1c reductions ranging from 0.3 to 0.5% vs insulin glargine and 0.8% vs lixisenatide. Xultophy demonstrated ETDs in HbA1c reductions of 1% vs insulin degludec monotherapy, 0.6% vs insulin glargine monotherapy, and 0.9% vs a GLP-1 receptor agonist (eg, liraglutide or exenatide twice daily). Across trials, Xultophy and Soliqua were associated with both weight losses and gains. Hypoglycemia rates were mostly similar to those observed within the basal insulin monotherapy arms; however, the GLP-1 receptor agonists were associated with fewer hypoglycemic events (Aroda et al 2016, Buse et al 2014, FDA summary review [Soliqua] 2016, Home et al 2020, Lingvay et al 2016, Linjawi et al 2017, Rosenstock et al 2016). Several CV outcomes trials have been conducted in patients with T2DM who were administered basal insulin monotherapy or GLP-1 receptor agonist monotherapy. Of these trials, the only trial which demonstrated a reduced CV risk was the LEADER trial, which compared liraglutide to placebo (Gerstein et al 2012, Marso et al 2016, Marso et al 2017, Pfeffer et al 2015).
- Overall, the safety profiles of these agents are similar. Xultophy has a boxed warning regarding the risk of thyroid C-cell tumors and is contraindicated in patients with a history of MTC or MEN 2. Other key warnings for these products include increased risks of pancreatitis, hypoglycemia or hyperglycemia, the potential for overdose due to medication errors, acute kidney injury, hypokalemia, and the potential for fluid retention and heart failure with use of thiazolidinediones. Soliqua has an additional warning and precaution regarding immunogenicity risks associated with the development of antibodies which may result in the loss of glycemic control. Common AEs include gastrointestinal effects (eg, nausea, diarrhea, etc), nasopharyngitis, headache, and upper respiratory tract infection.
- Guidelines from the ADA and EASD note that a basal insulin/GLP-1 agonist combination can be considered when first intensifying therapy to injectable products in patients with HbA1c > 10% and/or if the patient is above the target HbA1c by ≥ 1.5 to 2%. The combination can also be considered in patients who require additional control after the addition of a GLP-1 agonist in the intensification algorithm (ADA 2021[b], Buse et al 2020).

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