OPTUMRx

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] Diabetes Basics 2019).*
- 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 2019).*
- In 2015, an estimated 30.3 million people, or 9.4%, of the United States (US) population had diabetes mellitus, with 7.2 million estimated to be undiagnosed *(Centers for Disease Control and Prevention [CDC] 2017).*
- 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 *(Novo Nordisk news release 2017).* 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).*
  - 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. Additionally, Basaglar (insulin glargine) was approved under the FDA 505(b)(2) pathway. *(Fierce Biotech FDA press release 2015, Drugs@FDA 2019).*
- Insulin therapy is usually administered by subcutaneous (SC) injection, which allows for prolonged absorption and less pain compared to intramuscular (IM) injection. Currently there are no generic insulin products available. 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. FDA-approved products that do not have upcoming launch plans, such as

Ryzodeg 70/30 (insulin degludec/insulin aspart), have been excluded from this review *(Novo Nordisk press release 2015*).

- 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 (insulin aspart)	-
Humalog, Humalog Kwikpen, Humalog Junior Kwikpen (insulin lispro)	-
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 ReliOn (insulin, regular, human recombinant)	-
Intermediate-Acting Insulins	
Humulin N, Humulin N Kwikpen (insulin, NPH human recombinant isophane)	-
Novolin N, Novolin N ReliOn (insulin, NPH human recombinant isophane)	-
Long-Acting Insulins	
Basaglar (insulin glargine)	-
Lantus, Lantus SoloStar (insulin glargine)	-
Levemir, Levemir FlexTouch (insulin detemir)	-
Toujeo SoloStar, Toujeo Max SoloStar (insulin glargine U-300)	-
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 (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)	-
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)	-

(Drugs@FDA 2019)

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			✔
Afrezza		✔ §	
Apidra			✔
Fiasp		✔	
Humalog			✔
Novolog			✔
Short-Acting Insulins			
Humulin R			✔ *
Novolin R			✔
Intermediate-Acting Insulins			
Humulin N			✔
Novolin N			✔
Long-Acting Insulins†			
Basaglar			✔ ‡
Lantus			✔ ‡
Levemir			✔
Toujeo		✔	
Tresiba			✔ ‖
Combination Insulins, Rapid-Acting and Intermediate-Acting			
Humalog Mix 50/50 Humalog Mix 75/25	✔		
Novolog Mix 70/30		✔	
Combination Insulins, Short-Acting and Intermediate-Acting			
Humulin 70/30		✔	
Novolin 70/30			✔

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

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

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 2019, 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 large meta-analysis revealed that both insulin aspart and insulin lispro produced comparable lowering of glycosylated hemoglobin (HbA1c) in patients with T2DM compared to regular insulin *(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, Fullerton et al 2016, Garg et al 2005, Rayman et al 2007).*
- 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, 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, 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 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), severe hypoglycemia (RR, 0.68; 95% CI, 0.60 to 0.77), post-prandial glucose (mean difference [MD], -19.44 mg/dL; 95% CI, -21.49 to -17.39), and lower 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]).*
- Fiasp was evaluated in the Onset clinical trial program. Onset 1 *(Russell-Jones et al 2017)* was a 26-week, Phase 3, AC, RCT that compared Fiasp (mealtime and postmeal) to Novolog in patients with T1DM. Both mealtime and postmeal Fiasp were demonstrated to be noninferior to Novolog in change in HbA1c (Estimated treatment difference [ETD], -0.15; p < 0.0001; ETD 0.04%; p < 0.0001, respectively). Onset 2 *(Bowering et al 2017)* 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 noninferiority to Novolog in HbA1c lowering (ETD -0.02%; p < 0.0001). Onset 3 *(Rodbard et al 2017)* 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 (BG)-confirmed hypoglycemic episodes (RR, 8.24; p < 0.0001) and modest weight gain.
- The safety and efficacy of Admelog, the first “follow-on” rapid-acting insulin, were evaluated in two 26-wk, Phase 3, OL, PG, 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 noninferior 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.
- 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 patients with T1DM and T2DM as demonstrated by the results of several active-comparator trials and meta-analyses *(Bartley et al 2008, Bazzano et al 2008, Buse et al 2009, Chase et al 2008, 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, Home et al 2004, Horvath et al 2007, 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, 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, active-controlled, parallel studies of up to 26 weeks in patients with T1DM and T2DM. The reductions in HbA1c and fasting plasma glucose 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 meta-analysis 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 HbA1 reduction (effect size, -0.08; 95% CI, -0.14 to -0.01) (*Diez-Fernandez et al 2018*).
- 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) *(Philis-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 meta-analysis 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 meta-analysis 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 fasting plasma glucose 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)*.
- 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 2016).*
- 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, parallel group, randomized controlled trials (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. 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*).

- 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 meta-analysis similarly found no differences in HbA1c reduction between insulin degludec, determir, 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 2018).*
  - To further inform the differences between basal insulin agents, a network meta-analysis (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).*

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 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 adverse events between the biosimilar agents and their reference products (*Tieu et al 2018)*.
- 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).*
- 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 systematic review and meta-analysis evaluated the efficacy and safety of insulin degludec/liraglutide vs insulin glargine/lixisenatide treatment in T2DM (*Cai 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, active-comparator (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 ± 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).*
  - 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 ± 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).* Currently, results from DUAL I through VII are available, and DUAL VIII and IX trials are ongoing; therefore, these trials will not be discussed. The DUAL I, IV, VI, and VII trials were conducted in patients uncontrolled while administered OADs, and since insulin degludec/liraglutide is not FDA-approved for use in patients previously uncontrolled on OADs, these trials have been excluded from this review:
  - T2DM patients uncontrolled on basal insulin and OADs:
    - 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 estimated treatment difference (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 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).*
  - 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 multi-center (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 noninferiority; 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).*

CLINICAL GUIDELINES

- 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 2019, Chiang 2018, Handelsman et al 2015).*

- 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 2019, Davies 2018, Garber et al 2019, Handelsman et al 2015).*
- 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 2019, Davies 2018, Garber et al 2019, Handelsman et al 2015).*
  - The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACA) T2DM management algorithm identifies lifestyle therapies such as weight loss, comprehensive management of lipids and blood pressure, safety, and simplicity as crucial factors of a T2DM regimen. The guideline notes that patients are unlikely to achieve glycemic targets with a third oral antihyperglycemic agent if their HbA1c level > 8% or in those with long-standing disease. A GLP-1 agent may be considered, but many patients will eventually require insulin. The guideline suggests basal (long-acting) insulin 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 *(Garber et al 2019).*
    - The guideline also states that 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.
  - The ADA and European Association for the Study of Diabetes (EASD) offer similar emphasis on lifestyle modifications and CV disease risk management. In the 2019 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. The ADA guideline states that insulin therapy (with or without additional agents) should be initiated in patients with newly diagnosed T2DM with 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. 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. Due to the progressive nature of the disease, patients may eventually require insulin therapy (*ADA 2019, Davies 2018)*.
    - Certain patient factors can influence the choice of insulin therapy. For patients with established atherosclerotic cardiovascular disease (ASCVD) or chronic kidney disease (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).
    - A basal insulin/GLP-1 agonist combination can be considered when first intensifying therapy to injectable products in patients with a HbA1c > 10% and/or if the patient is above the target HbA1c by > 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.
- The American College of Cardiology published an expert consensus decision pathway for patients with T2DM and ASCVD (*Das 2018*). For the GLP-1 agonists, liraglutide is the only agent in the class with proven benefits of reducing CV events. In contrast, lixisenatide is not associated with a reduction in ASCVD event risk. Thus, both the ACC pathway and ADA guideline considers liraglutide as the preferred GLP-1 agent (*ADA 2019, Das 2018*).

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.
  - 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 that 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.
- Adverse Events (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 Interactons:
  - 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.
- Risk Evaluation and Mitigation Strategy (REMS)
  - The FDA previously required a communication plan to inform health care professionals about the serious risk of acute bronchospasm associated with Afrezza; however, in April 2018, the FDA determined that the communication plan has been completed and REMS is no longer needed. (https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2018/022472Orig1s017ltr.pdf).

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.
- REMS programs:
  - The FDA previously required a REMS program for Xultophy, which included a communication plan for alerting healthcare professionals about the risk of acute pancreatitis and the potential risk of MTC; however, in December 2017, the FDA determined that the communication plan is no longer necessary and that a REMS is no longer required (https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2017/208583Orig1s001ltr.pdf).
- 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.
Afrezza (insulin human)	Single-use cartridges: 4, 8, 12 units Available in cartons	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.

Drug	Available Formulations	Route	Usual Recommended Frequency*	Comments
	with a single dosage and in titration packs with multiple dosages			
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.	Safety and efficacy have not been established in children. 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, 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.
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. Use in a regimen with intermediate- or long-acting insulin when administered by SC injection.	Safety and efficacy in children < 2 years with T1DM and in children with T2DM have not been established. 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: 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-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-

Drug	Available Formulations	Route	Usual Recommended Frequency*	Comments
			U-100: Often used concomitantly with intermediate- or long-acting insulin when administered by SC injection.	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 Novolin R ReliOn (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 Novolin N ReliOn (insulin, NPH, human recombinant isophane)	100 U/mL: Vial	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. 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.
Levemir (insulin	100 U/mL:	SC	Daily to twice daily	Safety and efficacy in children <

Drug	Available Formulations	Route	Usual Recommended Frequency*	Comments
detemir)	FlexTouch pen, vial		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.	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 Administer at the same time each day.	Safety and efficacy in children have not been established. 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 200 U/mL: FlexTouch pen	SC	Daily May be administered at any time of day (should be same time of day in pediatric patients).	Safety and efficacy in children < 1 year have not been established (use in children ≥ 1 year with T2DM is supported by evidence from adult T2DM studies). The recommended number of days between dose increases is 3 to 4 days. Pediatric patients requiring < 5 units daily should use the U-100 vial. Use FlexTouch pen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Combination Insulins, Rapid-Acting and Intermediate-Acting				
Humalog Mix 50/50 Humalog Mix 75/25	100 U/mL: KwikPen, vial	SC	Administer within 15 minutes before meals. Typically	Safety and efficacy in children have not been established.

Drug	Available Formulations	Route	Usual Recommended Frequency*	Comments
(insulin lispro protamine/insulin lispro)			dosed twice daily.	Use Humalog Mix KwikPen and Novolog Mix FlexPen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Novolog Mix 70/30 (insulin aspart protamine/insulin aspart)	100 U/mL: FlexPen, vial	SC	Twice daily T1DM: administer within 15 minutes before meals T2DM: administer within 15 minutes before or after meal	
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	Safety and efficacy in children have not been established. Use KwikPen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Novolin 70/30 Novolin 70/30 ReliOn (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	The pen delivers doses from 15 to 60 U of insulin glargine with each injection. Not recommended for use in end-stage renal disease (ESRD). 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 renal or hepatic impairment.

Abbreviations: BG = blood glucose, IV = intravenous, SC = subcutaneous, T1DM = type 1 diabetes mellitus, T2DM = type 2 diabetes mellitus, U = unit

(Clinical Pharmacology 2019)

*Dose and frequency of insulin products should be individualized per patient needs.
See the current prescribing information for full details

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 are classified by their onset and duration of actions and may fall into one of four 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. No generic insulin products are currently available.
- Afrezza is 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. 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 2019, Chiang 2018, Handelsman et al 2015).*
- 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 2019, Davies 2018, Garber et al 2019, Handelsman et al 2015).*
- 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 2019, Davies 2018, Garber et al 2019, Handelsman et al 2015).*
- 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. 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 2019, Davies 2018)*.

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 estimated treatment differences 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 less hypoglycemic events *(Aroda et al 2016, Buse et al 2014, FDA summary review [Soliqua] 2016, 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.
- The ADA and EASD guidelines note that a basal insulin/GLP-1 agonist combination can be considered when first intensifying therapy to injectable products in patients with a HbA1c > 10% and/or if above the target HbA1c by over 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 2019, Davies 2018).*

REFERENCES

- Admelog [package insert]. Bridgewater, NJ: Sanofi-Aventis; November 2018.
- Afrezza [package insert], Danbury, CT: MannKind Corporation; October 2018.
- American Diabetes Association. Diabetes Basics. ADA Web site. 2019. http://www.diabetes.org/diabetes-basics/. Accessed February 4, 2019.
- American Diabetes Association. Standards of Medical Care in Diabetes – 2019. *Diabetes Care.* 2019;42(Suppl 1):S1-S193. http://care.diabetesjournals.org/content/42/Supplement_1. Accessed February 4, 2019.
- Anderson JH Jr, Brunelle RL, Koivisto VA, et al. Reduction of postprandial hyperglycemia and frequency of hypoglycemia in IDDM patients on insulin-analog treatment. Multicenter Insulin Lispro Study Group. *Diabetes*. 1997a;46(2):265-70.
- Anderson JH Jr, Brunelle RL, Koivisto VA, et al. Improved mealtime treatment of diabetes mellitus using an insulin analogue. Multicenter Insulin Lispro Study Group. *Clin Ther.* 1997b;19(1):62-72.
- Apidra [package insert], Bridgewater, NJ: Sanofi-Aventis U.S., LLC; December 2018.
- Aroda VR, Rosenstock J, Wysham C, et al. Efficacy and safety of LixiLan, a titratable fixed-ratio combination of insulin glargine plus lixisenatide in type 2 diabetes inadequately controlled on basal insulin and metformin: the LixiLan-L randomized trial. *Diabetes Care*. 2016;39(11):1972-1980.
- Bartley PC, Bogoev M, Larsen J, Philotheous A. Long-term efficacy and safety of insulin detemir compared to neutral protamine hagedorn insulin in patients with type 1 diabetes using a treat-to-target basal-bolus regimen with insulin aspart at meals: a 2-year, randomized, controlled trial. *Diabet Med.* 2008;25:442-9.
- Basaglar [package insert], Indianapolis, IN: Eli Lilly and Company; September 2018.
- Bazzano LA, Lee JL, Reynolds K, et al. Safety and efficacy of glargine compared to NPH insulin for the treatment of type 2 diabetes: a meta-analysis of randomized controlled trials. *Diabet Med.* 2008;25:924-32.
- Blevins TC, Dahl D, Rosenstock J, et al. Efficacy and safety of LY2963016 insulin glargine compared with insulin glargine (Lantus) in patients with type 1 diabetes in a randomized controlled trial: the ELEMENT 1 study. *Diabetes Obes Metab.* 2015;17(8):726-33.
- Bode BW, Buse JB, Fisher M, et al. Insulin degludec improves glycaemic control with lower nocturnal hypoglycaemia risk than insulin glargine in basal-bolus treatment with mealtime insulin aspart in Type 1 diabetes (BEGIN Basal-Bolus Type 1): 2-year results of a randomized clinical trial. *Diabet Med*. 2013;30(11):1293-97.
- Bode BW, McGill JB, Lorber DL, et al. Inhaled Technosphere Insulin compared with injected prandial insulin in type 1 diabetes: a randomized, 24-week trial. *Diabetes Care.* 2015;38(12):2266-73.
- Bolli GB, Riddle MC, Bergenstal RM, et al. New insulin glargine 300 U/ml compared with glargine 100 U/ml in insulin-naive people with type 2 diabetes on oral glucose-lowering drugs: a randomized controlled trial (EDITION 3). *Diabetes Obes Metab.* 2015;17:386-94.
- 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;40:951-7.
- 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 May;27(5):1023-7.
- Buse JB, Wolffenbuttel BHR, Herman WH, et al. DURAbility of basal vs lispro mix 75/25 insulin efficacy (DURABLE) trial 24-week results. *Diabetes Care*. 2009;32:1007-13.
- Buse JB, Vilsboll T, Thurman J, et al. Contribution of liraglutide in the fixed-ration combination of insulin degludec and liraglutide (IDegLira). *Diabetes Care.* 2014; 37(11):2926-33.
- Cai X, Gao X, Yang W, Ji L. Comparison between insulin degludec/liraglutide treatment and insulin glargine/lixisenatide treatment in type 2 diabetes: a systematic review and meta-analysis. *Expert Opin Pharmacother*. 2017 Dec;18(17):1789-1798.
- Centers for Disease Control and Prevention (CDC). National diabetes statistics report: estimates of diabetes and its burden in the United States, 2017. Atlanta, GA: U.S. Department of Health and Human Services; 2017. https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf. Accessed February 4, 2019.
- Chase HP, Arslanian S, White NH, et al. Insulin glargine vs intermediate-acting insulin at the basal component of multiple daily injection regimens for adolescents with type 1 diabetes. *J Pediatr.* 2008;153:547-53.
- Chen JW, Lauritzen T, Bojesen A, et al. Multiple mealtime administration of biphasic insulin aspart 30 vs traditional basal-bolus human insulin treatment in patients with type 1 diabetes. *Diabetes Obes Metab.* 2006 Nov;8(6):682-9.
- Chiang JL, Maahs DM, Garvey KC, et al. Type 1 diabetes in children and adolescents: a position statement by the American Diabetes Association. *Diabetes Care*. 2018;41(9):2026-2044. doi: 10.2337/dci18-0023.

- Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2019. http://www.clinicalpharmacology.com. Accessed February 4, 2019.
- Colquitt J, Royle P, Waugh N. Are analogue insulins better than soluble in continuous subcutaneous insulin infusion? Results of a meta-analysis. *Diabet Med*. 2003;20(10):863-6.
- Dailey G, Rosenstock J, Moses RG, et al. Insulin glulisine provides improved glycemic control in patients with type 2 diabetes. *Diabetes Care.* 2004;27(10):2363-8.
- Das SR, Everett BM, Birtcher KK, et al. 2018 ACC expert consensus decision pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes and atherosclerotic cardiovascular disease: a report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *J Am Coll Cardiol*. 2018;72(24):3200-3223. doi: 10.1016/j.jacc.2018.09.020.
- Davies MJ, D'Alessio DA, Fradkin J, et al. 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). *Diabetes Care*. 2018;41(12):2669-2701. doi: 10.2337/dci18-0033.
- Davies M, Gross J, Ono Y, et al. Efficacy and safety of insulin degludec given as part of basal-bolus treatment with mealtime insulin aspart in type 1 diabetes: A 26-week randomized, open-label, treat-to-target non-inferiority trial. *Diabetes Obes Metab.* 2014;16(10):922-30.
- 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;18:96-9.
- De Leeuw I, Vague P, Selam JL, et al. Insulin detemir used in basal-bolus therapy in people with type 1 diabetes is associated with a lower risk of nocturnal hypoglycemia and less weight gain over 12 months in comparison to NPH insulin. *Diabetes Obes Metab.* 2005;7(1):73-82.
- Derwahl KM, Bailey TS, Wernicke-Panten K, Ping L, Pierre S. Efficacy and safety of biosimilar SAR342434 insulin lispro in adults with type 2 diabetes, also using insulin glargine: SORELLA 2 study. *Diabetes Technol Ther*. 2018;20(2):160-70.
- Diamant M, Nauck MA, Shaginian R, et al. Glucagon-like peptide 1 receptor agonist or bolus insulin with optimized basal insulin in type 2 diabetes. *Diabetes Care.* 2014;37(10):2763-73.
- Diamant M, Van Gaal L, Stranks S, et al. Safety and efficacy of once-weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes over 84 weeks. *Diabetes Care.* 2012 Apr;35(4):683-9.
- Diez-Fernandez A, Cavero-Redondo I, Moreno-Fernandez J, et al. Effectiveness of insulin glargine U-300 versus insulin glargine U-100 on nocturnal hypoglycemia and glycemic control in type 1 and type 2 diabetes: a systematic review and meta-analysis. *Acta Diabetol*. 2018 Dec 3. [Epub ahead of print] doi: 10.1007/s00592-018-1258-0.
- Domeki N, Matsumura M, Monden T, et al. A randomized trial of step-up treatment with premixed insulin lispro 50/50 vs aspart 70/30 in patients with type 2 diabetes mellitus. *Diabetes Ther.* 2014;5:403-13.
- 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):702-7.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed February 4, 2019.
- Fairchild JM, Amber GR, Genoud-Lawton CH, et al. Insulin lispro vs regular insulin in children with type 1 diabetes on twice daily insulin. *Pediatr Diabetes*. 2000;1(3):135-41.
- FDA briefing document: Endocrinologic and Metabolic Drugs Advisory Committee Meeting - Soliqua/insulin glargine and lixisenatide. Food and Drug Administration Web site. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM502558.pdf. Accessed February 6, 2019.
- FDA summary review: Soliqua/insulin glargine and lixisenatide. Food and Drug Administration Web site. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/208673Orig1s000SumR.pdf. Accessed February 6, 2019.
- Food and Drug Administration. NDA 022472/S-017 Supplement Approval. April 24, 2018. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2018/022472Orig1s017ltr.pdf. Accessed February 6, 2019.
- Food and Drug Administration. NDA 208583/S-001. Supplement Approval. December 12, 2017. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2017/208583Orig1s001ltr.pdf. Accessed February 6, 2019.
- Fiasp [package insert]. Plainsboro, NJ: Novo Nordisk; September 2018.
- Fierce Biotech. FDA approves Basaglar, the first "follow-on" insulin glargine product to treat diabetes. December 16, 2015. https://www.fiercebiotech.com/biotech/fda-approves-basaglar-first-follow-on-insulin-glargine-product-to-treat-diabetes. Accessed February 6, 2019.
- Food and Drug Administration (FDA) Briefing Document. NDA 203313 and 203314: Insulin Degludec and Insulin Degludec/Aspart. Endocrinologic and Metabolic Drugs Advisory Committee Meeting. November 8, 2012.
- Food and Drug Administration news release. FDA approved Admelog, the first short-acting "follow-on" insulin product to treat diabetes. December 11, 2017. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm588466.htm. Accessed February 6, 2019.
- Freemantle N, Chou E, Frois C, et al. Safety and efficacy of insulin glargine 300 u/mL compared with other basal insulin therapies in patients with type 2 diabetes mellitus: a network meta-analysis. *BMJ Open.* 2016;6(2):e009421.
- Fritsche A, Schweitzer MA, Häring HU. Glimepiride combined with morning insulin glargine, bedtime neutral protamine Hagedorn insulin, or bedtime insulin glargine in patients with type 2 diabetes. *Ann Intern Med*. 2003;138(12):952-9.
- Fullerton B, Siebenhofer A, Jeitler K, et al. Short-acting insulin analogues versus regular human insulin for adults with type 1 diabetes mellitus. *Cochrane Database Syst Rev*. 2016 Jun 30;(6):CD012161. doi: 10.1002/14651858.CD012161.
- Fullerton B, Siebenhofer A, Jeitler K, et al. Short-acting insulin analogues versus regular human insulin for adult, non-pregnant persons with type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2018;12:CD013228. doi: 10.1002/14651858.CD013228.
- Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm – 2019 Executive Summary. *Endocr Pract.* 2019;25(1):69-100. https://www.aace.com/sites/all/files/CS-2018-0535.pdf. Accessed February 4, 2019.
- Garber AJ, Clauson P, Pedersen CB, et al. Lower risk of hypoglycemia with insulin detemir than with neutral protamine Hagedorn insulin in older persons with type 2 diabetes: a pooled analysis of phase III trials. *J Am Geriatr Soc*. 2007;55(11):1735-40.
- Garber AJ, King AB, Del Prato S, et al. Insulin degludec, an ultra-long acting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes (BEGIN Basal-Bolus Type 2): a phase 3, randomized, open-label, treat-to-target non-inferiority trial. *Lancet.* 2012;379(9825):1498-1507.

- Garg SK, Rosenstock J, Ways K. Optimized Basal-bolus insulin regimens in type 1 diabetes: insulin glulisine vs regular human insulin in combination with basal insulin glargine. *Endocr Pract.* 2005;11(1):11-7.
- Garg SK, Wernicke-Panten K, Rojeski M, Pierre S, Kirchhein Y, Jedynasty K. Efficacy and safety of biosimilar SAR342434 insulin lispro in adults with type 1 diabetes also using insulin glargine-SORELLA 1 study. *Diabetes Technol Ther.* 2017;19(9):516-26.
- Gerstein HC, Bosch J, Dagenais GR, et al; for the ORIGIN trial investigators. Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med.* 2012;367:319-28.
- Gough S, Bhargava A, Jain R, et al. Low-volume insulin degludec 200 units/ml once daily improves glycemic control similarly to insulin glargine with a low risk of hypoglycemia in insulin-naïve patients with type 2 diabetes: a 26-week, randomized, controlled, multinational, treat-to-target trial: the BEGIN LOW VOLUME trial. *Diabetes Care.* 2013;36(9):2536-42.
- 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.
- Handelsman Y, Bloomgarden Z, Grunberger G, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for developing a diabetes mellitus comprehensive care plan – 2015. *Endocr Pract*. 2015 Suppl 1:1-87. https://aace.com/files/dm-guidelines-ccp.pdf. Accessed February 6, 2019.
- Heller S, Buse J, Fischer M, et al. Insulin degludec, an ultra-long acting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN Basal-Bolus Type 1): a phase 3, randomized, open-label, treat-to-target, non-inferiority trial. *Lancet.* 2012;379(9825):1489-97.
- 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.
- 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):1269-74.
- Hermansen K, Fontaine P, Kukolja KK, et al. Insulin analogues (insulin detemir and insulin aspart) vs traditional human insulins (NPH insulin and regular human insulin) in basal-bolus therapy for patients with type 1 diabetes. *Diabetologia*. 2004;47(4):622-9.
- Hollander P, Cooper J, Bregnhøj J, et al. A 52-week, multinational, open-label, parallel-group, noninferiority, treat-to-target trial comparing insulin detemir with insulin glargine in a basal-bolus regimen with mealtime insulin aspart in patients with type 2 diabetes. *Clin Ther.* 2008;30(11):1976-87.
- Hollander P, King A, Del Prato S, et al. Insulin degludec improves long-term glycaemic control similarly to insulin glargine but with fewer hypoglycaemic episodes in patients with advanced type 2 diabetes on basal-bolus insulin therapy. *Diabetes Obes Metab.* 2015;17(2):202-6.
- Holmes RS, Crabtree E, McDonagh MS. Comparative effectiveness and harms of long-acting insulins for type 1 and type 2 diabetes: A systematic review and meta-analysis. *Diabetes Obes Metab*. 2018 Dec 15. [Epub ahead of print] doi: 10.1111/dom.13614.
- Home P, Bartley P, Russell-Jones D, et al. Insulin detemir offers improved glycemic control compared to NPH insulin in people with type 1 diabetes. *Diabetes Care*. 2004;27(5):1081-7.
- Home PD, Bergenstal RM, Bolli GB, et al. Glycaemic control and hypoglycaemia during 12 months of randomized treatment with insulin glargine 300 U/mL versus glargine 100 U/mL in people with type 1 diabetes (EDITION 4). *Diabetes Obes Metab*. 2018;20(1):121-128. doi: 10.1111/dom.13048.
- 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.
- Home PD, Hallgren P, Usadel KH, et al. Pre-meal insulin aspart compared to pre-meal soluble human insulin in type 1 diabetes. *Diabetes Clin Res Pract*. 2006;71(2):131-9.
- Horvath K, Jeitler K, Berghold A, et al. Long-acting insulin analogues vs NPH insulin (human isophane insulin) for type 2 diabetes mellitus. *Cochrane Database Sys Rev*. 2007 Apr 18;(2):CD005613.
- Humalog [package insert], Indianapolis, IN: Eli Lilly and Company; November 2018.
- Humalog Mix 50/50 [package insert], Indianapolis, IN: Eli Lilly and Company; September 2018.
- Humalog 75/25 [package insert], Indianapolis, IN: Eli Lilly and Company; September 2018.
- Humulin 70/30 [package insert], Indianapolis, IN: Eli Lilly and Company; November 2018.
- Humulin N [package insert], Indianapolis, IN: Eli Lilly and Company; November 2018.
- Humulin R [package insert], Indianapolis, IN: Eli Lilly and Company; May 2018.
- Humulin R U-500 [package insert], Indianapolis, IN: Eli Lilly and Company; November 2018.
- Inagaki N, Atsumi Y, Oura T, et al. Efficacy and safety profile of exenatide once weekly compared with insulin once daily in Japanese patients with type 2 diabetes treated with oral antidiabetes drug(s): results from a 26-week, randomized, open-label, parallel-group, multicenter, noninferiority study. *Clin Ther*. 2012;34(9):1892-908.
- Kølendorf K, Ross GP, Pavlic-Renar I, et al. Insulin detemir lowers the risk of hypoglycemia and provides more consistent plasma glucose levels compared to NPH insulin in Type 1 diabetes. *Diabet Med*. 2006;23(7):729-35.
- Lane W, Bailey TS, Gerety G, et al. Effect of insulin degludec vs insulin glargine U-100 on hypoglycemia in patients with type 1 diabetes: the SWITCH 1 randomized clinical trial. *JAMA*. 2017;318(1):33-44.
- Lantus [package insert], Bridgewater, NJ: Sanofi-Aventis; November 2018.
- Lee P, Chang A, Blaum C, et al. Comparison of safety and efficacy of insulin glargine and neutral protamine hagedorn insulin in older adults with type 2 diabetes mellitus: results from a pooled analysis. *J Am Geriatr Soc*. 2012;60(1):51-9
- Levemir [package insert], Plainsboro, NJ: Novo Nordisk, Inc.; January 2019.
- Lingvay I, Perez MF, Garcia-Hernandez P, et al. Effect of insulin glargine up titration vs insulin degludec/liraglutide on glycated hemoglobin levels in patients with uncontrolled type 2 diabetes: The DUAL V randomized clinical trial. *JAMA.* 2016;315(9):898-907.
- Linjawi S, Bode BW, Chaykin LB, et al. The efficacy of IDegLira (insulin degludec/liraglutide combination) in adults with type 2 diabetes inadequately controlled with a GLP-1 receptor agonist and oral therapy: DUAL III randomized clinical trial. *Diabetes Ther*. 2017;8(1):101-14.
- Mathieu C, Hollander P, Miranda-Palma B, et al. Efficacy and safety of insulin degludec in a flexible dosing regimen vs insulin glargine in patients with type 1 diabetes (BEGIN: Flex T1): a 26-week randomized, treat-to-target trial with a 26-week extension. *J Clin Endocrinol Metab.* 2013;98(3):1154-62.

- McSorley PT, Bell PM, Jacobsen LV, et al. Twice-daily biphasic insulin aspart 30 vs biphasic human insulin 30: a double-blind crossover study in adults with type 2 diabetes mellitus. *Clin Ther.* 2002 Apr;24(4):530-9.
- Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes (LEADER trial). *N Engl J Med.* 2016;375(4):311-322.
- Marso SP, McGuire DK, Zinman B, et al. Efficacy and safety of degludec versus glargine in type 2 diabetes. *N Engl J Med*. 2017 Jun 12. doi: 10.1056/NEJMoa1615692. [Epub ahead of print]
- Melo KFS, Bahia LR, Pasinato B, et al. Short-acting insulin analogues versus regular human insulin on postprandial glucose and hypoglycemia in type 1 diabetes mellitus: a systematic review and meta-analysis. *Diabetol Metab Syndr*. 2019;11:2. doi: 10.1186/s13098-018-0397-3.
- Meneghini L, Atkin S, Gough S, et al. The efficacy and safety of insulin degludec given in variable once-daily dosing intervals compared with insulin glargine and insulin degludec dosed at the same time daily. *Diabetes Care*. 2013[a];36(4):858-64.
- Meneghini L, Kesavadev J, Demissie M, et al. Once-daily initiation of basal insulin as add-on to metformin: a 26-week, randomized, treat-to-target trial comparing insulin detemir with insulin glargine in patients with type 2 diabetes. *Diabetes Obes Metab*. 2013[b]; 15(8): 729–36.
- Montañana CF, Herrero CH, Fernandez MR. Less weight gain and hypoglycemia with once-daily insulin detemir than NPH insulin in intensification of insulin therapy in overweight type 2 diabetes patients-the PREDICTIVE BMI clinical trial. *Diabet Med.* 2008;25:916-23.
- Mortensen H, Kocova M, Teng LY, et al. Biphasic insulin aspart vs human insulin in adolescents with type 1 diabetes on multiple daily insulin injections. *Pediatr Diabetes.* 2006;7(1):4-10.
- Novo Nordisk Briefing Document. Insulin Degludec and Insulin Degludec/Aspart: NDA 203313 and 203314. Endocrinologic and Metabolic Drugs Advisory Committee Meeting. November 8, 2012.
- Novo Nordisk press release (DEVOTE). Novo Nordisk has decided to resubmit the New Drug Applications of Tresiba and Ryzodeg in the US. March 26, 2015. https://www.novonordisk.com/media/news-details.1906649.html. Accessed February 6, 2019.
- Novo Nordisk press release. Novo Nordisk received FDA approve for Fiasp, a new fast-acting mealtime insulin. September 29, 2017. http://press.novonordisk-us.com/2017-09-29-Novo-Nordisk-Receives-FDA-Approval-for-Fiasp-R-a-New-Fast-Acting-Mealtime-Insulin. Accessed February 6, 2019.
- Novolin 70/30 [package insert], Princeton, NJ: Novo Nordisk Inc.; June 2018.
- Novolin N [package insert], Princeton, NJ: Novo Nordisk Inc.; June 2018.
- Novolin R [package insert], Princeton, NJ: Novo Nordisk Inc.; June 2018.
- Novolog [package insert], Princeton, NJ: Novo Nordisk Inc.; December 2018.
- Novolog Mix 70/30 [package insert], Princeton, NJ: Novo Nordisk Inc.; December 2018.
- Onishi Y, Iwamoto Y, Yoo S, et al. Insulin degludec compared with insulin glargine in insulin-naïve patients with type 2 diabetes: A 26-week, randomized, controlled, Pan-Asian, treat-to-target trial. *J Diabetes Investig*. 2013;4(6):605-12.
- Pan CY, Sinnassamy P, Chung KD, et al; LEAD Study Investigators Group. Insulin glargine vs NPH insulin therapy in Asian type 2 diabetes patients. *Diabetes Res Clin Pract.* 2007 Apr;76(1):111-8.
- Pfeffer MA, Claggett B, Diaz R, et al; ELIXA Investigators. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med.* 2015;373(23):2247-2257.
- 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):1569-81.
- Philis-Tsimikas A, Del Prato S, Satman I, et al. Effect of insulin degludec versus sitagliptin in patients with type 2 diabetes uncontrolled on oral antidiabetic agents. *Diabetes Obes Metab.* 2013;15(8):760-6.
- Philotheou A, Arslanian S, Blatniczky L, et al. Comparable efficacy and safety of insulin glulisine and insulin lispro when given as part of a Basal-bolus insulin regimen in a 26-week trial in pediatric patients with type 1 diabetes. *Diabetes Technol Ther.* 2011;13(3):327-34.
- 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 vs morning plus bedtime NPH insulin. *Diabet Med*. 2005;22(7):850-7.
- 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):635-42.
- Plank J, Siebenhofer A, Berghold A, et al. Systematic review and meta-analysis of short-acting insulin analogues in patients with diabetes mellitus. *Arch Intern Med.* 2005;165(12):1337-44.
- Pollom RK, Ilag LL, Lacaya LB, et al. Lilly insulin glargine versus Lantus® in insulin-naïve and insulin-treated adults with type 2 diabetes: a randomized, controlled trial (ELEMENT 5). *Diabetes Ther*. 2019;10(1):189-203. doi: 10.1007/s13300-018-0549-3.
- Powers AC, Niswender KD, Rickels MR. Diabetes mellitus: management and therapies. In: Jameson J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J, editors. *Harrison's Principles of Internal Medicine*. 20th edition. New York: McGraw-Hill; 2018.
- Raskin P, Gylvin T, Weng W, et al. Comparison of insulin detemir and insulin glargine using a basal-bolus regimen in a randomized, controlled clinical study in patients with type 2 diabetes. *Diabetes Metab Res Rev*. 2009;25(6):542-8.
- 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):583-8.
- Raslová K, Tamer SC, Clauson P, et al. Insulin detemir results in less weight gain than NPH insulin when used in basal-bolus therapy for type 2 diabetes mellitus, and this advantage increases with baseline body mass index. *Clin Drug Investig.* 2007;27(4):279-85.
- 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):639-43.
- Rayman G, Profozic V, Middle M. Insulin glulisine imparts effective glycemic control in patients with type 2 diabetes. *Diabetes Res Clin Pract*. 2007;76:304-12.
- REMS@FDA: Approved Risk Evaluation and Mitigation Strategies (REMS). FDA Web site. http://www.accessdata.fda.gov/scripts/cder/rems/. Accessed February 6, 2019.
- Riddle MC, Rosenstock J, Gerich J. 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):3080-6.

- Riddle MC, Rosenstock J, Vlajnic A, et al. Randomized, 1-year comparison of three ways to initiate and advance insulin for type 2 diabetes: twice-daily premixed insulin versus basal insulin with either basal-plus one prandial insulin or basal-bolus up to three prandial injections. *Diabetes Obes Metab.* 2014[a];16:396-402.
- Riddle MC, Bolli GB, Ziemen M, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using basal and mealtime insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 1). *Diabetes Care.* 2014[b];37:2755-62.
- 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.
- Robertson KJ, Schoenle E, Gucev Z, et al. Insulin detemir compared to NPH insulin in children and adolescents with type 1 diabetes. *Diabet Med.* 2007;24:27-34.
- Rodbard H, Cariou B, Zinman B, et al. Comparison of insulin degludec with insulin glargine in insulin-naïve subjects with Type 2 diabetes: A 2-year randomized, treat-to-target trial. *Diabetic Med.* 2013;30(11):1298-1304.
- Rodbard HW, Tripathy D, Vidrio Velazquez M, Demissie M, Tamer SC, Piletic M. Adding fast-acting insulin aspart to basal insulin significantly improved glycaemic control in patients with type 2 diabetes: a randomized, 18-week, open-label, phase 3 trial (onset 3). *Diabetes Obes Metab.* 2017;19:1389-96.
- Rosenstock J, Dailey G, Massi-Benedetti M, et al. Reduced hypoglycemia risk with insulin glargine: a meta-analysis comparing insulin glargine with human NPH insulin in type 2 diabetes. *Diabetes Care.* 2005;28(4):950-5.
- Rosenstock J, Davies M, Home PD, et al. A randomized, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes. *Diabetologia.* 2008;51:408-16.
- Rosenstock J, Fonsecca VA, Gross JL, et al. Advancing basal insulin replacement in type 2 diabetes inadequately controlled with insulin glargine plus oral agents: a comparison of adding albiglutide, a weekly GLP-1 receptor agonist, versus thrice-daily prandial insulin lispro. *Diabetes Care.* 2014; 37:2317-2325.
- Rosenstock J, Franco D, Korpachev V, et al. Inhaled technosphere insulin versus inhaled technosphere placebo in insulin-naïve subjects with type 2 diabetes inadequately controlled on oral antidiabetes agents. *Diabetes Care.* 2015[a];38(12):2274-81.
- Rosenstock J, Hollander P, Bhargava A, et al. Similar efficacy and safety of LY2963016 insulin glargine and insulin glargine (Lantus®) in patients with type 2 diabetes who were insulin-naïve or previously treated with insulin glargine: a randomized, double-blind controlled trial (the ELEMENT 2 study). *Diabetes Obes Metab.* 2015[b];17(8):734-41.
- Rosenstock J, Aronson R, Grunberger G, et al. Benefits of LixiLan, a titratable fixed-ratio combination of insulin glargine plus lixisenatide, versus insulin glargine and lixisenatide monocomponents in type 2 diabetes inadequately controlled on oral agents: The LixiLan-O randomized trial. *Diabetes Care*. 2016;39(11):2026-2035.
- 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;40:943-50.
- 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 1 diabetes mellitus using a basal-bolus regimen. *Clin Ther*. 2004;26(5):724-36.
- Siegmund T, Weber S, Blankenfeld H, et al. Comparison of insulin glargine vs NPH insulin in people with type 2 diabetes mellitus under outpatient-clinic conditions for 18 months using a basal-bolus regimen with a rapid-acting insulin analogue as mealtime insulin. *Exp Clin Endocrinol Diabetes.* 2007;115(6):349-53.
- Soliqua [package insert], Bridgewater, NJ: Lilly Sanofi-Aventis US, LLC; February 2019.
- Standl E, Lang H, Roberts A. The 12-month efficacy and safety of insulin detemir and NPH insulin in basal-bolus therapy for the treatment of type 1 diabetes. *Diabetes Technol Ther*. 2004;6(5):579-88.
- Swinnen SG, Dain MP, 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 insulin detemir twice-daily in patients with type 2 diabetes inadequately controlled on oral glucose-lowering drugs. *Diabetes Care*. 2010;33:1176-78.
- Swinnen SG, Simon AC, Holleman F, et al. Insulin detemir versus insulin glargine for type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2011;(7):CD006383.
- Tan CY, Wilson DM, Buckingham B. Initiation of insulin glargine in children and adolescents with type 1 diabetes. *Pediatr Diabetes.* 2004 Jun;5(2):80-6.
- The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med.* 1993;329(14):977-86.
- Tieu C, Lucas EJ, DePaola M, Rosman L, Alexander GC. Efficacy and safety of biosimilar insulins compared to their reference products: A systematic review. *PLoS One*. 2018;13(4):e0195012. doi: 10.1371/journal.pone.0195012.
- Toujeo [package insert], Bridgewater, NJ: Sanofi-Aventis; October 2018.
- Tresiba [package insert], Princeton, NJ: Novo Nordisk, Inc.; November 2018.
- Tricco AC, Ashoor H, Antony J, et al. Safety, effectiveness, and cost effectiveness of long acting versus intermediate acting insulin for patients with type 1 diabetes: systematic review and network meta-analysis. *BMJ*. 2014 Oct 1 [Epub]. doi: 10.1136/bmj.g5459.
- UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared to conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet.* 1998;352(9131):837-53.
- 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):590-6.
- Van Ban AC, Bode BW, Sert-Langeron C, et al. Insulin glulisine compared to insulin aspart and to insulin lispro administered by continuous subcutaneous insulin infusion in patients with type 1 diabetes: a randomized controlled trial. *Diabetes Technol Ther.* 2011;13(6):607-14.
- Vignati L, Anderson JH Jr, Iversen PW. Efficacy of insulin lispro in combination with NPH human insulin twice per day in patients with insulin-dependent or non-insulin-dependent diabetes mellitus. Multicenter Insulin Lispro Study Group. *Clin Ther.* 1997;19(6):1408-21.
- Weissman PN, Carr MC, Ye J, et al. HARMONY 4: randomized clinical trial comparing once-weekly albiglutide and insulin glargine in patients with type 2 diabetes inadequately controlled with metformin with or without sulfonylurea. *Diabetologia*. 2014 Dec;57(12):2475-84. doi: 10.1007/s00125-014-3360-3. Epub 2014 Sep 11.

- Wysham C, Bhargava A, Chaykin L, et al. Effect of insulin degludec vs insulin glargine U-100 on hypoglycemia in patients with type 2 diabetes: the SWITCH 2 randomized clinical trial. *JAMA*. 2017;318(1):45-56.
- Xultophy [dossier], Plainsboro, NJ: Novo Nordisk, Inc.; 2016.
- Xultophy [package insert], Plainsboro, NJ: Novo Nordisk, Inc.; February 2019.
- Yenigun M, Honka M. Switching patients from insulin glargine-based basal bolus regiments to a once daily insulin detemir-based basal-bolus regimen: results from a subgroup of the PREDICTIVE study. *Int J Clin Pract.* 2009 Mar;63(3):425-32.
- Yki-Järvinen H, Dressler A, Ziemen M. Less nocturnal hypoglycemia and better post-dinner glucose control with bedtime insulin glargine compared to bedtime NPH insulin during insulin combination therapy in type 2 diabetes. *Diabetes Care.* 2000;23(8):1130-6.
- Yki-Järvinen H, Kauppinen-Mäkelin RK, Tiikkainen M, et al. Insulin glargine or NPH combined with metformin in type 2 diabetes: the LANMET study. *Diabetologia*. 2006;49(3):442-51.
- Yki-Järvinen H, Bergenstal R, Ziemen M, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using oral agents and basal insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 2). *Diabetes Care*. 2014;37:3235-43.
- 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.
- Zinman B, Philis-Tsimikas A, Cariou B, et al. Insulin degludec versus insulin glargine in insulin-naïve patients with type 2 diabetes: a 1-year, randomized, treat-to-target trial (BEGIN Once Long). *Diabetes Care*. 2012;35(12):2464-71.

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