



# Hypoglycemics, Insulins

## Therapeutic Class Review (TCR)

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## FDA-APPROVED INDICATIONS<sup>1,2,3,4,5,6,7,8,9,10,11,12</sup>

Drug	Types Available	Manufacturer	Indication(s)
human insulin (Humulin <sup>®</sup> )	R, N, 70/30	Lilly	For the treatment of patients with diabetes mellitus for the control of hyperglycemia
human insulin (Novolin <sup>®</sup> )	R, N, 70/30	Novo Nordisk	
<b>Rapid-Acting Insulins</b>			
human insulin inhalation powder (Afrezza <sup>®</sup> )	--	Sanofi-Aventis	To improve glycemic control in adults with type 1 or type 2 diabetes mellitus
insulin aspart (Novolog <sup>®</sup> )	--	Novo Nordisk	To improve glycemic control in adults and children with diabetes mellitus
insulin glulisine (Apidra <sup>™</sup> )	--	Sanofi-Aventis	To improve glycemic control in adults and children with diabetes mellitus
insulin lispro (Humalog <sup>®</sup> )	--	Lilly	For the treatment of patients with diabetes mellitus for the control of hyperglycemia
<b>Long-Acting Insulins</b>			
insulin detemir (Levemir <sup>®</sup> )	--	Novo Nordisk	For once or twice daily subcutaneous administration for the treatment of adult and pediatric patients with type 1 diabetes mellitus or adult patients with type 2 diabetes mellitus who require basal insulin for the control of hyperglycemia
insulin glargine (Lantus <sup>®</sup> )	--	Sanofi-Aventis	To improve glycemic control in adults and children with type 1 diabetes mellitus and adults with 2 diabetes mellitus
insulin glargine (Toujeo <sup>®</sup> )	--	Sanofi-Aventis	To improve glycemic control in adults with diabetes mellitus
<b>Rapid / Intermediate-Acting Combination Insulins</b>			
insulin aspart (Novolog <sup>®</sup> Mix)	70/30	Novo Nordisk	To improve glycemic control in patients with diabetes mellitus
insulin lispro (Humalog <sup>®</sup> Mix)	50/50, 75/25	Lilly	For the treatment of patients with diabetes mellitus for the control of hyperglycemia

insulin detemir (Levemir), insulin glargine (Lantus, Toujeo) and insulin inhalation powder (Afrezza) are not recommended for treating diabetic ketoacidosis.

Use of insulin detemir with liraglutide (Victoza<sup>®</sup>) has been shown to be effective in clinical studies.

## OVERVIEW

It is estimated that 30 million Americans have diabetes mellitus (DM).<sup>13</sup> Diabetes results in a significant economic burden to society in terms of both direct and indirect costs. Diabetes is also responsible for increased morbidity and mortality. Adequate glycemic control is crucial to minimize chronic microvascular (e.g., blindness, renal dysfunction) and macrovascular (e.g., cardiovascular disease) complications.<sup>14</sup>

Exogenous insulin supplements deficient levels of endogenous insulin, and temporarily restores the ability of the body to properly utilize carbohydrates, fats, and proteins. Multiple insulin products are

available and are used as replacement therapy in the management of both type 1 diabetes and of type 2 diabetes when glycemic goals are not met with oral antidiabetic agents.

The American Diabetes Association (ADA) 2015 Standards of Medical Care in Diabetes advises that a reasonable HbA1C goal for nonpregnant adults is less than 7 percent; however more stringent HbA1c goals (less than 6.5 percent) for selected patients (e.g. those with short duration of diabetes, long life expectancy, and no significant CVD) may be considered if this can be achieved without significant hypoglycemia.<sup>15</sup> Less-stringent HbA1C goals (less than 8 percent) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain. For pediatric patients, the ADA now recommends a target HbA1c of less than 7 percent for all age groups. The ADA also supports that glycemic goals should be tailored to individual patient needs. Antidiabetic therapy for type 2 diabetes should generally start with metformin, unless contraindicated. If monotherapy at maximum tolerated dose does not achieve or maintain the HbA1c target over three months, a second oral agent, a glucagon-like peptide-1 (GLP-1) receptor agonist, or insulin should be added. Insulin monotherapy or in combination with other medications may be required to maintain glycemic control. In newly diagnosed type 2 diabetic patients with markedly symptomatic and/or elevated blood glucose levels or HbA1c, consider insulin therapy, with or without additional agents, from the outset.

In 2013, as replacement to the 2009 AACE/ACE diabetes algorithm for glycemic control, the American Academy of Clinical Endocrinologists (AACE) released an algorithm and consensus statement for type 2 diabetes treatment with a goal HbA1c less than or equal to 6.5 percent for healthy patients with low hypoglycemic risk.<sup>16</sup> For patients with concurrent illness and who are at risk of hypoglycemia goal HbA1c of greater than 6.5 percent is appropriate. AACE suggests patients with an HbA1c less than 7.5 percent start with monotherapy, usually with metformin; whereas, patients with an HbA1c at least 7.5 percent begin with dual therapy. Patients with an HbA1c greater than 9 percent and no symptoms may start either dual or triple antihyperglycemic therapy; patients with an HbA1c greater than 9 percent with symptoms should begin insulin therapy with or without other agents. The HbA1c should be reassessed every three months and failure to improve may warrant additional complementary therapy for optimal glycemic control.

According to the American Association of Clinical Endocrinologists (AACE) insulin is required in all patients with type 1 diabetes.<sup>17</sup> AACE also advises that insulin therapy should be considered for patients with type 2 diabetes, when HbA1c greater than 8 percent, or therapy with two or more oral antidiabetic agents or GLP-1 therapy fails to achieve target glycemic control, or in patients with long-standing type 2 diabetes and are unlikely to achieve their HbA1c goals.<sup>18</sup> When insulin therapy is indicated in patients with type 2 diabetes, therapy with long-acting basal insulin analogs (glargine and detemir) should be the initial choice in most cases; insulin analogues glargine and detemir are preferred over intermediate-acting neutral protamine Hagedorn (NPH) because basal insulin analogues provide a relatively flat serum insulin level and are associated with less hypoglycemia. Rapid-acting insulin analogs are preferred over regular insulin because they are more predictable. Premixed insulin analogue therapy, which contains rapid- and long-acting components in the same vial or pen, may be appropriate for patients in whom adherence to a drug regimen is problematic; although, these preparations lack component dosage flexibility and may increase the risk for hypoglycemia compared with basal insulin or basal-bolus insulin. Basal-bolus insulin therapy is flexible and is recommended for intensive insulin therapy.

Injectable insulins can be administered subcutaneously, obtained from an insulin cartridge, vial or insulin pen device, to deliver multiple doses to a single patient. In March 2009, the Food and Drug Administration (FDA) published an alert to healthcare professionals and patients to remind that insulin pens and insulin cartridges should not be used to give medication to multiple patients. Sharing insulin pens could result in the transmission of human immunodeficiency virus (HIV), the hepatitis viruses, and other blood-borne diseases. All insulin pens are approved only for single-patient use.<sup>19</sup> The FDA requires that a “single patient use only” warning be affixed to insulin pens and the pen cartons and additional warnings against the sharing of multidose pens be added to the prescribing information and the patient Medication Guides for products with multidose pen devices.<sup>20</sup>

It was estimated in 2005 that in the U.S. 20 to 30 percent of patients with type 1 diabetes and less than one percent of those with type 2 diabetes receive insulin therapy via an external insulin pump.<sup>21</sup> These patients require intensive management with at least four insulin injections and four self-monitoring blood glucose measurements each day. The rapid-acting insulins, insulin aspart (Novolog), insulin glulisine (Apidra) and insulin lispro (Humalog) are approved for use with insulin pumps.

In 2014, the FDA approved insulin inhalation powder (Afrezza) for mealtime use in patients with types 1 and 2 diabetes mellitus. The inhaled dosage form may be an option for patients that have barriers to injectable administration, such as visual impairment or neuropathy. A previously approved inhaled insulin product, Exubera®, was withdrawn from the market shortly after its market launch due to lower than expected utilization. Insulin inhalation powder is not included in practice guidelines at this time.

## PHARMACOLOGY<sup>22</sup>

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

## PHARMACOKINETICS

### Comparison of Insulin Products

Type of Insulin	Drug	Composition of Insulin	Onset (hrs)	Peak (hrs)	Duration (hrs)	Compatibility for Mixing
Short-acting	Human insulin regular (Humulin R, Novolin R) <sup>23,24,25</sup>	Crystalline regular insulin is prepared by precipitation in the presence of zinc chloride at a neutral pH.	0.5	2.5-5	8	NPH
Rapid-acting	human insulin (Afrezza®) <sup>26,27</sup>	Consists of Technosphere® particles that contain human insulin inhalation powder and an inert excipient, fumaryl diketopiperazine (FDKP).	More rapid than regular insulin and insulin lispro	0.2-0.25	2.5-3	-
	insulin aspart (Novolog) <sup>28,29</sup>	Consists of human insulin aspart in a clear aqueous solution. Created when the amino acid proline is substituted with aspartic acid at position B28.	.25	0.75-1.5	3-5	NPH
	insulin glulisine (Apidra) <sup>30, 31</sup>	Created when the amino acid asparagine at position B3 is replaced by lysine and the lysine at position B29 is replaced by glutamic acid.	0.33	0.92	5.3	NPH
	insulin lispro (Humalog) <sup>32, 33</sup>	Consists of zinc-insulin lispro crystals dissolved in clear aqueous fluid. Created when the amino acids at positions 28 and 29 on the insulin B-chain are reversed.	More rapid than regular insulin	0.5-1.5	3-4	NPH
Rapid/Intermediate-acting combination products	insulin aspart (Novolog Mix) <sup>34</sup>	Suspension containing insulin aspart protamine crystals and soluble insulin aspart.	0.17-0.33	1.6-3.2	Up to 24 hours	None
	insulin lispro (Humalog Mix) <sup>35,36</sup>	Suspension containing insulin lispro protamine suspension and insulin lispro solution.	More rapid than regular insulin	0.8-6.5	Similar to corresponding Humulin mixes	None
Intermediate-acting	human insulin NPH (Humulin N, Novolin N) <sup>37,38,39</sup>	Isophane (NPH) is modified, crystalline protamine zinc insulin. Its effects are comparable to a mixture of 2:1 to 3:1 regular insulin and protamine zinc insulin.	1-1.5	4-12	Up to 24	Regular, aspart, lispro, and glulisine

**Comparison of Insulin Products (continued)**

Type of Insulin	Drug	Composition of Insulin	Onset (hrs)	Peak (hrs)	Duration (hrs)	Compatibility for Mixing
Intermediate-acting	human insulin NPH (Humulin N, Novolin N) <sup>40,41,42</sup>	Isophane (NPH) is modified, crystalline protamine zinc insulin. Its effects are comparable to a mixture of 2:1 to 3:1 regular insulin and protamine zinc insulin.	1-1.5	4-12	Up to 24	Regular, aspart, lispro, and glulisine
Long-acting	insulin detemir (Levemir) <sup>43,44</sup>	Created when the amino acid threonine in position B30 is omitted and a C14 fatty acid chain is added to amino acid B29	0.8-2	6-8	5.7-23.2	None
	insulin glargine (Lantus) <sup>45</sup>	Created when the amino acids at position A21 of human insulin are replaced by glycine and two arginines are added to the C terminus of the B chain.	1.5	5 (no actual peak as insulin glargine is released slowly over 24 hours)	Up to 24 (only studied up to 24 hrs)	None
	insulin glargine (Toujeo) <sup>46</sup>		6	12-16	nr	

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

**CONTRAINDICATIONS/WARNINGS<sup>47,48,49,50,51,52,53,54,55,56,57,58</sup>**

Insulin therapy is contraindicated during episodes of hypoglycemia.

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

Insulin inhalation powder (Afrezza) must be used with a long-acting insulin in patients with T1DM and should not be used in patients who smoke or who have recently stopped smoking (less than six months ago), as safety and efficacy have not been established in this population.

Insulin inhalation powder is contraindicated in patients with chronic lung disease, such as asthma or chronic obstructive pulmonary disease (COPD), since acute bronchospasm has been experienced in these patients. Prior to initiating therapy, all patients should be evaluated for potential lung disease, including detailed medical history, physical examination, and spirometry. Insulin inhalation powder is also contraindicated in patients with a hypersensitivity to regular human insulin.

In long-term (up to two years) clinical studies, patients without chronic lung disease experienced a small decline (40 mL) in lung function as measured by forced expiratory volume in one second (FEV<sub>1</sub>). This decline was observed within the first three months of therapy and persisted throughout the studies. Impact of treatment longer than two years and reversal of impairment after discontinuation has not been assessed. Pulmonary function should be monitored at baseline, after six months of therapy, and annually in all patients; more frequently monitoring is needed in those with symptoms

such as wheezing, bronchospasm, cough, or difficulty breathing. Alternative therapy should be considered in patients who experience a decline of at least 20 percent in FEV<sub>1</sub> from baseline.

In clinical trials, the incidence of lung cancer was reported in patients treated with Technosphere insulin inhalation powder (0.8 cases per 1,000 patient-years) and did not exceed the rate that is expected in individuals with diabetes (one to two cases per 1,000 patient-years). Caution should be used in patients with current or previous lung cancer or who are at increased risk for lung cancer.

In clinical trials with type 1 diabetes patients, more patients using insulin inhalation powder experienced diabetic ketoacidosis (DKA) than those receiving comparators (0.43 versus 0.14 percent, respectively). In patients at risk for DKA, such as those with an acute illness or infection, carefully monitor blood glucose and switch to an alternate route of administration if necessary.

## Precautions

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

Insulin aspart (Novolog), insulin detemir (Levemir), insulin glulisine (Apidra), insulin glargine (Lantus, Toujeo), and insulin lispro (Humalog) contain cresol that has been reported to cause localized reactions and generalized myalgias. Insulin aspart contains approximately half the amount of metacresol that insulin lispro and insulin glulisine contain.

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

Alkaline phosphatase elevations have been reported with human insulin aspart.

All insulins may require a dose adjustment for patients with renal or hepatic impairment.

The full glucose lowering effect of insulin glargine 300 U/mL (Toujeo) may not be seen for at least five days, which should be considered prior to stopping intravenous insulin therapy in patients with type 1 diabetes.

In February 2015, the FDA began requiring labels of insulin pens and pens for other injectable diabetes medicines to include a warning against the sharing of these products among patients, even if the needle is changed.<sup>59</sup> The devices and packaging will also contain the warning “for single patient use only.” This change was made in an effort to reduce the spread of serious infections, such as the human immunodeficiency virus (HIV) and hepatitis viruses, since blood may be present in the pen after use.

## ***Risk Evaluation and Mitigation Strategies (REMS)***

Insulin inhalation powder (Afrezza) is subject to a REMS program to inform prescribers and patients of its contraindication of use in patients with chronic lung disease, such as asthma and COPD, due to the increased risk of acute bronchospasm and of the need to evaluate patients for lung disease before starting therapy.<sup>60</sup>

## **DRUG INTERACTIONS**<sup>61,62,63,64,65,66,67,68,69,70,71,72</sup>

Beta-blockers and clonidine are commonly used drugs that may mask the signs and symptoms of hypoglycemia.

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

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

Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood glucose-lowering effect of insulin. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.

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

## **ADVERSE EFFECTS**<sup>73,74,75,76,77,78,79,80,81,82,83,84</sup>

The most common adverse effect of all insulin products is hypoglycemia.

Glucose monitoring is recommended in all diabetic patients. Injection site reactions can occur with any type of injectable insulin. Other possible adverse effects of the injectable insulins include lipodystrophy, pruritus, and rash.

In clinical trials, insulin glargine (Lantus) had treatment-emergent injection site pain in 2.7 percent of patients versus 0.7 percent of patients on NPH insulin. Treatment discontinuation was not required. Insulin detemir (Levemir) was associated with more frequent mild injection site reactions than with insulin NPH.

Use of Insulin inhalation powder (Afrezza) is associated with cough (26.9 percent) and throat pain or irritation (4.8 percent). Coughing usually occurred within ten minutes, was generally mild, dry, intermittent, and tended to decrease over time.

Clinical trials in patients with type 1 diabetes, noted modest weight loss with insulin inhalation powder in contrast to weight gain with comparator insulin. In insulin-using type 2 diabetic patients, insulin inhalation powder was associated with a more modest weight gain than comparator over the 52-week trial duration.

Increases in anti-insulin antibodies have been reported more frequently with insulin inhalation powder use as compared to SC administered mealtime insulins; however, this was not associated with reduced efficacy.

Adverse effects data are obtained from prescribing information and therefore, should not be considered comparative or all-inclusive.

## SPECIAL POPULATIONS<sup>85,86,87,88,89,90,91,92,93,94,95,96</sup>

### Pediatrics

Safety and efficacy of insulin inhalation powder (Afrezza) and insulin glargine 300 u/mL (Toujeo) have not been established in pediatric patients.

Insulin lispro (Humalog) is approved to use in a continuous insulin infusion pump in the pediatric population.

In 2013, the American Academy of Pediatrics (AAP) issued new guidance for the management of newly diagnosed type 2 diabetes mellitus in children and adolescents.<sup>97</sup> They advise clinicians to initiate insulin therapy in children and adolescents with type 2 diabetes who are ketotic or in diabetic ketoacidosis, in patients whom the distinction between types 1 and 2 diabetes mellitus is unclear, and for any patient with a blood glucose level at least 250 mg/dL or HbA1c greater than 9 percent. The AAP suggests that clinicians monitor HbA1c concentrations every three months and intensify treatment if blood glucose and HbA1c goals are not being met.

Human insulin (Humulin, Novolin) products have been used in all age groups. Human insulin lispro (Humalog) can be used in children more than three years of age and older. Human insulin aspart (Novolog) can be given to pediatric patients two years of age and older. Insulin glulisine (Apidra) is approved for use in pediatric patients with type 1 diabetes from four to 17 years of age. The safety and efficacy of insulin NPH combinations with insulin aspart and insulin lispro in children have not been evaluated by the FDA, and little data exist. Insulin glargine 100 U/mL (Lantus) is approved for use in type 1 diabetic children from six to 15 years of age; insulin detemir (Levemir) has not been studied in children with type 1 diabetes less than two years of age. In general, intermediate and long-acting insulins can have slightly higher area-under-the-curves and maximum concentrations in children.

In one multicenter, open-label, randomized, six-month study, 349 type 1 diabetes mellitus patients ages five to 16 years received insulin glargine 100 U/mL once daily or NPH insulin either once or twice daily.<sup>98</sup> There was no difference between insulin glargine and NPH insulin in the primary efficacy measure of change in HbA1c from baseline to endpoint. Fasting blood glucose (FBG) levels decreased significantly more in the insulin glargine group (-1.29 mmol/L) than in the NPH insulin group (-0.68 mmol/L,  $p=0.02$ ). The percentage of patients that reported at least one symptomatic hypoglycemic episode was similar between groups; however, fewer patients in the insulin glargine group reported severe hypoglycemia (23 versus 29 percent, respectively) and severe nocturnal hypoglycemia (13 versus 18 percent, respectively), although these differences were not statistically significant. Fewer serious adverse events occurred in the insulin glargine group than in the NPH insulin group ( $p<0.02$ ).

The clinical efficacy and safety of two treatment regimens, biphasic insulin aspart at all three meals plus NPH insulin at bedtime versus premixed human insulin at breakfast and regular insulin at lunch and dinner plus NPH at bedtime, were compared in 167 adolescents with type 1 diabetes.<sup>99</sup> This open-label, parallel-group trial reported that after four months on biphasic insulin aspart therapy, HbA1c was not significantly different from that with human insulin (9.39 versus 9.30 percent, respectively). The body mass index increased in both groups, but significantly ( $p=0.005$ ) less in the biphasic insulin aspart group. No significant group differences were found for the rate of hypoglycemic episodes.

In a 26-week, open-label, randomized, parallel-group study, 347 children with type 1 diabetes, aged six to 17 years, received insulin detemir or NPH insulin once or twice daily plus insulin aspart before

meals.<sup>100</sup> The mean HbA1c decreased by approximately 0.8 percent with both treatments. Within-subject variation in self-measured fasting plasma glucose was significantly lower with insulin detemir than with NPH insulin ( $p < 0.001$ ), as was mean fasting plasma glucose (8.4 versus 9.6 mmol/L,  $p = 0.022$ ). The risk of nocturnal hypoglycemia was 26 percent lower with insulin detemir ( $p = 0.041$ ).

A one-year open-labeled, parallel group trial compared insulin detemir with NPH insulin, in combination with mealtime insulin aspart in 348 patients aged two to 16 years with type 1 diabetes mellitus.<sup>101,102</sup> Randomization was stratified by age (two to five years,  $n = 82$ ; six to 16 years,  $n = 265$ ). Mean HbA1c was similar between groups at baseline (8.2 versus 8.1 percent), and changed little over one year (8.1 versus 8.3 percent). Fasting plasma glucose (FPG) was similar at baseline (8.44 versus 8.56 mmol/L) and decreased during the study (-1.0 versus -0.45 mmol/L). A lower rate of hypoglycemia was observed with insulin detemir compared with NPH (24-h; 50.6 versus 78.3 episodes per patient-year; nocturnal hypoglycemia, eight versus 17.4 episodes per patient-year). No severe hypoglycemic episodes occurred with insulin detemir, while three subjects reported six episodes with NPH.

In an effort to compare the safety and efficacy of insulin glulisine to that of insulin lispro in children and adolescents with type 1 diabetes, 572 patients aged four years and older were randomized to receive either insulin glulisine or insulin lispro, administered subcutaneously within 15 minutes before a meal, in an open-label, active-controlled, non-inferiority trial.<sup>103</sup> During this 26-week study, patients also received insulin glargine 100 U/mL (administered once daily in the evening) or NPH insulin (administered once in the morning and once in the evening). There were no significant differences observed between the two treatment groups with respect to glycemic control.

## Pregnancy

The human insulins, insulin aspart, insulin detemir, and insulin lispro are Pregnancy Category B. Insulin glargine 100 U/mL (Lantus), insulin glulisine, and insulin inhalation powder are Pregnancy Category C. There are no clinical studies of the use of insulin glargine 300 U/mL (Toujeo) in pregnant women.

In 2012, the pregnancy category for insulin detemir was modified from C to B. In an open-label study 310 women with type 1 diabetes who were pregnant or intended to become pregnant were randomized to insulin detemir (once or twice daily) or NPH insulin (one to three times daily). Insulin aspart was administered before each meal. Mean HbA1c was less than 7 percent at 10, 12, and 24 weeks of gestation in both arms. In the intent-to-treat population, the adjusted mean HbA1c at gestational week 36 was similar in each arm. There were no differences in pregnancy outcomes or the health of the fetus and newborn between the groups.

The ADA 2015 Standards of Medical Care in Diabetes states because there is an increase in red blood cell turnover during pregnancy, HbA1c levels decrease during pregnancy.<sup>104</sup> In addition, HbA1c may not fully reflect glycemic parameters during pregnancy since it represents an average; therefore, HbA1c should be used as a secondary measure, next to self-monitoring of blood glucose. The recommended HbA1c target during pregnancy is less than 6 percent if this can be achieved without hypoglycemia. Due to the altered red blood cell kinetics during pregnancy, more frequent (e.g., monthly) monitoring of HbA1c levels should be considered.

According to AACE, the preferred treatment for postprandial hyperglycemia in pregnant women is regular or rapid-acting insulin analogues.<sup>105</sup> Basal insulin can be controlled with the use of rapid-acting insulin via infusion pump or long-acting insulin.

In 322 pregnant women with type 1 diabetes, meal-time regular insulin (given 30 minutes before the meal) or insulin aspart (given immediately before the meal) was administered in an open-label, parallel-group, multicenter study.<sup>106</sup> Patients had HbA1c equal to 8 percent or less at confirmation of pregnancy, and insulin doses were titrated toward predefined glucose targets and HbA1c less than 6.5 percent. Major hypoglycemia occurred at a rate of 1.4 versus 2.1 episodes per year-exposure with insulin aspart and regular insulin, respectively (relative risk 0.72 [95% CI, 0.36 to 1.46]). The risk of major nocturnal hypoglycemia was 52 percent (RR 0.48 [0.20 to -1.143]) lower with insulin aspart compared with regular insulin. The HbA1c for insulin aspart patients was comparable with human insulin in second and third trimesters, and a total of 80 percent of subjects achieved HbA1c of 6.5 percent or less. Maternal safety profiles and pregnancy outcomes were similar between treatments.

## Renal impairment

Renally impaired patients are subject to increased levels of circulating insulin. Dose adjustments may be warranted in this patient population.

## Hepatic impairment

Dose adjustments may be needed in patients with hepatic impairment.

## Other

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

## DOSAGES<sup>107,108,109,110,111,112,113,114,115,116,117,118</sup>

Drug	Dosing	Time of administration related to mealtime	Availability
human insulin (Humulin, Novolin)	Dosing should be titrated to glycemic control in combination with an intermediate or long acting insulin (and/or with oral antidiabetic agents for type 2 diabetics)	30-60 minutes prior to meal	10 mL vials (Humulin N 100, Humulin R 100; Novolin N 100, Novolin R 100) 20 mL vials (Humulin 500) 3 mL prefilled pen (Humulin N 100, 70/30) 3 mL prefilled Kwikpen (Humulin 70/30, Humulin N 100)
human insulin inhalation powder (Afrezza)	Dosing should be titrated to glycemic control in combination with a long acting insulin.	At the beginning of the meal	Cartridge: 4 and 8 Units
insulin aspart (Novolog)	Dosing should be titrated to glycemic control in combination with an intermediate or long acting insulin (and/or with oral antidiabetic agents for type 2 diabetics)	5-10 minutes before eating	10 mL vial, 3 mL prefilled FlexPen 3 mL cartridge (Novolog 100)
insulin glulisine (Apidra)		Within 15 minutes before a meal or within 20 minutes after starting a meal	10 mL vial, 3 mL prefilled SoloStar pen
insulin lispro (Humalog)		No more than 15 minutes before a meal or immediately after a meal	10 mL vial, 3 mL vial, 3 mL cartridge, 3 mL prefilled KwikPen

**Dosages continued**

Drug	Dosing	Time of administration related to mealtime	Availability
insulin aspart/ protamine aspart (Novolog Mix 70/30)	Dosing should be titrated to glycemic control	Typically dosed on a twice-daily basis (breakfast and dinner) Type 1 diabetes: within 15 minutes before meal initiation Type 2 diabetes: within 15 minutes before or after meal initiation	10 mL vial, 3 mL prefilled FlexPen
insulin lispro/ protamine lispro (Humalog Mix 75/25, Humalog Mix 50/50)		Within 15 minutes before meal initiation or immediately after a meal	10 mL vial, 3 mL prefilled KwikPen
insulin detemir (Levemir)	0.1-0.2 units/kg once daily or 10 units once or twice daily	Once daily (with the evening meal or at bedtime) or twice daily (with the evening meal, at bedtime, or 12 hours after the morning dose)	10 mL vial, 3 mL FlexTouch
insulin glargine 100 U/mL (Lantus)	Dosing should be individualized based on the type of diabetes and whether the patient is insulin-naïve. Initial dose in patients with Type 1 diabetes is one-third of the total daily insulin requirements. Short-acting, pre-meal insulin should be used to satisfy the remainder of the daily insulin requirement.	Administer SC once daily at anytime during the day, at the same time every day	10 mL vial, 3 mL prefilled SoloStar pen
insulin glargine 300 U/mL (Toujeo)			1.5 mL prefilled SoloStar pen

Regular insulin, insulin glulisine (Apidra), insulin lispro (Humalog), and insulin aspart (Novolog) can be administered intravenously. Insulin aspart/protamine aspart (Novolog Mix), insulin lispro/ protamine lispro (Humalog Mix), insulin detemir (Levemir), and insulin glargine (Lantus, Toujeo) should not be given intravenously or used in insulin infusion pumps.

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

All of the injectable insulin products are available in vials, cartridge and/or pen delivery systems.

The FlexPen® delivery system is a disposable prefilled pen for insulin aspart (Novolog), and insulin aspart/protamine aspart (Novolog Mix). The FlexPen is able to dial up to 60 units of insulin in one-unit increments. FlexPen for use with insulin detemir was discontinued in October 2014. The FlexTouch® delivers insulin detemir (Levemir) from one to 80 units.<sup>119</sup>

The KwikPen™ prefilled pen device for insulin lispro (Humalog) and insulin lispro/ protamine lispro (Humalog Mix) is able to provide up to 60 units of insulin in one-unit increments utilizing a dial

mechanism. In addition, Eli Lilly began phasing out Humulin N and Humulin 70/30 original prefilled pens in the first quarter of 2014; the original pens have been replaced with Humulin N Kwikpen and Humulin 70/30 Kwikpen.

For patients that may require smaller doses of insulin (e.g., children), there are two reusable pen devices currently available. The HumaPen® Luxura™ HD allows patients to dial insulin in half-unit increments (from one to 30 units), and should only be used with insulin lispro (Humalog) cartridges.<sup>120</sup>

The NovoPen Echo®, will replace the NovoPen® Junior. NovoPen Echo provides half-unit dosing capabilities (from 0.5 to 30 units) and a memory function that records the dose and the date and time since the previous dose. NovoPen Echo should only be used with the Novo Nordisk product line of insulin cartridges.<sup>121</sup>

The SoloStar® prefilled pen devices for insulin glargine (Lantus, Toujeo) and insulin glulisine (Apidra) are useful for patients that require larger doses of insulin.<sup>122,123</sup> This pen system is able to dial up to 80 units of insulin in one-unit increments. Most pens and their compatible cartridges are refrigerated before use. Following the first use, these formulations should be stored at room temperature. Expiration dates are typically 10-14 days for regular insulin and insulin NPH, as well as mixes of regular insulin, insulin aspart, or insulin lispro with insulin NPH at room temperature. The rapid-acting insulins and insulin glargine cartridges and pens expire in 28 days, while those for insulin detemir last 42 days.

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

Multiple cartridges are needed for insulin inhalation powder dosages above 8 U. Administer a single inhalation per cartridge. Only one inhaler should be used at a time. Replace the inhaler every 15 days. Insulin inhalation powder cartridges should be kept refrigerated and must be used within ten days at room temperature and three days once the foil package is opened.

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

## CLINICAL TRIALS

### Search Strategies

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

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

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

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

### Injectable insulin

#### *insulin aspart (Novolog) and regular human insulin*

A prospective, multicenter, randomized, parallel-group, open-label study was performed in 423 basal-bolus treated patients with type 1 diabetes.<sup>124</sup> Main outcome measures included blood glucose control assessed by HbA1c, nine-point self-monitored blood glucose profiles, insulin dose, quality of life, hypoglycemia, and adverse events. An algorithm-driven increase occurred in the dose and number of daily injections of basal insulin, particularly in the insulin aspart group. After 12 weeks of treatment, HbA1c was significantly lower in the insulin aspart group compared to regular human insulin subjects by 0.17 percent (95% CI, 0.30 to 0.04,  $p < 0.05$ ). Comparison of the blood glucose profiles showed lower blood glucose levels with insulin aspart after breakfast ( $p < 0.0001$ ) and dinner ( $p < 0.01$ ). There were no differences between treatments in the incidence of hypoglycemic episodes or in the adverse event profiles. The WHO Diabetes Treatment Satisfaction Questionnaire score for perceived hyperglycemia was lower with insulin aspart ( $p = 0.005$ ).

In a six-month, similarly designed trial in 1,070 adults with type 1 diabetes, HbA1c was significantly lower in the insulin aspart group (0.12 percent reduction in HbA1c) after six months.<sup>125</sup> The insulin aspart group had lower post-prandial blood glucose levels, but had higher preprandial glucose levels before breakfast and dinner ( $p < 0.01$ ). Major hypoglycemia episodes overall were similar in both treatment groups, but major hypoglycemia episodes occurring at night that required parenteral treatment occurred more often in the regular insulin group.

Another similarly designed study was performed over six months with a six-month extension period. In 882 men and women with type 1 diabetes, HbA1c values were significantly lower with insulin aspart than with regular insulin (7.78 versus 7.93 percent;  $p = 0.005$ ) at six months.<sup>126</sup> In the extension period ( $n = 714$ ), the difference in HbA1c continued to remain significant at 12 months. The mean basal NPH dose at 12 months was significantly higher for the insulin aspart group than that for the regular insulin group (0.314 versus 0.296 units/kg;  $p = 0.011$ ). A similar percentage of patients in each treatment group had a major hypoglycemic episode by six months. Fewer subjects in the insulin aspart group than in the regular insulin group (four versus eight percent) experienced a major hypoglycemic episode during the night.

A trial was conducted in patients with type 1 diabetes who were randomized to mealtime insulin aspart with up to four daily NPH doses and a 25 percent increase in bedtime NPH dose ( $n = 187$ ) or to mealtime human unmodified insulin with once or twice daily basal NPH insulin ( $n = 181$ ).<sup>127</sup> Efficacy and safety were evaluated at 12 weeks (primary evaluation period) and 64 weeks. At 12 and 64 weeks, there was no statistically significant difference in HbA1c reduction between the insulin aspart and regular insulin groups (-0.09 and -0.14 percent, respectively). Post-prandial glucose values were lower with insulin aspart, and no significant differences were found in mild or severe hypoglycemia or adverse event rates. At 64 weeks, treatment satisfaction was higher in the insulin aspart group while quality of life was not different.

To compare quality of life (QOL) and treatment satisfaction, 424 patients were randomized to basal-bolus treatment with either insulin aspart ( $n = 283$ ) or regular human insulin ( $n = 141$ ) in the six-month, multinational, randomized, open-label trial.<sup>128</sup> After six months, insulin aspart was associated with significantly greater improvement in treatment satisfaction than human insulin in two different scales ( $p < 0.01$ ), and in QOL with respect to diet restrictions ( $p < 0.01$ ). Improved satisfaction was mainly due to increased dietary and leisure time flexibility ( $p < 0.0001$ ).

In the multinational, double-blind, crossover trial, 155 patients with type 1 diabetes were randomized to two 16-week treatment periods on either insulin aspart or human insulin.<sup>129</sup> NPH insulin was given as basal insulin once or twice daily as needed. Treatment periods were separated by a four-week washout. The rate of major nocturnal hypoglycemic episodes was 72 percent lower with insulin aspart than with human insulin (0.067 versus 0.225 events/month;  $p = 0.001$ ). The total rate of major hypoglycemia did not differ significantly between treatments (insulin aspart/human insulin relative risk 0.72; 95% CI, 0.47 to 1.09,  $p = 0.12$ ). Mean HbA1c remained constant, slightly below 7.7 percent on both treatments.

A total of 231 type 2 diabetic patients were randomized to insulin aspart ( $n = 75$ ), regular insulin ( $n = 80$ ), or insulin 70/30 ( $n = 76$ ) for three months with or without bedtime NPH insulin.<sup>130</sup> A total of 204 patients completed the trial according to protocol. The primary endpoint was change in HbA1c from baseline. HbA1c decreased  $0.91 \pm 1$  percent for insulin aspart,  $0.73 \pm 0.87$  percent for regular insulin, and  $0.65 \pm 1.10$  percent for insulin 70/30. Postprandial blood glucose decreased more in the insulin aspart group compared with regular insulin and insulin 70/30. Hypoglycemic events per month were 0.56 with regular insulin, 0.40 with insulin aspart, and 0.19 with insulin 70/30.

***biphasic insulin aspart (Novolog Mix 70/30) and human insulin 70/30***

In a randomized, open-label, parallel trial, 177 patients with type 2 diabetes were assigned to meal-related injection of biphasic insulin aspart three times a day or biphasic human insulin twice a day over a study period of 24 weeks.<sup>131</sup> The mean difference between treatment groups in HbA1c after 24 weeks of treatment was 0.08 percent ( $p=0.6419$ ). Significant differences in blood glucose levels were observed after lunch (156 versus 176 mg/dL,  $p=0.0289$ ), before dinner (142 versus 166 mg/dL  $p=0.006$ ), and after dinner (154 versus 182 mg/dL  $p=0.002$ ) in favor of biphasic insulin aspart. No differences were found regarding safety parameters in the two treatment groups.

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

In the double-blind study of 403 patients with type 2 diabetes not controlled on oral hypoglycemic agents, patients were randomized to receive either biphasic insulin aspart or NPH insulin immediately before breakfast and dinner for 16 weeks.<sup>132</sup> Oral hypoglycemic agents were discontinued. In both groups, HbA1c decreased by greater than 0.6 percent ( $p<0.0001$  versus baseline). The biphasic insulin aspart group had a decreased daily postprandial glycemic exposure (mean difference 0.69 mmol/L;  $p<0.0001$ ). Overall safety profile of both groups was similar.

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

Patients ( $n=137$ ) with type 2 diabetes mellitus currently receiving insulin treatment were randomized to a multicenter, open-label, crossover comparison of biphasic insulin aspart and biphasic insulin lispro.<sup>133</sup> Efficacy and safety profiles were assessed after 12 weeks of treatment. Treatment with biphasic insulin aspart was not inferior to treatment with biphasic insulin lispro. Adverse event profiles were similar between treatments, as was the incidence of hypoglycemic episodes (0.69 episodes/month with biphasic insulin aspart and 0.62 episodes/month with biphasic insulin lispro,  $p=NS$ ). For all device features assessed, the biphasic insulin aspart FlexPen consistently received higher scores (all  $p<0.005$ ). Furthermore, 74.6 percent of patients preferred to continue using the FlexPen, whereas 14.3 percent preferred the biphasic insulin lispro pen ( $p<0.001$ ).

***insulin detemir (Levemir) and insulin NPH (Novolin N)***

A six-month, prospective, randomized, open-label, controlled, parallel-group trial conducted at 92 sites included 749 men and women with type 1 diabetes with HbA1c less than 12 percent who were already taking daily intermediate- or long-acting insulin and a fast-acting human insulin or insulin analogue as bolus insulin.<sup>134</sup> Patients were randomized to insulin detemir or NPH at bedtime in combination with human insulin with main meals. Main outcome measures included HbA1c, FPG, and hypoglycemia. After six months, FPG was lower with insulin detemir than with NPH (-1.16 mmol/L difference;  $p=0.001$ ), whereas HbA1c did not differ significantly between treatments (-0.12 percent;  $p=NS$ ). Day-to-day variability in self-measured fasting blood glucose was lower with insulin detemir (2.82 versus 3.60 mmol/L;  $p<0.001$ ). Lower glucose levels were seen before breakfast with insulin detemir compared to NPH ( $p<0.001$ ). There was a 26 percent reduction in the relative risk of nocturnal hypoglycemia with insulin detemir compared with NPH ( $p=0.003$ ). The adverse effect profiles were similar between treatment groups.

In the 20-week, multicenter, randomized, open-label, parallel-group trial, 504 (intent-to-treat group [ITT]  $n=498$ ) type 2 diabetic patients, poorly controlled on oral antidiabetic therapy, were randomly assigned to receive an evening SC injection of insulin detemir, a pre-breakfast injection of insulin

detemir, or an evening injection of NPH insulin, in addition to their existing oral antidiabetic regimen.<sup>135</sup> Morning and evening detemir were associated with reductions in HbA1c similar to those receiving evening NPH (-1.58, -1.48, and -1.74 percent, respectively). Compared with evening NPH, 24-hour and nocturnal hypoglycemia were reduced by 53 percent ( $p=0.019$ ) and 65 percent ( $p=0.031$ ), respectively, with evening insulin detemir. Incidences of hypoglycemia did not differ significantly between groups that received morning and evening insulin detemir, but nocturnal hypoglycemia was reduced further, by 87 percent, with morning insulin detemir compared with evening NPH ( $p<0.001$ ). Weight gain was 1.2, 0.7, and 1.6 kg with morning insulin detemir, evening insulin detemir, and NPH, respectively ( $p=0.005$  for evening detemir versus NPH).

Patients with type 2 diabetes ( $n=476$ ) with HbA1c 7.5-10 percent were randomized to the addition of insulin detemir or NPH insulin twice daily to existing oral antidiabetic agent therapy in a parallel-group, open-label, multicenter trial.<sup>136</sup> At 24 weeks, HbA1c had decreased by 1.8 and 1.9 percent for insulin detemir and NPH insulin, respectively ( $p=NS$ ). In both groups, 70 percent of participants achieved an HbA1c less than 7 percent, but the proportion achieving this without hypoglycemia was higher with insulin detemir than with NPH insulin (26 versus 16 percent,  $p=0.008$ ). Compared with NPH insulin, the risk for all hypoglycemia with insulin detemir was reduced by 47 percent ( $p<0.001$ ) and nocturnal hypoglycemia by 55 percent ( $p<0.001$ ). The mean weight gain was 1.2 kg with insulin detemir and 2.8 kg with NPH insulin ( $p<0.001$ ).

#### ***insulin detemir (Levemir), insulin aspart (Novolog), and biphasic insulin aspart (Novolog Mix 70/30)***

In an open-label, controlled, multicenter trial, 708 patients with HbA1c levels between 7 to 10.0 percent who were receiving maximally tolerated doses of metformin and sulfonylurea were randomly assigned to receive biphasic insulin aspart twice daily, prandial insulin aspart three times daily, or basal insulin detemir once daily (twice if necessary).<sup>137</sup> The Primary outcome measure at one year was HbA1c. Secondary measures included the proportion of patients with an HbA1c of 6.5 percent or less, the rate of hypoglycemia, and weight gain. At one year, HbA1c was similar in the biphasic group and the insulin aspart group (7.3 versus 7.2 percent, respectively;  $p=0.08$ ), but higher in the basal group (7.6 percent,  $p<0.001$  for both comparisons). The proportions of patients with a HbA1c less than or equal to 6.5 percent were similar in the biphasic and prandial groups (17 and 23.9 percent respectively,  $p=0.08$ ), but was lower in the basal group (8.1 percent;  $p\leq 0.01$  for both comparisons). Mean numbers of hypoglycemic events per patient per year were 5.7, 12, and 2.3 percent, for the biphasic, prandial and basal groups, respectively; and mean weight gains were 4.7 kg, 5.7 kg, and 1.9 kg, respectively. Rates of adverse events were similar among the three groups.

#### ***insulin detemir (Levemir), insulin NPH (Novolin N), and insulin aspart (Novolog)***

The study was an open-label, parallel-group comparison conducted at 46 centers in five countries and included 448 patients ( $n=447$  ITT) with type 1 diabetes. Patients were randomized to insulin detemir or NPH insulin before breakfast and at bedtime. Insulin aspart was given to both groups at meals.<sup>138</sup> After six months, comparable HbA1c levels were found between the two treatment groups. FPG was lower in patients treated with insulin detemir (-0.76 mmol/L), but this difference was not statistically significant ( $p=0.097$ ). Within-subject variation of self-measured FPG was lower with insulin detemir than with NPH insulin (3.37 versus 3.78 mmol/L,  $p<0.001$ ). Risk of hypoglycemia was 22 percent lower with insulin detemir than with NPH insulin ( $p<0.05$ ) and 34 percent lower for nocturnal hypoglycemia ( $p<0.005$ ). Nightly plasma glucose profiles were smoother and more stable with insulin detemir ( $p=0.05$ ). Body weight was significantly lower with insulin detemir at the end of the trial ( $p<0.001$ ).

Patients with type 1 diabetes (n=408) were randomized in a 16-week, open-label, parallel-group trial to insulin detemir administered twice daily either before breakfast and at bedtime or at a 12-hour interval or NPH insulin administered before breakfast and at bedtime.<sup>139</sup> Insulin aspart was the mealtime insulin. Although HbA1c for each insulin detemir group was not different from the NPH group at endpoint, HbA1c for the pooled insulin detemir groups was significantly lower than the NPH group (mean difference -0.18 percent; p=0.027). With both insulin detemir groups, before breakfast and at bedtime or at a 12-hour interval, clinician measured FPG was lower than with NPH insulin (-1.5 mmol/L, p=0.004; -2.3 mmol/L, p<0.001, respectively), as was self-measured pre-breakfast plasma glucose (p=0.006 and p=0.004, respectively). Within-person between-day variation of self-measured pre-breakfast plasma glucose was lower for both detemir groups (both p<0.001). The risk of minor hypoglycemia was lower in both insulin detemir groups (25 percent, p=0.046; 32 percent, p=0.002; respectively) compared with NPH insulin in the last 12 weeks of treatment, mainly attributable to a reduction in nocturnal hypoglycemia in the insulin detemir breakfast/bedtime group (p<0.001). Few severe hypoglycemic episodes were recorded, with no statistical differences between the groups. The NPH group gained weight during the study, but there was no clinically significant change in weight in either of the insulin detemir groups (-0.8 kg, p=0.006; -0.6 kg, p=0.04, respectively).

A multinational, open-label, parallel-group trial studied 505 patients with type 2 diabetes.<sup>140</sup> Patients were randomized to insulin detemir or NPH, receiving basal insulin either once or twice daily, according to their pretrial insulin treatment, and insulin aspart at mealtimes. After 26 weeks of treatment, significant reductions in HbA1c were observed for insulin detemir (p=0.004) and NPH (p=0.0001), resulting in comparable levels at study end (insulin detemir, 7.6 percent; NPH insulin, 7.5 percent). The number of basal insulin injections administered per day had no effect on HbA1c levels (p=0.50). At study end, FPG concentrations were similar for the two treatment groups (p=0.66), as were reductions in FPG (insulin detemir, 0.5 mmol/L; NPH insulin, 0.6 mmol/L). However, within-subject day-to-day variation in fasting FPG was significantly lower with insulin detemir (p=0.021). The frequency of adverse events and the risk of hypoglycemia were comparable for the two treatment groups.

The multinational, 16-week, open-label, parallel-group trial included 400 people with type 1 diabetes randomized to insulin detemir in the morning and before dinner or morning and bedtime, or to NPH morning and bedtime, all in combination with mealtime insulin aspart.<sup>141</sup> HbA1c was comparable among the three groups after 16 weeks, with reductions of 0.39-0.49 percent (p=0.64). Lower FPG was observed with insulin detemir morning/dinner and insulin detemir morning/bedtime compared with NPH groups (9.8 and 9.1 versus 11.1 mmol/L, p=0.006), but the insulin detemir groups did not differ significantly (p=0.15). Within-person variation in self-measured FPG was significantly lower for both insulin detemir regimens than for NPH (SD: insulin detemir morning/dinner 2.5, insulin detemir morning/bedtime 2.6, NPH 3.1 mmol/L, p<0.001) but was comparable between the two insulin detemir groups (p=0.48). Ten-point plasma glucose profiles were lower between dinner and breakfast in the insulin detemir morning/dinner group (p=0.043) compared with the two other groups. Risk of overall and nocturnal hypoglycemia was similar for the three groups.

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

In the 18-week, randomized, open-label, parallel trial, 595 patients with type 1 diabetes received insulin detemir or NPH insulin in the morning and at bedtime in combination with mealtime insulin aspart or regular human insulin, respectively.<sup>142</sup> Glycemic control with insulin detemir/insulin aspart

was improved in comparison with NPH insulin/regular human insulin (HbA1c: 7.88 versus 8.11 percent;  $p < 0.001$ ). Lower postprandial plasma glucose levels were seen in the insulin detemir/insulin aspart group ( $p < 0.001$ ), as well as lower within-person day-to-day variation in plasma glucose (SD: 2.88 versus 3.12 mmol/L;  $p < 0.001$ ). Risk of overall and nocturnal hypoglycemia was 21 percent ( $p = 0.036$ ) and 55 percent ( $p < 0.001$ ) lower in the insulin detemir/insulin aspart group than in the NPH insulin/regular human insulin group, respectively.

A 22-week, multinational, open-label, randomized, parallel-group trial enrolled 395 patients with type 2 diabetes. Patients were randomized to treatment with either basal insulin detemir in combination with insulin aspart at meals or basal insulin NPH in combination with regular human insulin at meals.<sup>143</sup> At 22 weeks, HbA1c was comparable between treatments (insulin detemir group: 7.46 percent, NPH group: 7.52 percent,  $p = 0.515$ ) with decreases from baseline of 0.65 and 0.58 percent, respectively. The insulin detemir group was associated with a significantly lower within-person variation in self-measured FPG (SD: 1.20 versus 1.54 mmol/L,  $p < 0.001$ ), as well as a lower body weight gain (0.51 versus 1.13 kg,  $p = 0.038$ ) than with the NPH group. The risk of nocturnal hypoglycemia was 38 percent lower with the insulin detemir group compared to the NPH group ( $p = 0.14$ ). The overall safety profile was similar between the two treatments.

### ***insulin glargine 100 U/mL (Lantus) and NPH human insulin***

In an open-label study to determine the safety and efficacy of insulin glargine 100 U/mL in type 1 diabetics, patients were randomized to receive insulin glargine once daily ( $n = 310$ ) or NPH insulin ( $n = 309$ ) over 16 weeks.<sup>144</sup> NPH insulin patients maintained their regimen of either once daily or twice daily injections whereas insulin glargine patients received once daily injections at bedtime. All patients continued to administer individually titrated insulin lispro before meals. Insulin glargine patients had lower self-reported fasting blood glucose concentrations. More patients achieved a fasting blood glucose concentration of less than 119 mg/dL in the insulin glargine group (29.6 percent) than in the NPH insulin group (16.8 percent). No differences were noted in the HbA1c or hypoglycemic episodes between the groups. Less variability of blood glucose concentrations was noted in the insulin glargine group. More injection site pain was reported in the insulin glargine group (6.1 percent) than in the NPH group (0.3 percent).

In a multicenter, randomized, open-label, parallel-group study, 534 type 1 diabetics were randomized to receive pre-meal regular insulin and either daily insulin glargine 100 U/mL or NPH insulin (once or twice daily) for up to 28 weeks.<sup>145</sup> A small decrease in HbA1c levels was noted with both insulin glargine (-0.16 percent) and NPH insulin (-0.21 percent;  $p > 0.05$ ). Significant reductions in median FPG levels from baseline (-1.67 versus -0.33 mmol/L with NPH insulin,  $p = 0.0145$ ) were achieved with insulin glargine compared to NPH insulin. After the one-month titration phase, significantly fewer subjects receiving insulin glargine experienced symptomatic hypoglycemia (39.9 versus 49.2 percent,  $p = 0.0219$ ) or nocturnal hypoglycemia (18.2 versus 27.1 percent,  $p = 0.0116$ ) compared with subjects receiving NPH insulin.

Patients with type 1 diabetes were treated for up to 28 weeks with once-daily insulin glargine 100 U/mL ( $n = 199$ ) or twice-daily NPH insulin ( $n = 195$ ) in addition to preprandial regular insulin in a randomized, parallel-group study.<sup>146</sup> A greater mean decrease in FBG was achieved at endpoint with insulin glargine compared with NPH insulin (-21 versus -10 mg/dL;  $p = 0.015$ ), and a greater percentage of patients treated with insulin glargine reached the target FBG (32.6 versus 21.3 percent;  $p = 0.015$ ). Similar percentages of patients in both treatment groups achieved HbA1c values of 7 percent or less at

endpoint. After the one-month titration phase, the percentage of patients who reported at least one symptomatic hypoglycemic event confirmed by a blood glucose value of less than 50 mg/dL was significantly lower with insulin glargine than with NPH insulin (73.3 versus 81.7 percent;  $p=0.021$ ). Severe hypoglycemia was also significantly reduced in insulin glargine patients.

One hundred and twenty-one patients with type 1 diabetes mellitus on four times a day NPH and lispro insulin at each meal were randomized to either continuation of NPH four times a day ( $n=60$ ) or once daily insulin glargine 100 U/mL at dinnertime ( $n=61$ ) for one year.<sup>147</sup> Lispro insulin at meal-time was continued in both groups. Mean daily blood glucose was lower with insulin glargine ( $p<0.05$ ). HbA1c at four months did not change with NPH but decreased with insulin glargine from 7.1 to 6.7 percent, and remained lower than NPH at 12 months (6.6 percent,  $p<0.05$  versus NPH). The frequency of mild hypoglycemia was lower with insulin glargine versus NPH (7.2 versus 13.2 episodes/patient-month,  $p<0.05$ ). After one year, NPH treatment resulted in no change of responses to hypoglycemia, while plasma glucose, thresholds and maximal responses of plasma adrenaline and symptoms to hypoglycemia improved with insulin glargine ( $p<0.05$ ).

In an open-label, 24-week, multicenter trial, 765 patients with type 2 diabetes on one or two oral medications with inadequate glycemic control (HbA1c greater than 7.5 percent) were randomized to either bedtime insulin glargine 100 U/mL or NPH insulin once daily and also continued their prestudy medications.<sup>148</sup> Mean FPG at end point was similar with insulin glargine and NPH (117 versus 120 mg/dL), as was HbA1c (6.96 versus 6.97 percent). A majority of patients (approximately 60 percent) attained HbA1c less than 7 percent with each insulin type. However, nearly 25 percent more patients attained this without documented nocturnal hypoglycemia ( $\leq 72$  mg/dL) with insulin glargine (33.2 versus 26.7 percent,  $p<0.05$ ). Rates of other categories of symptomatic hypoglycemia were 21 to 48 percent lower with insulin glargine.

A total of 518 type 2 diabetics who were receiving NPH insulin with or without regular insulin for postprandial control were randomized to receive insulin glargine 100 U/mL once daily ( $n=259$ ) or NPH insulin once or twice daily ( $n=259$ ) for 28 weeks in an open-label, multicenter trial.<sup>149</sup> The treatment groups showed similar improvements in HbA1c from baseline to end point on intent-to-treat analysis. The mean change in HbA1c from baseline to endpoint was similar in the insulin glargine group ( $-0.41 \pm 0.1$  percent) and the NPH group ( $-0.59 \pm 0.1$  percent). The treatments were associated with similar reductions in fasting glucose levels. Overall, mild symptomatic hypoglycemia was similar in insulin glargine subjects (61.4 percent) and NPH insulin subjects (66 percent). However, nocturnal hypoglycemia in the insulin glargine group was reduced by 25 percent more than the NPH group during the treatment period after the dose-titration phase (26.5 versus 35.5 percent,  $p=0.0136$ ). Patients in the insulin glargine group experienced less weight gain than those in the NPH group (0.4 versus 1.4 kg,  $p<0.0007$ ).

In an open-label, randomized, controlled trial, 695 patients with type 2 diabetes mellitus previously treated with oral antidiabetic agents were randomized to treatment with morning insulin glargine 100 U/mL, bedtime NPH insulin, or bedtime insulin glargine for 24 weeks in addition to 3 mg of glimepiride.<sup>150</sup> HbA1c levels improved by -1.24 percent with morning insulin glargine, -0.96 percent with bedtime insulin glargine, and -0.84 percent with bedtime NPH insulin. HbA1c improvement was more pronounced with morning insulin glargine than with NPH insulin ( $p=0.001$ ) or bedtime insulin glargine ( $p=0.008$ ). Baseline to endpoint fasting blood glucose levels improved similarly in all three groups. Nocturnal hypoglycemia was less frequent with morning (17 percent) and bedtime insulin glargine (23 percent) than with bedtime NPH insulin (38 percent,  $p<0.001$ ).

In a multicenter, open-label, randomized study, 570 patients with type 2 diabetes were treated with insulin glargine 100 U/mL or NPH insulin given once daily at bedtime.<sup>151</sup> Previous oral antidiabetic therapy was continued throughout the study. At 52 weeks, there was a trend toward a decrease in HbA1c values from baseline to endpoint with both drugs (insulin glargine: -0.46 percent; NPH insulin: -0.38 percent;  $p=0.415$ ). Over the entire treatment period, NPH insulin-treated patients (41 percent) and insulin glargine-treated patients (35 percent) experienced a similar level of symptomatic hypoglycemia, but there was a statistically significant difference in the percentage of patients that experienced nocturnal hypoglycemia in NPH patients compared with those treated with insulin glargine in the overall population (24 versus 12 percent,  $p=0.002$ ). The incidence of adverse events was similar for the two treatments.

Glycemic control and symptomatic hypoglycemia rates with insulin glargine 100 U/mL versus NPH were studied in 125 poorly controlled type 1 diabetes patients.<sup>152</sup> Patients received preprandial insulin lispro and either insulin glargine or NPH at bedtime for 30 weeks in a randomized, single-blinded fashion. Basal insulin dosage was titrated to achieve FBG values under 5.5 mmol/L. At endpoint, mean HbA1c was 8.3 versus 9.1 percent for the insulin glargine versus NPH groups, but HbA1c was lower in the insulin glargine versus NPH group at study initiation (9.2 versus 9.7 percent). Adjusted least-squares mean change from baseline was -1.04 versus -0.51 percent, a significant treatment benefit in favor of insulin glargine ( $p<0.01$ ). The mean values for end-point FBG were 7.9 versus 9 mmol/L in favor of insulin glargine ( $p<0.05$ ). Significantly fewer moderate or severe nocturnal hypoglycemic episodes were observed in the insulin glargine group ( $p=0.04$  and  $p=0.02$ ).

An open-label, 24-week, randomized study compared the efficacy and safety of insulin glargine 100 U/mL and insulin NPH, both in combination with a daily fixed dose of glimepiride, in terms of glycemic control and incidence of hypoglycemia.<sup>153</sup> Patients with poorly controlled type 2 diabetes on oral antidiabetic agents (HbA1c 7.5 to 10.5 percent) received glimepiride plus insulin glargine ( $n=231$ ) or insulin NPH ( $n=250$ ) using a forced titration algorithm. Insulin glargine and insulin NPH achieved similar HbA1c reductions. Confirmed nocturnal hypoglycemia was significantly lower with insulin glargine versus insulin NPH (16.9 versus 30 percent;  $p<0.01$ ).

### ***insulin glargine 100 U/mL (Lantus) and human insulin 70/30***

In a 24-week, multinational, multicenter, open-label, parallel-group clinical trial, 371 insulin-naïve patients with poor glycemic control on a sulfonylurea plus metformin were randomized to daily morning insulin glargine 100 U/mL plus glimepiride and metformin or to insulin 70/30 twice daily without oral antidiabetic agents.<sup>154</sup> Mean HbA1c decrease from baseline was significantly more pronounced (-1.64 versus -1.31 percent,  $p=0.0003$ ), and more patients reached HbA1c less than 7 percent without confirmed nocturnal hypoglycemia (45.5 versus 28.6 percent,  $p=0.0013$ ) with the insulin glargine arm than with insulin 70/30. Similarly, FBG decrease was greater in the insulin glargine group (adjusted mean difference -17 mg/dL;  $p<0.0001$ ), and more patients reached target FBG under 100 mg/dL with insulin glargine than with insulin 70/30 (31.6 versus 15 percent,  $p=0.0001$ ). Insulin glargine patients had fewer confirmed hypoglycemic episodes than insulin 70/30 patients (4.07 versus 9.87 episodes/patient-year,  $p<0.0001$ ).

### ***insulin glargine 100 U/mL (Lantus) and insulin detemir (Levemir)***

In a 52-week multinational, open-label, parallel-group, treat-to-target, non-inferiority trial 443 patients with type 1 diabetes and a mean age of 42 years; a mean body mass index of 26.5; a mean HbA1c of

8.1 percent and a mean duration of diabetes of 17.2 years were randomized to receive either insulin detemir or insulin glargine 100 U/mL for 52 weeks.<sup>155</sup> Insulin aspart was administered in both groups as the mealtime insulin. The basal insulin was initially administered once daily in the evening for both groups. If patients in the insulin detemir group achieved target plasma glucose levels before breakfast but not before dinner, administration was changed to twice a day regimen. Insulin glargine patients continued with once daily administration throughout the trial. The primary efficacy endpoint was HbA1c after 52 weeks while the secondary endpoints included the number of patients achieving an HbA1c level less than or equal to 7 percent with or without a major hypoglycemic episode in the last month of treatment and FBG. Results after 52 weeks showed no significant differences in mean HbA1c between insulin detemir and insulin glargine groups (7.57 and 7.56 percent, respectively; mean difference, 0.01%; 95% CI, -0.13 to 0.16). Additionally, there was no significant difference in the proportion of patients receiving insulin detemir and insulin glargine in achieving an HbA1c value equal to or lower than 7 percent without major hypoglycemia (31.9 and 28.9 percent, respectively). In addition, there were no significant differences in estimated mean FPG (8.58 and 8.81 mmol/L; mean difference, -0.23 mmol/L; 95% CI, -1.04 to 0.58) or in basal insulin doses. The relative risks for total and nocturnal hypoglycemia were not significantly different between insulin detemir and insulin glargine (0.94 and 1.12, respectively; p=NS).

In a 24-week, multinational, open-label, treat-to-target trial, 973 insulin-naïve patients with type 2 diabetes and an HbA1c of 7 to 10.5 percent were randomized to insulin detemir twice daily or insulin glargine 100 U/mL once daily.<sup>156</sup> Patients in this study had been treated with metformin for three months or greater prior to the study. The primary outcome was the percentage of patients reaching an HbA1c of less than 7 percent without symptomatic hypoglycemia. In the insulin glargine and insulin detemir groups, 27.5 and 25.6 percent of patients, respectively, reached HbA1c of less than 7 percent. It was demonstrated that insulin glargine once-daily is non-inferior to insulin detemir twice-daily regarding the percentage of patients who achieve a target HbA1c without hypoglycemia. Insulin detemir-treated patients had less weight gain and more often achieved HbA1c of less than 6.5 percent (p=0.017). However, the drop-out rate and daily insulin doses were lower in the insulin glargine group.

***insulin glargine 100 U/mL (Lantus), insulin detemir (Levemir), and insulin aspart (Novolog)***

In a 26-week, multicenter, open-label, parallel-group trial, 320 type 1 diabetics received either insulin detemir twice daily or insulin glargine 100 U/mL once daily, each in combination with pre-meal insulin aspart.<sup>157</sup> After 26 weeks, HbA1c decreased from 8.8 to 8.2 percent in the insulin detemir group and from 8.7 to 8.2 percent in the insulin glargine group. The overall risk of hypoglycemia was similar; however, the risk of severe and nocturnal hypoglycemia was 72 and 32 percent lower, respectively, with insulin detemir than with insulin glargine (p<0.05). Body weight gain was not significantly different between treatment arms.

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

The 28-week parallel-group study randomized 233 insulin-naïve patients on more than 1,000 mg daily metformin alone or in combination with other oral antidiabetic agents to receive biphasic insulin aspart twice daily or insulin glargine 100 U/mL at bedtime and titrated to target blood glucose.<sup>158</sup> At study end, the mean HbA1c value was lower in the biphasic insulin aspart group than in the insulin glargine group (6.91 versus 7.41 percent, p<0.01). The HbA1c reduction was greater in the biphasic insulin aspart group than in the insulin glargine group (-2.79 versus -2.36 percent, p<0.01), especially for subjects with baseline HbA1c greater than 8.5 percent (p<0.05). Minor hypoglycemia was greater in

the biphasic insulin aspart group than in the insulin glargine group (3.4 and 0.7 episodes/year;  $p < 0.05$ ), and weight gain at study end was greater for biphasic insulin aspart-treated subjects than for insulin glargine-treated subjects (5.4 versus 3.5 kg,  $p < 0.01$ ).

In the randomized, open-label, parallel study, biphasic insulin aspart plus metformin twice daily were compared with insulin glargine 100 U/mL plus glimepiride daily in 255 insulin-naïve patients.<sup>159</sup> The primary endpoint was the difference in absolute change in HbA1c between groups after 26 weeks of treatment. HbA1c change was significantly greater in the insulin aspart group than the insulin glargine group (between-group difference: -0.5 percent;  $p = 0.0002$ ). During the maintenance phase, one major hypoglycemic episode occurred in each group; 20.3 and 9 percent of patients experienced minor hypoglycemic episodes in the insulin aspart and insulin glargine groups, respectively ( $p = 0.0124$ ). Insulin glargine patients experienced significant weight gain of 1.5 kg ( $p < 0.0001$ ); the weight change with insulin aspart patients of +0.7 kg was not statistically significant ( $p = 0.0762$ ).

In a 26-week, open-labeled, randomized, parallel-group, multinational, treat-to-target trial, 480 insulin-naïve type 2 patients with diabetes with inadequate control on oral anti-diabetic medications were randomized to receive either biphasic insulin aspart prior to dinner or insulin glargine 100 U/mL at bedtime in combination with metformin and glimepiride.<sup>160</sup> A total of 433 patients completed the trial. At the end of treatment, biphasic insulin aspart and insulin glargine reduced the mean HbA1c levels by -1.41 percent and 1.25 percent, respectively (95% CI, -0.3 to -0.02;  $p = 0.029$ ). After 26 weeks, the mean HbA1c levels were 7.1 percent for the biphasic insulin aspart group and 7.3 percent for the insulin glargine group. The relative risk for a nocturnal hypoglycemic episode was greater in the biphasic insulin aspart group than for insulin glargine (relative risk: 2.41; 95%CI, 1.34 to 4.34;  $p = 0.003$ ), although hypoglycemic rates were overall low with three major episodes occurring in each group.

### ***insulin glargine 100 U/mL (Lantus) and insulin lispro (Humalog)***

In an open-label, multicenter study, 418 patients with type 2 diabetes inadequately controlled with oral hypoglycemic agents were randomized to receive either insulin glargine 100 U/mL administered once daily ( $n = 205$ ) or insulin lispro administered three times daily ( $n = 210$ ).<sup>161</sup> The primary efficacy endpoint was the change in HbA1c from baseline to endpoint (week 44). There was no significant difference between the two treatment groups relative to mean reduction in HbA1c. The percentage of patients that reached HbA1c of 7 percent or less was 57 percent in the glargine group and 69 percent in the lispro group. However, the mean change in fasting blood glucose was significantly greater in the insulin glargine group (-4.3 mmol/L) compared to the insulin lispro group (-1.8 mmol/L;  $p < 0.0001$ ). Patients treated with insulin glargine were also shown to have greater reductions in nocturnal blood glucose compared with patients treated with insulin lispro (-3.3 mmol/L versus -2.6 mmol/L;  $p = 0.0041$ ). Hypoglycemic episodes occurred at a rate of 5.2 events per patient per year for insulin glargine and 24 events per patient per year for insulin lispro ( $p < 0.001$ ). There was no significant difference in mean weight gain between the two treatment groups.

In an open-label 24-week trial, 383 insulin-treated patients with type 2 diabetes were randomized to insulin lispro protamine suspension (ILPS) plus lispro or glargine 100 U/mL plus lispro.<sup>162</sup> Mean changes at week 24 were -1.05 percent (ILPS) and -1.20 percent (glargine). HbA1c less than seven percent was achieved by 21.7 versus 29.4 percent of patients. Mean basal/mealtime insulin doses at week 24 were 29.6/36.2 IU/day (ILPS) versus 32.8/42.2 IU/day (glargine); the difference was not statistically significant for total dose ( $p = 0.7$ ). In both groups, 56.1/25.7 percent versus 63.6/19.3 percent of patients experienced any/nocturnal hypoglycemia ( $p = 0.2$  for both).

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

Type 2 diabetics (n=374) were randomly assigned to insulin lispro mix 50/50 three times daily with meals or insulin glargine 100 U/mL at bedtime plus mealtime insulin lispro in a 24-week, multicenter, open-label, non inferiority trial.<sup>163</sup> Investigators could replace insulin lispro mix 50/50 with 75/25 at the evening meal if the fasting plasma glucose target was unachievable. At week 24, HbA1c was lower with insulin glargine (6.78 versus 6.95 percent, p=0.021), but HbA1c was reduced significantly from baseline for both therapies (p<0.0001). Non-inferiority of insulin lispro mix to insulin glargine was not demonstrated based on the prespecified noninferiority margin of 0.3 percent. The percentages of patients achieving target HbA1c varied depending on the specific target; statistically significant differences did occur in favor of insulin glargine at HbA1c less than 7 percent and HbA1c less than 6.5 percent. Rates of hypoglycemia were similar for both groups.

***insulin glargine 300 U/mL (Toujeo) and insulin glargine 100 U/mL (Lantus)***

In a 26-week open-label study, 546 adults with type 1 diabetes were randomized to basal-bolus treatment with insulin glargine 300 U/mL or 100 u/mL administered once daily in the morning (time period covering from pre-breakfast until pre-lunch) or in the evening (time period defined as prior to the evening meal until at bedtime).<sup>164</sup> A mealtime insulin analogue was administered before each meal. At week 26, treatment with insulin glargine 300 U/mL provided a similar reduction in HbA1c as insulin glargine 100 U/mL (-0.4 versus -0.44 percent, respectively) that met the pre-specified non-inferiority margin of 0.4 percent. Patients treated with insulin glargine 300 U/mL used 17.5 percent more basal insulin than patients treated with insulin glargine 100 U/mL. There were no clinically important differences in glycemic control when insulin glargine 300 U/mL was administered once daily in the morning or in the evening. There were no clinically important differences in body weight between treatment groups.

In a 26-week open-label study, 804 adults with type 2 diabetes were randomized to a once daily treatment in the evening with insulin glargine 300 U/mL or 100 U/mL. Patients also received mealtime insulin analogues with or without metformin.<sup>165</sup> At week 26, insulin glargine 300 U/mL provided a mean reduction in HbA1c that met the pre-specified non-inferiority margin of 0.4 percent compared to insulin glargine 100 U/mL. Patients treated with insulin glargine 300 U/mL used eleven percent more basal insulin compared to those treated with insulin glargine 100 U/mL. There were no clinically important differences in body weight between treatment groups.

In two 26-week, open-label studies, 1,670 adults with type 2 diabetes mellitus were randomized to either insulin glargine 300 U/mL or 100 U/mL once daily in combination with non-insulin anti-diabetic drugs.<sup>166</sup> At the time of randomization, 808 patients were treated with basal insulin for more than six months (Study 1) and 862 patients were insulin-naïve (Study 2). At week 26, treatment with insulin glargine 300 U/mL provided a mean reduction in HbA1c that met the pre-specified non-inferiority margin of 0.4 percent compared to insulin glargine 100 U/mL. Patients treated with insulin glargine 300 U/mL used 12 (Study 1) and 15 (Study 2) percent more basal insulin than patients treated with insulin glargine 100 U/mL. There were no clinically important differences in body weight between treatment groups.

***insulin glulisine (Apidra) and regular human insulin***

Patients with type 1 diabetes (n=860) received daily insulin glargine 100 U/mL and were randomized to either insulin glulisine injected within 15 minutes before or immediately after meals or regular human

insulin, injected 30 to 45 minutes before meals in an open-label, controlled, multicenter, parallel-group, 12-week study.<sup>167</sup> Changes in mean HbA1c were -0.26, -0.11, and -0.13 percent in the pre-meal insulin glulisine, post-meal insulin glulisine, and regular insulin groups, respectively. The reduction in HbA1c was greater for the pre-meal insulin glulisine group in comparison with the regular insulin group ( $p=0.02$ ) and the post-meal insulin glulisine group ( $p=0.006$ ); no significant difference was found between post-meal insulin glulisine versus regular insulin. Overall, blood glucose profiles were similar in all three treatment groups but were significantly lower for pre-meal insulin glulisine post-breakfast and post-dinner measurements. Severe hypoglycemic episodes were comparable for all groups. Body weight increased (+0.3 kg) in the regular insulin and pre-meal insulin glulisine groups; however, weight decreased in the post-meal insulin glulisine group (-0.3 kg;  $p=0.03$ ).

Patients with type 2 diabetes who had received at least six months of continuous insulin therapy were randomized in a multinational, controlled, open-label, parallel group, 26-week study.<sup>168</sup> Patients ( $n=890$ ) received NPH insulin twice daily and either insulin glulisine or regular insulin at least twice daily. There were no differences in HbA1c reductions (insulin glulisine: -0.32 percent; regular insulin: -0.35 percent;  $p=0.57$ ). Insulin glulisine lowered plasma glucose significantly more versus regular insulin at two hours (14.14 mmol/L versus 15.28 mmol/L;  $p=0.0025$ ). Nocturnal hypoglycemia from the fourth month to the end of treatment was less frequent with insulin glulisine versus regular insulin (9.1 versus 14.5 percent;  $p=0.029$ ).

### ***insulin glulisine (Apidra) and insulin lispro (Humalog)***

The objective of the multinational, multicenter, controlled, open-label, randomized, parallel-group study was to compare the efficacy and safety of insulin glulisine to that of insulin lispro in adults diagnosed with type 1 diabetes.<sup>169</sup> Of the 683 patients randomized, 672 received treatment. Over the 26-week study, a similar reduction in mean HbA1c occurred in both groups (adjusted mean change from baseline -0.14 percent in both groups). The basal insulin dose was relatively unchanged from baseline in the insulin glulisine group but increased in the insulin lispro group (insulin glulisine: 0.12 units versus insulin lispro: 1.82 units;  $p=0.0001$ ). There was no relevant difference between the two groups in the reporting of symptomatic hypoglycemia (overall, nocturnal, or severe).

### ***insulin lispro (Humalog) and regular human insulin***

In a 5.5-month randomized, open-label, parallel study of 148 patients with type 2 diabetes receiving either insulin lispro ( $n=70$ ) or regular human insulin ( $n=78$ ), eight-point blood glucose profiles and HbA1c measurements were collected at baseline, 1.5, 3.5, and 5.5 months.<sup>170</sup> Two-hour post-breakfast and two-hour post-supper blood glucose levels were significantly lower for insulin lispro than for regular human insulin at the end point ( $p=0.02$  in both cases). HbA1c improved from 10.5 percent (insulin lispro) and 10.3 percent (regular human insulin) to 8 percent in each treatment arm. Hypoglycemia rates were similar during the day with a trend towards a reduced incidence in the night hours with insulin lispro (0.08 episodes/month versus 0.16 episodes/month,  $p=0.057$ ).

## **Inhalation insulin**

### ***insulin inhalation powder (Afrezza) for Type 1 diabetes mellitus***

A 24-week open-label, active-controlled study enrolled patients with inadequately controlled T1DM to evaluate the glucose lowering effect of mealtime insulin inhalation powder used in combination with a basal insulin.<sup>171</sup> During a four-week run-in period, subjects were converted to mealtime insulin aspart

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

In a 52-week, open-label trial, 539 patients with T1DM were randomized to insulin glargine 100 U/mL (basal) plus either insulin inhalation powder or insulin aspart.<sup>172</sup> Dose titration was permitted during the entire trial based on pre-meal and postprandial blood glucose levels. This trial did not meet its primary efficacy endpoint of noninferiority margin of 0.4 percent for insulin inhalation powder compared with insulin aspart. At Week 52 mean change in HbA1c was -0.13 and -0.37 percent for insulin inhalation powder and insulin aspart, respectively (difference 0.24; 95% CI 0.08, 0.404). A similar proportion of patients achieved HbA1c less than or equal to 7 percent in both groups (16.3 versus 16 percent, respectively). Patients treated with insulin inhalation powder reported a mean decrease in weight of 0.5 kg, while those treated with insulin aspart showed a mean increase of 1.4 kg. Incidence of hypoglycemia was reported in 0.08 events/subject-month for the inhaled insulin group and 0.1 events/subject-month for the insulin aspart group.

### ***insulin inhalation powder (Afrezza) for type 2 diabetes mellitus***

A 24-week double-blind, placebo-controlled trial, enrolled adults with T2DM inadequately controlled on optimal or maximally tolerated doses of metformin monotherapy, or at least two oral antidiabetic agents.<sup>173</sup> Following a six-week run-in period, 353 patients were randomized (1:1) to add-on therapy with insulin inhalation powder or an inhaled placebo powder. Insulin doses were titrated for the first 12 weeks and remained stable thereafter. Oral antidiabetic doses remained unchanged. Open-label rescue therapy (insulin glargine 100 U/mL or glimepiride) in addition to the study treatment was allowed in patients who experienced persistent or worsening hyperglycemia greater than pre-specified thresholds. At Week 24, the insulin group reported statistically significantly greater mean reduction in

HbA1c compared to the placebo group (0.82 versus 0.42 percent;  $p < 0.0001$ ). A greater proportion of patients in the insulin group achieved the HbA1c target of less than or equal to 7 percent (32.2 versus 15.3 percent, respectively;  $p = 0.0005$ ). Patients in the insulin group experienced a mean increase in weight of 0.5 kg, while those in the placebo group reported a mean decrease of 1.1 kg. Severe hypoglycemia was reported in 5.7 percent of patients on inhaled insulin and 1.7 percent of those who received placebo. Cough was reported in 24 percent of the active treatment group and 20 percent of the placebo group.

A 52-week, open-label trial randomized 618 patients with T2DM who had been receiving SC insulin therapy to a basal/bolus regimen with insulin glargine 100 U/mL plus insulin inhalation powder or to a twice daily regimen with 70/30 biphasic insulin.<sup>174</sup> For patients assigned to insulin glargine plus inhaled insulin, half of the total daily pre-randomization insulin dose was replaced with mealtime inhaled insulin and the remaining was replaced by basal insulin glargine. Dose titration was permitted throughout the study. At Week 52, mean change in HbA1c were -0.59 and -0.71 percent for insulin glargine/inhaled insulin and biphasic insulin, respectively. Non-inferiority (margin 0.4 percent) of inhaled insulin plus basal insulin was demonstrated compared to biphasic insulin (difference 0.12 percent; 95% CI -0.05 to 0.29 percent). A greater proportion of patients in the biphasic insulin group achieved the HbA1c target of less than or equal to 7 percent (26.8 versus 22.1 percent, respectively;  $p = 0.28$ ). A lower incidence of severe hypoglycemia, defined as blood glucose less than 37 mg/dL, was reported with inhaled insulin/insulin glargine than biphasic insulin (4.3 versus 10 percent, respectively;  $p < 0.01$ ). Patients in the inhaled insulin/insulin glargine group experienced a mean increase in weight of 0.9 kg and those in the biphasic insulin group reported a mean increase of 2.5 kg.

## META-ANALYSES

A systematic review of 45 studies was performed to compare premixed insulin analogues with any other antidiabetic agents for the treatment of type 2 diabetes in adults.<sup>175</sup> The outcomes examined included fasting glucose, postprandial glucose, HbA1c, and weight gain. Mortality data are scant. Of the 45 studies, 43 were randomized controlled trials. The studies included a total of 14,603 patients with a mean age of 59 years, a median HbA1c of 8.7 percent, and a mean body mass index (BMI) of 29.4 kg/m<sup>2</sup>. When compared with long-acting insulin analogues, premixed insulin analogues were found to be more effective in reducing postprandial glucose levels (pooled difference, -27.9 mg/dL; CI, -34.3 to -21.5 mg/dL) and HbA1c (pooled difference, -0.39%; CI, -0.5% to -0.3%). However, premixed insulin analogues were found to be less effective than long-acting insulin analogues in reducing fasting glucose levels (pooled difference, 12 mg/dL; CI, 6 to 18.1 mg/dL). Premixed insulin analogues were also associated with an increased incidence of hypoglycemia (OR, 2 [CI, 1.3 to 3]) and weight gain (pooled difference, 2 kg [CI, 1.1 to 3 kg]) compared with long-acting insulins. Premixed insulin analogues were similar to premixed human insulin in decreasing fasting glucose levels, HbA1c levels, and the incidence of hypoglycemia but were more effective in decreasing postprandial glucose levels (mean difference, 21.1 mmol/L; 95% CI, 21.4 to 20.7 mmol/L [219.2 mg/dL; 95% CI, 225.9 to 212.5 mg/dL]). Compared to other non-insulin anti-diabetic agents, premixed insulin analogues were more effective in decreasing fasting glucose levels, postprandial glucose levels and HbA1c levels, but were associated with a higher incidence of hypoglycemia.

## SUMMARY

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

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

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

Insulin detemir (Levemir) and insulin glargine (Lantus, Toujeo) have changes in the amino acid sequence. They produce a longer duration of action with minimal peak effect and are used as basal insulins. Both may be used in type 1 diabetics as basal insulin, and in combination with oral antidiabetic medications in patients with type 2 diabetes. Each agent consistently controls glycemic levels better than insulin NPH, with less hypoglycemia. Compared to human insulin, these injectable agents decrease episodes of hypoglycemia by 25 to 50 percent, decrease nocturnal hypoglycemic episodes by 25-33 percent, and generally have lower FPG levels. Effects on HbA1c are comparable with human insulin.

Insulin inhalation powder (Afrezza) provides an alternative dosage form to prandial (mealtime) insulin and should be prescribed with injectable basal insulin for type 1 diabetes mellitus and injectable basal insulin or oral antidiabetic agents for patients with type 2 diabetes mellitus. The inhaled dosage form could be an option for adults with diabetes in whom the injectable administration is a barrier to insulin therapy. Insulin inhalation powder is contraindicated in patients with chronic lung disease due to increased risk of bronchospasm. The long-term pulmonary safety of insulin inhalation is unknown.

## REFERENCES

- 1 Humulin [package insert]. Indianapolis, IN; Eli Lilly; February 2015.
- 2 Novolin [package insert]. Princeton, NJ; Novo Nordisk; March 2013.
- 3 Afrezza [package insert]. Danbury, CT; Mankind Corporation; June 2014.
- 4 Novolog [package insert]. Princeton, NJ; Novo Nordisk; February 2015.
- 5 Apidra [package insert]. Kansas City, MO; Aventis Pharmaceuticals; February 2015.
- 6 Humalog [package insert]. Indianapolis, IN; Eli Lilly; February 2015.
- 7 Levemir [package insert]. Princeton, NJ; Novo Nordisk; February 2015.

- 8 Lantus [package insert]. Kansas City, MO; Aventis Pharmaceuticals; February 2015.
- 9 Novolog Mix 70/30 [package insert]. Princeton, NJ; Novo Nordisk; February 2015.
- 10 Toujeo [package insert]. Bridgewater, NJ; Sanofi-Aventis. February 2015.
- 11 Humalog Mix 75/25 [package insert]. Indianapolis, IN; Eli Lilly; February 2015.
- 12 Humalog Mix 50/50 [package insert]. Indianapolis, IN; Eli Lilly; February 2015.
- 13 Diabetes Statistics. <http://www.diabetes.org/diabetes-basics/statistics/infographics.html>. Accessed March 13, 2015.
- 14 Skyler JS. Glucose control in type 2 diabetes mellitus. *Ann Intern Med.* 1997; 127:837-839.
- 15 American Diabetes Association Position Statement: Standards of Medical Care in Diabetes-2015. *Diabetes Care* . 2015; 37:S14-S80. doi: 10.2337/dc15-S003 Available at: [http://care.diabetesjournals.org/content/38/Supplement\\_1](http://care.diabetesjournals.org/content/38/Supplement_1). Accessed January 30, 2015.
- 16 Garber AJ, Abrahamson MJ, Barzilay JI, et al. AACE comprehensive diabetes management algorithm 2013 consensus statement. *Endocr Pract.* 2013; 19(Suppl 1):1-48. DOI:10.4158/EP13176.CSUPPL. Available at: <https://www.aace.com/files/algorithm-07-11-2013.pdf>. Accessed March 15, 2015.
- 17 Handelsman Y, Mechanick JI, Blonde L, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for developing a diabetes mellitus comprehensive care plan. *Endocrine Practice*; 2011 17(S2):1-53. Available at: <https://www.aace.com/files/dm-guidelines-ccp.pdf>. Accessed March 15, 2015.
- 18 Garber AJ, Abrahamson MJ, Barzilay JI, et al. AACE comprehensive diabetes management algorithm 2013 consensus statement. *Endocr Pract.* 2013; 19(Suppl 1):1-48. DOI:10.4158/EP13176.CSUPPL. Available at: <https://www.aace.com/files/algorithm-07-11-2013.pdf>. Accessed March 15, 2015.
- 19 Available at: <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm129955.htm>. Accessed March 15, 2015.
- 20 Available at: <http://www.fda.gov/Drugs/DrugSafety/ucm435271.htm>. Accessed March 16, 2015.
- 21 Grunberger G, Abelson JM, Bailey TS, et al. Consensus Statement by the American Association of Clinical Endocrinologists/American College of Endocrinology Insulin Pump Management Task Force. *Endocrine Practice*; 2014 20(5):463-489. Available at: <https://www.aace.com/files/insulin-pump-management-cs.pdf>. Accessed March 15, 2015.
- 22 Clinical Pharmacology. <http://www.clinicalpharmacology-ip.com/Default.aspx>. Accessed March 15, 2015.
- 23 Humulin [package insert]. Indianapolis, IN; Eli Lilly; February 2015.
- 24 Novolin [package insert]. Princeton, NJ; Novo Nordisk; June 2010.
- 25 MICROMEDEX. Available at: [www.micromedexsolutions.com](http://www.micromedexsolutions.com). Accessed March 16, 2015.
- 26 Afrezza [package insert]. Danbury, CT; Mankind Corporation; June 2014.
- 27 Mankind Corp. Afrezza Briefing Document for Endocrine and Metabolic Drug Advisory Committee. April, 2014. Available at: <http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm390865.pdf>. Accessed March 13, 2015.
- 28 Novolog [package insert]. Princeton, NJ; Novo Nordisk; February 2015.
- 29 MICROMEDEX. Available at: [www.micromedexsolutions.com](http://www.micromedexsolutions.com). Accessed March 15, 2015.
- 30 Apidra [package insert]. Kansas City, MO; Aventis Pharmaceuticals; February 2015.
- 31 MICROMEDEX. Available at: [www.micromedexsolutions.com](http://www.micromedexsolutions.com). Accessed March 15, 2015.
- 32 Humalog [package insert]. Indianapolis, IN; Eli Lilly; February 2015.
- 33 MICROMEDEX. Available at: [www.micromedexsolutions.com](http://www.micromedexsolutions.com). Accessed March 15, 2015.
- 34 Novolog Mix70/30 [package insert]. Princeton, NJ; Novo Nordisk; May 2010.
- 35 Humalog Mix 75/25 [package insert]. Indianapolis, IN; Eli Lilly; February 2015.
- 36 Humalog Mix 50/50 [package insert]. Indianapolis, IN; Eli Lilly; February 2015.
- 37 Humulin [package insert]. Indianapolis, IN; Eli Lilly; February 2015.
- 38 Novolin [package insert]. Princeton, NJ; Novo Nordisk; March 2013.
- 39 Facts and Comparisons. Available at: <http://online.factsandcomparisons.com>. Accessed March 16, 2015.
- 40 Humulin [package insert]. Indianapolis, IN; Eli Lilly; February 2015.
- 41 Novolin [package insert]. Princeton, NJ; Novo Nordisk; March 2013.
- 42 Facts and Comparisons. Available at: <http://online.factsandcomparisons.com>. Accessed March 15, 2015.
- 43 Levemir [package insert]. Princeton, NJ; Novo Nordisk; February 2015.
- 44 Plank J, Bodenlenz M, Sinner F, et al. A double-blind, randomized, dose-response study investigating the pharmacodynamic and pharmacokinetic properties of the long-acting insulin analog detemir. *Diabetes Care.* 2005; 28(5):1107-12.
- 45 Lantus [package insert]. Kansas City, MO; Aventis Pharmaceuticals; February 2015.
- 46 Toujeo [package insert]. Kansas City, MO; Aventis Pharmaceuticals; February 2015.
- 47 Humulin [package insert]. Indianapolis, IN; Eli Lilly; February 2015.
- 48 Novolin [package insert]. Princeton, NJ; Novo Nordisk; March 2013.
- 49 Afrezza [package insert]. Danbury, CT; Mankind Corporation; June 2014.
- 50 Novolog [package insert]. Princeton, NJ; Novo Nordisk; May 2010.
- 51 Apidra [package insert]. Kansas City, MO; Aventis Pharmaceuticals; February 2015.
- 52 Humalog [package insert]. Indianapolis, IN; Eli Lilly; February 2015.
- 53 Levemir [package insert]. Princeton, NJ; Novo Nordisk; February 2015.
- 54 Lantus [package insert]. Kansas City, MO; Aventis Pharmaceuticals; February 2015.
- 55 Novolog Mix 70/30 [package insert]. Princeton, NJ; Novo Nordisk; February 2015.
- 56 Humalog Mix 75/25 [package insert]. Indianapolis, IN; Eli Lilly; February 2015.
- 57 Humalog Mix 50/50 [package insert]. Indianapolis, IN; Eli Lilly; February 2015.
- 58 Toujeo [package insert]. Kansas City, MO; Aventis Pharmaceuticals; February 2015.
- 59 Available at: <http://www.fda.gov/Drugs/DrugSafety/default.htm>. Accessed March 13, 2015.
- 60 Available at: <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM403785.pdf>. Accessed March 15, 2015.
- 61 Humulin [package insert]. Indianapolis, IN; Eli Lilly; February 2015.
- 62 Novolin [package insert]. Princeton, NJ; Novo Nordisk; March 2013.

- 63 Afrezza [package insert]. Danbury, CT; Mankind Corporation; June 2014.
- 64 Novolog [package insert]. Princeton, NJ; Novo Nordisk; February 2015.
- 65 Apidra [package insert]. Kansas City, MO; Aventis Pharmaceuticals; February 2015.
- 66 Humalog [package insert]. Indianapolis, IN; Eli Lilly; February 2015.
- 67 Levemir [package insert]. Princeton, NJ; Novo Nordisk; February 2015.
- 68 Lantus [package insert]. Kansas City, MO; Aventis Pharmaceuticals; February 2015.
- 69 Novolog Mix 70/30 [package insert]. Princeton, NJ; Novo Nordisk; July 2009.
- 70 Humalog Mix 75/25 [package insert]. Indianapolis, IN; Eli Lilly; February 2015.
- 71 Humalog Mix 50/50 [package insert]. Indianapolis, IN; Eli Lilly; February 2015.
- 72 Toujeo [package insert]. Kansas City, MO; Aventis Pharmaceuticals; February 2015.
- 73 Humulin [package insert]. Indianapolis, IN; Eli Lilly; February 2015.
- 74 Novolin [package insert]. Princeton, NJ; Novo Nordisk; March 2013.
- 75 Afrezza [package insert]. Danbury, CT; Mankind Corporation; June 2014.
- 76 Novolog [package insert]. Princeton, NJ; Novo Nordisk; February 2015.
- 77 Apidra [package insert]. Kansas City, MO; Aventis Pharmaceuticals; February 2015.
- 78 Humalog [package insert]. Indianapolis, IN; Eli Lilly; February 2015.
- 79 Levemir [package insert]. Princeton, NJ; Novo Nordisk; February 2015.
- 80 Lantus [package insert]. Kansas City, MO; Aventis Pharmaceuticals; February 2015.
- 81 Novolog Mix 70/30 [package insert]. Princeton, NJ; Novo Nordisk; July 2009.
- 82 Humalog Mix 75/25 [package insert]. Indianapolis, IN; Eli Lilly; February 2015.
- 83 Humalog Mix 50/50 [package insert]. Indianapolis, IN; Eli Lilly; February 2015.
- 84 Toujeo [package insert]. Kansas City, MO; Aventis Pharmaceuticals; February 2015.
- 85 Humulin [package insert]. Indianapolis, IN; Eli Lilly; February 2015.
- 86 Novolin [package insert]. Princeton, NJ; Novo Nordisk; March 2013.
- 87 Afrezza [package insert]. Danbury, CT; Mankind Corporation; June 2014.
- 88 Novolog [package insert]. Princeton, NJ; Novo Nordisk; February 2015.
- 89 Apidra [package insert]. Kansas City, MO; Aventis Pharmaceuticals; February 2015.
- 90 Humalog [package insert]. Indianapolis, IN; Eli Lilly; February 2015.
- 91 Levemir [package insert]. Princeton, NJ; Novo Nordisk; February 2015.
- 92 Lantus [package insert]. Kansas City, MO; Aventis Pharmaceuticals; February 2015.
- 93 Novolog Mix 70/30 [package insert]. Princeton, NJ; Novo Nordisk; July 2009.
- 94 Humalog Mix 75/25 [package insert]. Indianapolis, IN; Eli Lilly; February 2015.
- 95 Humalog Mix 50/50 [package insert]. Indianapolis, IN; Eli Lilly; February 2015.
- 96 Toujeo [package insert]. Kansas City, MO; Aventis Pharmaceuticals; February 2015.
- 97 Copeland KC, Silverstein J, Moore KR, et al. Management of newly diagnosed type 2 diabetes mellitus (T2DM) in children and adolescents. *Pediatrics*. 2013; 131(2): 364-382. Available at: <http://pediatrics.aappublications.org/content/early/2013/01/23/peds.2012-3494.full.pdf+html>. Accessed March 15, 2015.
- 98 Schober E, Schoenle E, Van Dyk J, et al. Comparative trial between insulin glargine and NPH insulin in children and adolescents with type 1 diabetes mellitus. *J Pediatr Endocrinol Metab*. 2002; 15(4):369-376.
- 99 Mortensen H, Kocova M, Teng LY, et al. Biphasic insulin aspart versus human insulin in adolescents with type 1 diabetes on multiple daily insulin injections. *Pediatr Diabetes*. 2006; 7(1):4-10.
- 100 Robertson KJ, Schoenle E, Gucev Z, et al. Insulin detemir compared with NPH insulin in children and adolescents with Type 1 diabetes. *Diabet Med*. 2007; 24(1):27-34.
- 101 Thalange N, Bereket A, Larsen J, et al. Treatment with insulin detemir or NPH insulin in children aged 2-5 yr with type 1 diabetes mellitus. *Pediatr Diabetes*. 2011; 12(7):632-41.
- 102 Levemir [package insert]. Princeton, NJ; Novo Nordisk; February 2015.
- 103 Apidra [package insert]. Kansas City, MO; Aventis Pharmaceuticals; February 2015.
- <sup>104</sup> American Diabetes Association Position Statement: Standards of Medical Care in Diabetes-2015. Management of Diabetes in Pregnancy. *Diabetes Care* . 2015; 37:S14-S80. doi: 10.2337/dc15-S003 Available at: [http://care.diabetesjournals.org/content/38/Supplement\\_1](http://care.diabetesjournals.org/content/38/Supplement_1). Accessed March 26, 2015.
- 105 Handelsman Y, Mechanick JI, Blonde L, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for developing a diabetes mellitus comprehensive care plan. *Endocrine Practice*; 2011 17(S2):1-53.
- 106 Mathiesen ER, Kinsley B, Amiel SA, et al. Maternal glycemic control and hypoglycemia in type 1 diabetic pregnancy: a randomized trial of insulin aspart versus human insulin in 322 pregnant women. *Diabetes Care*. 2007; 30(4):771-776.
- 107 Humulin [package insert]. Indianapolis, IN; Eli Lilly; February 2015.
- 108 Novolin [package insert]. Princeton, NJ; Novo Nordisk; March 2013.
- 109 Afrezza [package insert]. Danbury, CT; Mankind Corporation; June 2014.
- 110 Novolog [package insert]. Princeton, NJ; Novo Nordisk; February 2015.
- 111 Apidra [package insert]. Kansas City, MO; Aventis Pharmaceuticals; February 2015.
- 112 Humalog [package insert]. Indianapolis, IN; Eli Lilly; February 2015.
- 113 Levemir [package insert]. Princeton, NJ; Novo Nordisk; February 2015.
- 114 Lantus [package insert]. Kansas City, MO; Aventis Pharmaceuticals; February 2015.
- 115 Novolog Mix 70/30 [package insert]. Princeton, NJ; Novo Nordisk; June 2010.
- 116 Humalog Mix 75/25 [package insert]. Indianapolis, IN; Eli Lilly; February 2015.
- 117 Humalog Mix 50/50 [package insert]. Indianapolis, IN; Eli Lilly; February 2015.
- 118 Toujeo [package insert]. Kansas City, MO; Aventis Pharmaceuticals; February 2015.
- 119 Available at: [https://www.levemirpro.com/content/dam/novonordisk/levemirpro/general/generaldocuments/Levemir\\_FlexTouch\\_HCP\\_FAQ.pdf](https://www.levemirpro.com/content/dam/novonordisk/levemirpro/general/generaldocuments/Levemir_FlexTouch_HCP_FAQ.pdf). Accessed March 16, 2015.

- 120 Available at: <http://www.insidehumalog.com/Pages/type2-luxura.aspx>. Accessed on March 16, 2015.
- 121 Available at: <http://www.novolog.com/insulindiabetes/otherdeliversystems.aspx>. Accessed on March 16, 2015.
- 122 Available at: <http://www.lantus.com/considering/lantus-solostar-features>. Accessed on March 16, 2015.
- 123 Available at: <http://www.apidra.com/>. Accessed on March 16, 2015.
- 124 Tamas G, Marre M, Astorga R, et al. Glycaemic control in type 1 diabetic patients using optimised insulin aspart or human insulin in a randomised multinational study. *Diabetes Res Clin Pract.* 2001; 54(2):105-114.
- 125 Home RD, Lindholm A, Riis A. Insulin aspart versus human insulin in the management of long-term blood glucose control in type 1 diabetes mellitus: a randomized controlled trial. *Diabet Med.* 2000;17:762-770.
- 126 Raskin P, Guthrie RA, Leiter L, et al. Use of insulin aspart, a fast-acting insulin analog, as the mealtime insulin in the management of patients with type 1 diabetes. *Diabetes Care.* 2000; 23(5):583-588.
- 127 DeVries JH, Lindholm A, Jacobsen JL, et al. A randomized trial of insulin aspart with intensified basal NPH insulin supplementation in people with Type 1 diabetes. *Diabet Med.* 2003; 20(4):312-8.
- 128 Bott U, Ebrahim S, Hirschberger S, et al. Effect of the rapid-acting insulin analogue insulin aspart on quality of life and treatment satisfaction in patients with Type 1 diabetes. *Diabet Med.* 2003; 20(8):626-634.
- 129 Heller SR, Colagiuri S, Vaaler S, et al. Hypoglycaemia with insulin aspart: a double-blind, randomised, crossover trial in subjects with Type 1 diabetes. *Diabet Med.* 2004; 21(7):769-775.
- 130 Bretzel RG, Arnolds S, Medding J, et al. A direct efficacy and safety comparison of insulin aspart, human soluble insulin, and human premix insulin (70/30) in patients with type 2 diabetes. *Diabetes Care.* 2004; 27(5):1023-1027.
- 131 Abrahamian H, Ludvik B, Scherthner G, et al. Improvement of glucose tolerance in type 2 diabetic patients: traditional versus modern insulin regimens (results from the Austrian Biaspart Study). *Horm Metab Res.* 2005; 37(11):684-689.
- 132 Christiansen JS, Vaz JA, Metelko Z, et al. Twice daily biphasic insulin aspart improves postprandial glycaemic control more effectively than twice daily NPH insulin, with low risk of hypoglycaemia, in patients with type 2 diabetes. *Diabetes Obes Metab.* 2003; 5(6):446-454.
- 133 Niskanen L, Jensen LE, Rastam J, et al. Randomized, multinational, open-label, 2-period, crossover comparison of biphasic insulin aspart 30 and biphasic insulin lispro 25 and pen devices in adult patients with type 2 diabetes mellitus. *Clin Ther.* 2004; 26(4):531-540.
- 134 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):724-736.
- 135 Philis-Tsimikas A, Charpentier G, Clauson P, et al. Comparison of once-daily insulin detemir with NPH insulin added to a regimen of oral antidiabetic drugs in poorly controlled type 2 diabetes. *Clin Ther.* 2006; 28(10):1569-1581.
- 136 Hermansen K, Davies M, Derezinski T, et al. A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naive people with type 2 diabetes. *Diabetes Care.* 2006; 29(6):1269-1274.
- 137 Holman RR, Thorne KI, Farmer AJ, et al. Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. *N Engl J Med.* 2007; 357(17):1716-30.
- 138 Vague P, Selam JL, Skeie S, et al. Insulin detemir is associated with more predictable glycemic control and reduced risk of hypoglycemia than NPH insulin in patients with type 1 diabetes on a basal-bolus regimen with premeal insulin aspart. *Diabetes Care.* 2003; 26(3):590-596.
- 139 Home P, Bartley P, Russell-Jones D, et al. Insulin detemir offers improved glycemic control compared with NPH insulin in people with type 1 diabetes: a randomized clinical trial. *Diabetes Care.* 2004; 27(5):1081-1087.
- 140 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.
- 141 Pieber TR, Draeger E, Kristensen A, et al. Comparison of three multiple injection regimens for Type 1 diabetes: morning plus dinner or bedtime administration of insulin detemir versus morning plus bedtime NPH insulin. *Diabet Med.* 2005; 22(7):850-857.
- 142 Hermansen K, Fontaine P, Kukulja KK, et al. Insulin analogues (insulin detemir and insulin aspart) versus traditional human insulins (NPH insulin and regular human insulin) in basal-bolus therapy for patients with type 1 diabetes. *Diabetologia.* 2004; 47(4):622-629.
- 143 Raslova K, Bogoev M, Raz I, et al. Insulin detemir and insulin aspart: a promising basal-bolus regimen for type 2 diabetes. *Diabetes Res Clin Pract.* 2004; 66(2):193-201.
- 144 Raskin P. A 16-week comparison of the novel insulin analog insulin glargine (HOE 901) and NPH human insulin used with insulin lispro in patients with type 1 diabetes. *Diabetes Care.* 2000; 23(11):1666-1671.
- 145 Ratner RE, Hirsch IB, Neifing JL, et al. Less hypoglycemia with insulin glargine in intensive insulin therapy for type 1 diabetes. U.S. Study Group of Insulin Glargine in Type 1 Diabetes. *Diabetes Care.* 2000; 23(5):639-643.
- 146 Hershon KS et al. Once-daily insulin glargine compared with twice-daily NPH insulin in patients with type 1 diabetes. *Endocr Pract.* 2004; 10(1):10-17.
- 147 Porcellati F, Rossetti P, Pampanelli S, et al. Better long-term glycaemic control with the basal insulin glargine as compared with NPH in patients with Type 1 diabetes mellitus given meal-time lispro insulin. *Diabet Med.* 2004; 21(11):1213-1220.
- 148 Riddle MC, Rosenstock J, Gerich J, et al. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care.* 2003; 26(11):3080-3086.
- 149 Rosenstock J, Schwartz SL, Clark CM Jr, et al. Basal insulin therapy in type 2 diabetes: 28-week comparison of insulin glargine (HOE 901) and NPH insulin. *Diabetes Care.* 2001; 24(4):631-636.
- 150 Fritsche A, Schweitzer MA, Haring HU. Glimperide combined with morning insulin glargine, bedtime neutral protamine hagedorn insulin, or bedtime insulin glargine in patients with type 2 diabetes. A randomized, controlled trial. *Ann Intern Med.* 2003; 138(12):952-959.
- 151 Massi Benedetti M, Humburg E, Dressler A, et al. A one-year, randomised, multicentre trial comparing insulin glargine with NPH insulin in combination with oral agents in patients with type 2 diabetes. *Horm Metab Res.* 2003; 35(3):189-196.
- 152 Fulcher GR, Gilbert RE, Yue DK. Glargine is superior to neutral protamine Hagedorn for improving glycated haemoglobin and fasting blood glucose levels during intensive insulin therapy. *Intern Med J.* 2005; 35(9):536-542.
- 153 Eliaschewitz FG, Calvo C, Valbuena H, et al. Therapy in type 2 diabetes: insulin glargine versus NPH insulin both in combination with glimepiride. *Arch Med Res.* 2006; 37(4):495-501.
- 154 Janka HU, Plewe G, Riddle MC, et al. Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial insulin therapy for type 2 diabetes. *Diabetes Care.* 2005; 28(2):254-259.

- 155 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.
- 156 Swinnen S, Dain M, Aronson R, et al. A 24-Week, Randomized, Treat-to-Target Trial Comparing Initiation of Insulin Glargine Once-Daily With Insulin Determir Twice-Daily in Patients With Type 2 Diabetes Inadequately Controlled on Oral Glucose-lowering Drugs. *Diabetes Care*, 2010; 33(6) :1176-1178.
- 157 Pieber TR, Treichel HC, Hompesch B, et al. Comparison of insulin detemir and insulin glargine in subjects with Type 1 diabetes using intensive insulin therapy. *Diabet Med*. 2007; 24(6):635-642.
- 158 Raskin P, Allen E, Hollander P, et al. Initiating insulin therapy in type 2 Diabetes: a comparison of biphasic and basal insulin analogs. *Diabetes Care*. 2005; 28(2):260-265.
- 159 Kann PH, Wascher T, Zackova V, et al. Starting insulin therapy in type 2 diabetes: twice-daily biphasic insulin Aspart 30 plus metformin versus once-daily insulin glargine plus gliimepiride. *Exp Clin Endocrinol Diabetes*. 2006; 114(9):527-532.
- 160 Strojek K, Bebakar WM, Khutsoane DT, et al. Once-daily initiation with biphasic insulin aspart 30 versus insulin glargine in patients with type 2 diabetes inadequately controlled with oral drugs: an open-label, multinational. RCT. *Curr Med Res Opin*. 2009; 25(12):2887-94.
- 161 Bretzel RG, Nuber U, Landgraf W, et al. Once-daily basal insulin glargine versus thrice-daily prandial insulin lispro in people with type 2 diabetes on oral hypoglycaemic agents (APOLLO): an open randomized controlled trial. *Lancet*. 2008; 371(9618):1073-84.
- 162 Koivisto V, Cleall S, Pontiroli AE, Giugliano D. Comparison of insulin lispro protamine suspension versus insulin glargine once daily in basal-bolus therapies with insulin lispro in type 2 diabetes patients: a prospective randomized open-label trial. *Diabetes Obes Metab*. 2011; 13(12):1149-57.
- 163 Rosenstock J, Ahmann AJ, Colon G, et al. Advancing insulin therapy in type 2 diabetes previously treated with glargine plus oral agents: prandial premixed (insulin lispro protamine suspension/lispro) versus basal/bolus (glargine/lispro) therapy. *Diabetes Care*. 2008; 31(1):20-25.
- 164 Toujeo [package insert]. Bridgewater, NJ; Sanofi-Aventis. February 2015.
- 165 Toujeo [package insert]. Bridgewater, NJ; Sanofi-Aventis. February 2015.
- 166 Toujeo [package insert]. Bridgewater, NJ; Sanofi-Aventis. February 2015.
- 167 Garg SK, Rosenstock J, Ways K. Optimized Basal-bolus insulin regimens in type 1 diabetes: insulin glulisine versus regular human insulin in combination with Basal insulin glargine. *Endocr Pract*. 2005; 11(1):11-17.
- 168 Rayman G, Profozic V, Middle M. Insulin glulisine imparts effective glycaemic control in patients with Type 2 diabetes. *Diabetes Res Clin Pract*. 2007; 76(2):304-312.
- 169 Dreyer M, Prager R, Robinson A, et al. Efficacy and safety of insulin glulisine in patients with type 1 diabetes. *Horm Metab Res*. 2005; 37(11):702-707.
- 170 Ross SA, Zinman B, Campos RV, et al. A comparative study of insulin lispro and human regular insulin in patients with type 2 diabetes mellitus and secondary failure of oral hypoglycemic agents. *Clin Invest Med*. 2001; 24(6):292-8.
- 171 Afrezza [package insert]. Danbury, CT; Mankind Corporation; June 2014.
- 172 Afrezza [package insert]. Danbury, CT; Mankind Corporation; June 2014.
- 173 Afrezza [package insert]. Danbury, CT; Mankind Corporation; June 2014.
- 174 Afrezza [package insert]. Danbury, CT; Mankind Corporation; June 2014.
- 175 Qayyum R, Bolen S, Maruthur N, et al. Systematic review: comparative effectiveness and safety of premixed insulin analogues in type 2 diabetes. *Ann Intern Med*. 2008; 149.