Hypoglycemics, Insulins and Related Agents Therapeutic Class Review (TCR)

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6950 Columbia Gateway Drive
Columbia, Maryland 21046

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FDA-APPROVED INDICATIONS[1,2,3,4,5,6,7,8,9,10,11,12,13,14]

Drug	Types Available	Manufacturer	Indication(s)
Rapid-Acting Insulins			
human insulin inhalation powder (Afrezza®)	--	Sanofi-Aventis	To improve glycemic control in adults with type 1 or type 2 diabetes mellitus
insulin aspart (Novolog®)	--	Novo Nordisk	To improve glycemic control in adults and children with diabetes mellitus
insulin glulisine (Apidra™)	--	Sanofi-Aventis	To improve glycemic control in adults and children with diabetes mellitus
insulin lispro (Humalog®)	--	Lilly	For the treatment of patients with diabetes mellitus for the control of hyperglycemia
Regular (R) Insulins			
human insulin (Humulin® R)	--	Lilly	For the treatment of patients with diabetes mellitus for the control of hyperglycemia * Human insulin 500 IU/mL (Humulin R U-500) is for use in patients requiring daily doses > 200 units.
human insulin (Novolin® R)	--	Novo Nordisk	
Intermediate (N) Insulins			
human insulin NPH (Humulin N)	--	Lilly	For the treatment of patients with diabetes mellitus for the control of hyperglycemia
human insulin NPH (Novolin N)	--	Novo Nordisk	
Long-Acting Insulins			
insulin degludec (Tresiba®)	--	Novo Nordisk	To improve glycemic control in adults with diabetes mellitus.
insulin detemir (Levemir®)	--	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®)	--	Sanofi-Aventis	To improve glycemic control in adults and children with type 1 diabetes mellitus and adults with 2 diabetes mellitus
insulin glargine (Toujeo®)	--	Sanofi-Aventis	To improve glycemic control in adults with diabetes mellitus
Rapid/Intermediate-Acting Combination Insulins			
insulin aspart (Novolog® Mix)	70/30	Novo Nordisk	To improve glycemic control in patients with diabetes mellitus
insulin lispro (Humalog® Mix)	50/50, 75/25	Lilly	For the treatment of patients with diabetes mellitus for the control of hyperglycemia

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FDA-Approved Indications (continued)

Drug	Types Available	Manufacturer	Indication(s)
Regular/Intermediate-Acting Combination Insulins			
human insulin (Humulin)	70/30	Lilly	For the treatment of patients with diabetes mellitus for the control of hyperglycemia
human insulin (Novolin)	70/30	Novo Nordisk	

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

OVERVIEW

It is estimated that 30 million Americans have diabetes mellitus (DM).[15] 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.[16]

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) 2016 Standards of Medical Care in Diabetes advises that a reasonable HbA1c goal for nonpregnant adults is less than 7%; however more stringent HbA1c goals (less than 6.5%) 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.[17] Less-stringent HbA1c goals (less than 8%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain. For pediatric patients, the ADA now recommends a target HbA1c of less than 7.5% 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 3 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 patients newly diagnosed with type 2 diabetes with markedly symptomatic and/or elevated blood glucose levels or HbA1c, consider insulin therapy, with or without additional agents, from the outset.

In 2016, the American Academy of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) released an updated diabetes management algorithm and clinical practice guidelines for developing a diabetes care plan. They recommend diabetes treatment with a goal HbA1c less than or equal to 6.5% for healthy patients with low hypoglycemic risk.[18,19] For patients with concurrent illness and who are at risk of hypoglycemia, a goal HbA1c of greater than 6.5% is appropriate. The initial choice of antidiabetic agent should be based on glycemic profile, HbA1c, body weight, and presence of comorbidities. Minimizing the risks of hypoglycemia and weight gain are a

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main concern. AACE/ACE suggests patients with type 2 diabetes and an HbA1c < 7.5% start with monotherapy, preferably with metformin. Alternatives to metformin as initial therapy include, glucagon-like peptide 1 (GLP-1) receptor agonists, sodium-glucose cotransporter 2 (SGLT2) inhibitors, dipeptidyl peptidase 4 (DPP-4) inhibitors, α-glucosidase inhibitors (AGI); monotherapy with a thiazolidinedione (TZD) or sulfonylurea should be used with caution. Patients with an HbA1c ≥ 7.5% should begin with dual therapy with metformin (unless contraindicated) plus a second agent, including a GLP-1 agonist, SGLT2 inhibitor, or DPP-4 inhibitor, TZDs, or basal insulin. TZDs, basal insulin, and sulfonylureas should be used with caution. Patients with an HbA1c > 9% and no symptoms of hyperglycemia may start either dual or triple antihyperglycemic therapy; patients with an HbA1c > 9% with symptoms should begin insulin therapy with or without other agents. The HbA1c should be reassessed every 3 months and failure to improve may warrant additional complementary therapy for optimal glycemic control.

According to AACE/ACE guidelines, insulin is required in all patients with type 1 diabetes.[20] AACE/ACE also advises that insulin therapy can be considered for patients with type 2 diabetes, when HbA1c > 8%, or therapy with 2 or more oral antidiabetic agents or GLP-1 therapy fails to achieve target glycemic control, or in patients with long-standing type 2 diabetes who are unlikely to achieve their HbA1c goals. When insulin therapy is indicated in patients with type 2 diabetes, therapy with long-acting basal insulin analogs (degludec, 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 (insulin degludec was not available at the time these guidelines were published). Rapid-acting insulin analogs (lispro aspart, glulisine, inhaled insulin) are preferred over regular insulin for postprandial hyperglycemia because they have a more rapid onset and offset of action and result in less hypoglycemia. Premixed insulin 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, administered subcutaneously, can be obtained from an insulin cartridge, vial or insulin pen device, to deliver multiple doses to a single patient. 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.[21] 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.

It was estimated in 2005 that in the U.S. 20% to 30% of patients with type 1 diabetes and < 1% of those with type 2 diabetes receive insulin therapy via an external insulin pump.[22] These patients require intensive management with at least 4 insulin injections and 4 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

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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[23]

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[24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44]

Comparison of Insulin Products

Type of Insulin	Drug	Composition of Insulin	Onset (hrs)	Peak (hrs)	Duration (hrs)	Compatibility for Mixing
Rapid-acting	human insulin (Afrezza®)[45]	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)	Consists of human insulin aspart in a clear aqueous solution; Created when the amino acid proline is substituted with aspartic acid at position B28	0.25	0.75-1.5	3-5	NPH
	insulin glulisine (Apidra)	Created when the amino acid asparagine at position B3 is replaced by lysine and the lysine at position B29 is replaced by glutamic acid	0.33	0.92	5.3	NPH
	insulin lispro (Humalog)	Consists of zinc-insulin lispro crystals dissolved in clear aqueous fluid; Created when the amino acids at positions 28 and 29 on the insulin B-chain are reversed	0.25-0.5	0.5-1.5	3-5	NPH
Rapid/ Intermediate-acting combination products	insulin aspart (Novolog Mix)	Suspension containing insulin aspart protamine crystals and soluble insulin aspart	0.17-0.33	1.6-3.2	Up to 24 hours	None
	insulin lispro (Humalog Mix)	Suspension containing insulin lispro protamine suspension and insulin lispro solution	0.25-0.5	0.8-6.5	Similar to corre-sponding Humulin mixes	None

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Comparison of Insulin Products (continued)

Type of Insulin	Drug	Composition of Insulin	Onset (hrs)	Peak (hrs)	Duration (hrs)	Compatibility for Mixing
Regular-acting	human insulin regular 100 IU/mL (Humulin R, Novolin R)	Crystalline regular insulin is prepared by precipitation in the presence of zinc chloride at a neutral pH	0.5	2.5-5	8-12	NPH
	human insulin 500 IU/mL (Humulin R U-500)	A solution identical to human insulin that is produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of *Escherichia coli*	< 0.25	4-8	13-24	None
Regular/ Intermediate-acting combination products	human insulin (Humulin 70/30, Novolin 70/30)	Crystalline regular insulin and isophane (NPH) is modified, crystalline protamine zinc insulin	0.5-0.8	2.2-5	Up to 24	None
Intermediate-acting	human insulin NPH (Humulin N, Novolin N)	Isophane (NPH) is modified, crystalline protamine zinc insulin; Its effects are comparable to a mixture of 2:1 to 3:1 regular insulin and protamine zinc insulin	1.5	4-12	Up to 24	Regular, aspart, lispro, and glulisine
Long-acting	insulin degludec (Tresiba)	Created when the amino acid threonine in position B30 is omitted and a side-chain consisting of glutamic acid and a C16 fatty acid is attached	1	12	>42	None
	insulin detemir (Levemir)[46]	Created when the amino acid threonine in position B30 is omitted and a C14 fatty acid chain is added to amino acid B29	0.8-2	6-8	Up to 24	None
	insulin glargine (Lantus)	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)[47]		6	12-16	Up to 36	

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

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The glucose lowering effect of insulin glargine 300 U/mL increases with subsequent daily administration.

CONTRAINDICATIONS/WARNINGS[48,49,50,51,52,53,54,55,56,57,58,59,60,61]

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 (< 6 months ago), as safety and efficacy have not been established in this population.

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

In clinical trials, the incidence of lung cancer was reported in patients treated with 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 (1 to 2 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%, respectively). In patients at risk for DKA, such as those with an acute illness or infection, carefully monitor blood glucose and switch to an alternate route of administration if necessary.

Precautions

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

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

Insulin aspart (Novolog), insulin degludec (Tresiba), 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.

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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 as they may be at higher risk of hypoglycemia.

The full glucose lowering effect of insulin glargine 300 U/mL (Toujeo) may not be seen for at least 5 days, which should be considered prior to stopping intravenous insulin therapy in patients with 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.[62] 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 the risk of acute bronchospasm when used in patients with chronic lung disease, such as asthma and COPD and of the need to evaluate patients for lung disease before starting therapy.[63]

DRUG INTERACTIONS[64,65,66,67,68,69,70,71,72,73,74,75,76,77]

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[78,79,80,81,82,83,84,85,86,87,88,89,90,91]

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

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Glucose monitoring is recommended in all patients with diabetes. 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 U-100 (Lantus) had treatment-emergent injection site pain in 2.7% of patients versus 0.7% of patients on NPH insulin. Treatment discontinuation was not required. Insulin detemir (Levemir) was associated with more frequent mild injection site reactions than with insulin NPH. In clinical trials, injection site reactions occurred in 3.8% of patients treated with insulin degludec.

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

The potential for weight gain is associated with insulin therapy. In clinical studies insulin detemir was associated with a mean weight loss of 0.5 kg compared to a weight gain of 1 kg with insulin glargine; however, it was also found to be slightly less effective than insulin glargine in reducing HbA1c (0.48% versus 0.74%).[92] 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 patients with type 2 diabetes, insulin inhalation powder was associated with a more modest weight gain than comparator over the 52-week trial duration. Adverse effects data are obtained from prescribing information and therefore, should not be considered comparative or all-inclusive.

SPECIAL POPULATIONS[93,94,95,96,97,98,99,100,101,102,103,104,105,106]

Pediatrics

Safety and efficacy of insulin inhalation powder (Afrezza), insulin degludec (Tresiba), 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.[107] 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%. The AAP suggests that clinicians monitor HbA1c concentrations every 3 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. Although no well-controlled studies of human insulin 500 IU/mL (Humulin R U-500) have been performed in children, standard precautions for its use in adults can be applied to children. Human insulin lispro (Humalog) can be used in children more than 3 years of age and older. Human insulin aspart (Novolog) can be given to pediatric patients 2 years of age and older. Insulin glulisine (Apidra) is approved for use in pediatric patients with type 1 diabetes from 4 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 6 to 15 years of age; insulin detemir (Levemir) has not been studied in children with type 1 diabetes

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less than 2 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, 6-month study, 349 type 1 diabetes mellitus patients ages 5 to 16 years received insulin glargine 100 U/mL once daily or NPH insulin either once or twice daily.[108] 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%, respectively) and severe nocturnal hypoglycemia (13% versus 18%, respectively), although these differences were not statistically significant. Fewer serious adverse events occurred in the insulin glargine group than in the NPH insulin group (p<0.02).

The clinical efficacy and safety of 2 treatment regimens, biphasic insulin aspart at all 3 meals plus NPH insulin at bedtime versus premixed human insulin at breakfast and regular insulin at lunch and dinner plus NPH at bedtime, were compared in 167 adolescents with type 1 diabetes.[109] This open-label, parallel-group trial reported that after 4 months on biphasic insulin aspart therapy, HbA1c was not significantly different from that with human insulin (9.39% versus 9.3%, respectively). The body mass index increased in both groups, but significantly (p=0.005) less in the biphasic insulin aspart group. No significant group differences were found for the rate of hypoglycemic episodes.

In a 26-week, open-label, randomized, parallel-group study, 347 children with type 1 diabetes, aged 6 to 17 years, received insulin detemir or NPH insulin once or twice daily plus insulin aspart before meals.[110] The mean HbA1c decreased by approximately 0.8% with both treatments. Within-subject variation in self-measured fasting plasma glucose was significantly lower with insulin detemir than with NPH insulin (p<0.001), as was mean fasting plasma glucose (8.4 versus 9.6 mmol/L, p=0.022). The risk of nocturnal hypoglycemia was 26% lower with insulin detemir (p=0.041).

A 1-year open-labeled, parallel group trial compared insulin detemir with NPH insulin, in combination with mealtime insulin aspart in 348 patients aged 2 to 16 years with type 1 diabetes mellitus.[111,112] Randomization was stratified by age (2 to 5 years, n=82; 6 to 16 years, n=265). Mean HbA1c was similar between groups at baseline (8.2% versus 8.1%), and changed little over 1 year (8.1% versus 8.3%). 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, 8 versus 17.4 episodes per patient-year). No severe hypoglycemic episodes occurred with insulin detemir, while 3 subjects reported 6 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 4 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.[113] During this 26-week study, patients also received insulin glargine 100 U/mL (administered once daily in the evening) or NPH insulin (administered once in the morning and once in the evening). There were no significant differences observed between the 2 treatment groups with respect to glycemic control.

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Pregnancy

The human insulins, insulin aspart, insulin detemir, and insulin lispro are Pregnancy Category B. Insulin degludec, 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 (1 to 3 times daily). Insulin aspart was administered before each meal. Mean HbA1c was less than 7% at 10, 12, and 24 weeks of gestation in both arms. In the intent-to-treat population, the adjusted mean HbA1c at gestational week 36 was similar in each arm. There were no differences in pregnancy outcomes or the health of the fetus and newborn between the groups.

The ADA 2016 Standards of Medical Care in Diabetes states because there is an increase in red blood cell turnover during pregnancy, HbA1c levels decrease during pregnancy.[114] 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 6% to 6.5%; this target can be relaxed or tightened depending on hypoglycemia risk. 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.[115] 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.[116] Patients had HbA1c equal to 8% or less at confirmation of pregnancy, and insulin doses were titrated toward predefined glucose targets and HbA1c less than 6.5%. 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 [RR] 0.72; 95% CI, 0.36 to 1.46). The risk of major nocturnal hypoglycemia was 52% (RR, 0.48; 95% CI, 0.2 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% of subjects achieved HbA1c of 6.5% or less. Maternal safety profiles and pregnancy outcomes were similar between treatments.

A randomized, controlled noninferiority trial compared use of insulin detemir and NPH insulin for the treatment of gestational diabetes mellitus and type 2 diabetes mellitus in pregnancy.[117] Insulin aspart was added as needed. Patients were instructed to test blood glucose levels 4 times a day (fasting and 2-hour postprandial). Insulin dosages were adjusted to meet targets of FPG <90 mg/dL and PPG <120 mg/dL. The primary outcome was overall mean blood glucose during insulin treatment. Results from 87 women were analyzed. The difference in the mean blood glucose of the groups was 2.1 mg/dL (p=0.2937). The time to achieve glycemic control was similar in both groups. There were no differences in perinatal outcomes and maternal weight gain among the groups. There were more hypoglycemic events per patient in the NPH group.

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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[118,119,120,121,122,123,124,125,126,127,128,129,130,131]

Drug	Dosing	Time of administration related to mealtime	Availability
Rapid-Acting Insulins			
human insulin inhalation powder (Afrezza)	Dosing should be titrated to glycemic control in combination with a long acting insulin	At the beginning of the meal	Cartridge: 4, 8, and 12 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	U-100 (100 units/mL): 10 mL vial, 3 mL vial, 3 mL cartridge, 3 mL prefilled KwikPen U-200 (200 units/mL): 3 mL prefilled KwikPen
Regular (R) Insulins			
human insulin (Humulin R, Novolin R)	Dosing should be titrated to glycemic control in combination with an intermediate or long acting insulin (and/or with oral antidiabetic agents for type 2 diabetics)	30 minutes prior to meal	10 mL vials (Humulin R 100; Novolin R 100) 20 mL vials (Humulin R U-500) Prefilled pen: 3 mL 500 IU/mL KwikPen (Humulin R U-500)

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Dosages (continued)

Drug	Dosing	Time of administration related to mealtime	Availability
Intermediate (N) Insulins			
human insulin NPH (Humulin N, Novolin N)	Dosing should be titrated to glycemic control. Can be used in combination with an quick- or long-acting insulin (and/or with oral antidiabetic agents for type 2 diabetics); Total daily dose is given as 1 to 2 injections per day	30-60 minutes prior to meal or bedtime	10 mL vials (Humulin N 100; Novolin N 100) 3 mL prefilled pen (Humulin N 100) 3 mL prefilled KwikPen (Humulin N 100)
Long-Acting Insulins			
insulin degludec (Tresiba)	Dosing should be individualized based on the type of diabetes and whether the patient is insulin-naïve; Initial dose in patients with 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 There should be a minimum interval of 8 hours after the last injection	U-100 (100 U/mL) : 3 mL FlexTouch pen U-200 (200 U/mL) : 3 mL FlexTouch pen
insulin detemir (Levemir)		Once daily (with the evening meal or at bedtime) or twice daily (with the evening meal, at bedtime, or 12 hours after the morning dose)	10 mL vial, 3 mL FlexTouch
insulin glargine 100 U/mL (Lantus)		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
Rapid/Intermediate-Acting Combination Products			
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
Regular/Intermediate-Acting Combination Products			
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 70/30; Novolin 70/30) 3 mL prefilled pen (Humulin 70/30) 3 mL prefilled KwikPen (Humulin 70/30)

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Regular insulin, insulin glulisine (Apidra), insulin lispro 100 units/mL (Humalog U-100), and insulin aspart (Novolog) can be administered intravenously. Insulin lispro 200 units/mL (Humalog U-200), 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.

Two open-label phase 3 studies in patients with type 1 diabetes (n=493) or type 2 diabetes (n=687) evaluated insulin degludec given in flexible once-daily dosing intervals compared with insulin degludec and insulin glargine administered once daily at the same time each day. The flexible dosing intervals were predefined with variations between 8 and 40 hours. In patients with type 1 or type 2 diabetes flexible dosing was shown to be non-inferior (upper limit of the 95% confidence interval for the treatment difference was ≤ 0.4%) with respect to HbA1c reduction versus same time dosing for insulin degludec and insulin glargine. In addition, nocturnal hypoglycemic events were reduced by 40% ($p < 0.01$) in the flexible dosing group versus the insulin glargine group. In patients with type 2 diabetes, rates for hypoglycemia were comparable between all groups.

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 from one to 80 units of insulins detemir (Levemir) and degludec U-100 and up to 160 units of insulin degludec U-200.[132]

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. No dose conversion is needed when using the Humulin R U-500 KwikPen since the dose window shows the number of units to be injected.

Human insulin 500 IU/mL use in combination with other insulins and its use as a continuous subcutaneous infusion have not been established. Becton-Dickenson has created a new syringe specific for U-500 insulin administration that does not require dose conversion as previously needed when using U-100 insulin/TB syringe to deliver U-500 insulin.[133] The new syringes are only available by prescription and should be co-prescribed with U-500 insulin.

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.[134] The NovoPen Echo®, has replaced 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

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since the previous dose. NovoPen Echo should only be used with the Novo Nordisk product line of insulin cartridges.[135]

The SoloStar® prefilled pen devices for insulin glargine (Lantus, Toujeo) and insulin glulisine (Apidra) are useful for patients that require larger doses of insulin.[136,137] 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 to 14 days for regular insulin and insulin NPH, as well as mixes of regular insulin, insulin aspart, or insulin lispro with insulin NPH at room temperature. The rapid-acting insulins and insulin glargine cartridges and pens expire in 28 days, while those for insulin detemir last 42 days.

Insulin inhalation powder (Afrezza) should only be administered via oral inhalation using the breath-powered inhaler provided. The recommended initial mealtime dose is 4 units at each meal for insulin-naïve individuals. For patient using 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 units injected mealtime insulin is equal to 4 units inhaled mealtime insulin. Doses should be rounded up to the nearest 4 units 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 12 units. Administer a single inhalation per cartridge. Only 1 inhaler should be used at a time. Replace the inhaler every 15 days. Insulin inhalation powder cartridges should be kept refrigerated and must be used within 10 days at room temperature and 3 days once the foil package is opened.

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

CLINICAL TRIALS

Search Strategies

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all brand names in this class. Randomized, comparative, controlled trials comparing agents within this class in an outpatient setting for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies,

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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) versus regular human insulin

A prospective, multicenter, randomized, parallel-group, open-label study was performed in 423 basal-bolus treated patients with type 1 diabetes.[138] Main outcome measures included blood glucose control assessed by HbA1c, 9-point self-monitored blood glucose profiles, insulin dose, quality of life, hypoglycemia, and adverse events. An algorithm-driven increase occurred in the dose and number of daily injections of basal insulin, particularly in the insulin aspart group. After 12 weeks of treatment, HbA1c was significantly lower in the insulin aspart group compared to regular human insulin subjects by 0.17% (95% CI, 0.3 to 0.04; $p<0.05$). Comparison of the blood glucose profiles showed lower blood glucose levels with insulin aspart after breakfast ($p<0.0001$) and dinner ($p<0.01$). There were no differences between treatments in the incidence of hypoglycemic episodes or in the adverse event profiles. The WHO Diabetes Treatment Satisfaction Questionnaire score for perceived hyperglycemia was lower with insulin aspart ($p=0.005$).

In a 6-month, similarly designed trial in 1,070 adults with type 1 diabetes, HbA1c was significantly lower in the insulin aspart group (0.12% reduction in HbA1c) after 6 months.[139] The insulin aspart group had lower post-prandial blood glucose levels, but had higher preprandial glucose levels before breakfast and dinner ($p<0.01$). Major hypoglycemia episodes overall were similar in both treatment groups, but major hypoglycemia episodes occurring at night that required parenteral treatment occurred more often in the regular insulin group.

Another similarly designed study was performed over 6 months with a 6-month extension period. In 882 men and women with type 1 diabetes, HbA1c values were significantly lower with insulin aspart than with regular insulin (7.78% versus 7.93%; $p=0.005$) at 6 months.[140] 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

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versus 0.296 units/kg; p=0.011). A similar percentage of patients in each treatment group had a major hypoglycemic episode by 6 months. Fewer subjects in the insulin aspart group than in the regular insulin group (4% versus 8%) experienced a major hypoglycemic episode during the night.

A trial was conducted in patients with type 1 diabetes who were randomized to mealtime insulin aspart with up to 4 daily NPH doses and a 25% increase in bedtime NPH dose (n=187) or to mealtime human unmodified insulin with once or twice daily basal NPH insulin (n=181).[141] Efficacy and safety were evaluated at 12 weeks (primary evaluation period) and 64 weeks. At 12 and 64 weeks, there was no statistically significant difference in HbA1c reduction between the insulin aspart and regular insulin groups (-0.09% and -0.14%, respectively). Post-prandial glucose values were lower with insulin aspart, and no significant differences were found in mild or severe hypoglycemia or adverse event rates. At 64 weeks, treatment satisfaction was higher in the insulin aspart group while quality of life was not different.

To compare quality of life (QOL) and treatment satisfaction, 424 patients were randomized to basal-bolus treatment with either insulin aspart (n=283) or regular human insulin (n=141) in the 6-month, multinational, randomized, open-label trial.[142] After 6 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.[143] NPH insulin was given as basal insulin once or twice daily as needed. Treatment periods were separated by a 4-week washout. The rate of major nocturnal hypoglycemic episodes was 72% lower with insulin aspart than with human insulin (0.067 versus 0.225 events/month; p=0.001). The total rate of major hypoglycemia did not differ significantly between treatments (insulin aspart/human insulin relative risk 0.72; 95% CI, 0.47 to 1.09; p=0.12). Mean HbA1c remained constant, slightly below 7.7% on both treatments.

A total of 231 patients with type 2 diabetes were randomized to insulin aspart (n=75), regular insulin (n=80), or insulin 70/30 (n=76) for 3 months with or without bedtime NPH insulin.[144] A total of 204 patients completed the trial according to protocol. The primary endpoint was change in HbA1c from baseline. HbA1c decreased 0.91% ± 1% for insulin aspart, 0.73% ± 0.87% for regular insulin, and 0.65% ± 1.1% for insulin 70/30. Postprandial blood glucose decreased more in the insulin aspart group compared with regular insulin and insulin 70/30. Hypoglycemic events per month were 0.56 with regular insulin, 0.4 with insulin aspart, and 0.19 with insulin 70/30.

biphasic insulin aspart (Novolog Mix 70/30) versus 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 3 times a day or biphasic human insulin twice a day over a study period of 24 weeks.[145] The mean difference between treatment groups in HbA1c after 24 weeks of treatment was 0.08% (p=0.6419). Significant differences in blood glucose levels were observed after lunch (156 versus 176 mg/dL, p=0.0289), before dinner (142 versus 166 mg/dL p=0.006), and after dinner (154 versus 182 mg/dL p=0.002) in favor of biphasic insulin aspart. No differences were found regarding safety parameters in the two treatment groups.

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biphasic insulin aspart (Novolog Mix 70/30) versus 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.[146] Oral hypoglycemic agents were discontinued. In both groups, HbA1c decreased by greater than 0.6% (p<0.0001 versus baseline). The biphasic insulin aspart group had a decreased daily postprandial glycemic exposure (mean difference 0.69 mmol/L; p<0.0001). Overall safety profile of both groups was similar.

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

Patients (n=137) with 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.[147] 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% of patients preferred to continue using the FlexPen, whereas 14.3% preferred the biphasic insulin lispro pen (p<0.001).

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

A 6-month, prospective, randomized, open-label, controlled, parallel-group trial conducted at 92 sites included 749 men and women with type 1 diabetes with HbA1c less than 12% who were already taking daily intermediate- or long-acting insulin and a fast-acting human insulin or insulin analogue as bolus insulin.[148] 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 6 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%; p=NS). Day-to-day variability in self-measured fasting blood glucose was lower with insulin detemir (2.82 versus 3.6 mmol/L; p<0.001). Lower glucose levels were seen before breakfast with insulin detemir compared to NPH (p<0.001). There was a 26% reduction in the relative risk of nocturnal hypoglycemia with insulin detemir compared with NPH (p=0.003). The adverse effect profiles were similar between treatment groups.

In the 20-week, multicenter, randomized, open-label, parallel-group trial, 504 (intent-to-treat group [ITT] n=498) patients with type 2 diabetes, 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.[149] Morning and evening detemir were associated with reductions in HbA1c similar to those receiving evening NPH (-1.58%, -1.48%, and -1.74%, respectively). Compared with evening NPH, 24-hour and nocturnal hypoglycemia were reduced by 53% (p=0.019) and 65% (p=0.031), respectively, with evening insulin detemir. Incidences of hypoglycemia did not differ significantly between groups that received morning and evening insulin detemir, but nocturnal hypoglycemia was reduced further, by 87%, with morning insulin detemir compared with evening NPH (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).

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Patients with type 2 diabetes (n=476) with HbA1c 7.5% to 10% 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.[150] At 24 weeks, HbA1c had decreased by 1.8% and 1.9% for insulin detemir and NPH insulin, respectively (p=NS). In both groups, 70% of participants achieved an HbA1c less than 7%, but the proportion achieving this without hypoglycemia was higher with insulin detemir than with NPH insulin (26% versus 16%, p=0.008). Compared with NPH insulin, the risk for all hypoglycemia with insulin detemir was reduced by 47% (p<0.001) and nocturnal hypoglycemia by 55% (p<0.001). The mean weight gain was 1.2 kg with insulin detemir and 2.8 kg with NPH insulin (p<0.001).

insulin degludec (Tresiba) versus insulin detemir (Levemir)

The efficacy and safety of insulin degludec used in combination with mealtime insulin aspart for the treatment type 1 diabetes mellitus were evaluated in an open-label, active-controlled clinical trial. A total of 455 patients with inadequately controlled diabetes were randomized to insulin degludec U-100 or insulin detemir once-daily in the evening.[151] After 8 weeks, insulin detemir could be dosed twice-daily. By trial end, 32.9% of patients on insulin detemir dosed twice daily. At week 26, the difference in HbA1c reduction from baseline between insulin degludec and insulin detemir was -0.09% (95% CI, -0.23 to 0.05). Non-inferiority was met. At week 26, 41.1% of patients on insulin degludec and 37.3% of those on insulin detemir achieved HbA1c < 7%. The incidence of severe hypoglycemia was similar between treatment groups (10.5% versus 10.6%). Mean weight gain reported was 1.5 kg for insulin degludec versus 0.4 kg for insulin detemir.

insulin degludec (Tresiba) versus insulin glargine (Lantus)

In a 52-week, open-label study, 629 patients with inadequately controlled type 1 diabetes mellitus were randomized to insulin degludec U-100 once-daily with the evening meal or insulin glargine U-100 once-daily according to the package insert.[152] Mealtime insulin aspart was also administered in both arms. At week 52, the difference in HbA1c reduction from baseline between insulin degludec and insulin glargine was -0.01% (95% CI, -0.14 to 0.11). Non-inferiority was met. At week 52, 39.8% of patients on insulin degludec and 42.7% of those on insulin glargine achieved HbA1c < 7%. Severe hypoglycemia occurred in 12.3% of patients in the insulin degludec group and 10.4% in the insulin glargine group. Mean weight gain reported was comparable between the groups (2.1 kg versus 2 kg).

In a 26-week open-label study, 493 patients with inadequately controlled type 1 diabetes mellitus were randomized to insulin degludec U-100 injected once daily with the main evening meal, or insulin degludec injected once daily at any time of day, or insulin glargine dosed once daily in the evening. [153] Mealtime insulin aspart was administered in all groups. At week 26, the difference in HbA1c reduction from baseline between insulin degludec administered at the same time and at alternating times, each compared to insulin glargine was 0.16% and 0.17%, respectively. Non-inferiority was met. Severe hypoglycemia occurred in 10.4% of patients in the insulin degludec flexible dose group, 12.7% of patients in the insulin degludec evening meal dose group and 9.9% in the insulin glargine group. Mean weight gain reported was 1.3 kg for insulin degludec flexible dose group, 0.9 kg in the insulin degludec evening meal dose group, and 1.7 kg in the insulin glargine group.

An open-label study randomized 1,030 insulin-naïve patients with inadequately controlled type 2 diabetes mellitus to insulin degludec U-100 once-daily with the evening meal or insulin glargine U-100 once-daily.[154] Background therapy consisted of metformin with or without a dipeptidyl peptidase-4 (DPP-4) inhibitor in both groups. At week 52, the difference in HbA1c reduction from baseline between

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insulin degludec and insulin glargine was 0.09% (95% CI, -0.04 to 0.22). Non-inferiority was met. At week 52, 51.7% of patients on insulin degludec and 54.1% of those on insulin glargine achieved HbA1c < 7%. Severe hypoglycemia was reported in 0.3% of patients in the insulin degludec group, 1.9% of patients in the insulin glargine group.[155] Mean weight gain reported was similar between the groups (2.6 kg versus 2.3 kg).

A total of 457 insulin-naïve patients with type 2 diabetes were randomized to insulin degludec U-200 once-daily with the evening meal or insulin glargine U-100 once-daily in an open-label study.[156] Background therapy consisted of metformin with or without a DPP-4 inhibitor in both groups. At week 26, the difference in HbA1c reduction from baseline between insulin degludec and insulin glargine was 0.04% (95% CI, -0.11 to 0.19). Non-inferiority was met. At week 26, 52.2% of patients on insulin degludec and 55.9% of those on insulin glargine achieved HbA1c < 7%. No incidences of severe hypoglycemia were reported it either group.[157] Mean weight gain reported was similar between the groups (2.3 kg versus 1.9 kg).

In an open-label study, 435 insulin-naïve patients with type 2 diabetes were randomized to insulin degludec U-100 once-daily with the evening meal or insulin glargine U-100 once-daily.[158] Background therapy with 1 or more oral anti-diabetic drugs (OADs) was continued. At week 26, the difference in HbA1c reduction from baseline between insulin degludec and insulin glargine was 0.11% (95% CI, -0.03 to 0.24). At week 26, 40.8% of patients on insulin degludec and 48.6% of those on insulin glargine achieved HbA1c < 7%. Non-inferiority was met. No incidence of severe hypoglycemia was reported it either group.[159] Mean weight gain reported was similar between the groups (1.6 kg and 1.7 kg).

In an open-label study, 687 patients with type 2 diabetes were randomized to insulin degludec U-100 injected once-daily with the main evening meal, insulin degludec injected once daily at any time each day, or to insulin glargine U-100 injected once-daily according to the approved labeling.[160] Background therapy with up to 3 of the following agents was continued, metformin, a sulfonylurea, a glinide, or a TZD. At week 26, the difference in HbA1c reduction from baseline between insulin degludec administered at the same time and at alternating times, each compared to insulin glargine was 0.18% and 0.04%, respectively. Non-inferiority was met. The proportion of patients who achieved HbA1c < 7% were 40.8% for those given insulin degludec dosed at the same time each day, 38.9% for insulin degludec dosed at varying times, and 43.9% for insulin glargine. Severe hypoglycemia occurred in < 1% of patients in all treatment groups.[161] Mean weight gain reported was similar between the groups (1.9 kg and 1.6 kg).

A total of 992 patients with type 2 diabetes were randomized to insulin degludec U-100 injected once-daily with the main evening meal, or insulin glargine U-100 injected once-daily.[162] Insulin aspart was administered before each meal in both treatment arms in an open-label study. Metformin and/or pioglitazone were used as background therapy in both treatment arms. At week 52, the difference in HbA1c reduction from baseline between insulin degludec and insulin glargine was 0.08% (95% CI, -0.05 to 0.21). Non-inferiority was met. A similar proportion of patients achieved HbA1c < 7% in each group. The incidence in severe hypoglycemia was similar between treatment groups (4.5% versus 4.4%).[163] Mean weight gain was also similar between the groups (3.2 kg versus 3.5 kg).

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

In an open-label, controlled, multicenter trial, 708 patients with HbA1c levels between 7% to 10.0% 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).[164] The primary outcome measure at 1 year was HbA1c. Secondary measures included the proportion of patients with an HbA1c of 6.5% or less, the rate of hypoglycemia, and weight gain. At 1 year, HbA1c was similar in the biphasic group and the insulin aspart group (7.3% versus 7.2%, respectively; p=0.08), but higher in the basal group (7.6%, p<0.001 for both comparisons). The proportions of patients with a HbA1c less than or equal to 6.5% were similar in the biphasic and prandial groups (17% and 23.9%, respectively; p=0.08), but was lower in the basal group (8.1%; p≤0.01 for both comparisons). Mean numbers of hypoglycemic events per patient per year were 5.7%, 12%, and 2.3%, for the biphasic, prandial and basal groups, respectively; and mean weight gains were 4.7 kg, 5.7 kg, and 1.9 kg, respectively. Rates of adverse events were similar among the 3 groups.

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

The study was an open-label, parallel-group comparison conducted at 46 centers in 5 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.[165] After 6 months, comparable HbA1c levels were found between the 2 treatment groups. FPG was lower in patients treated with insulin detemir (-0.76 mmol/L), but this difference was not statistically significant (p=0.097). Within-subject variation of self-measured FPG was lower with insulin detemir than with NPH insulin (3.37 versus 3.78 mmol/L, p<0.001). Risk of hypoglycemia was 22% lower with insulin detemir than with NPH insulin (p<0.05) and 34% lower for nocturnal hypoglycemia (p<0.005). Nightly plasma glucose profiles were smoother and more stable with insulin detemir (p=0.05). Body weight was significantly lower with insulin detemir at the end of the trial (p<0.001).

Patients with 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.[166] Insulin aspart was the mealtime insulin. Although HbA1c for each insulin detemir group was not different from the NPH group at endpoint, HbA1c for the pooled insulin detemir groups was significantly lower than the NPH group (mean difference -0.18%; p=0.027). With both insulin detemir groups, 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%, p=0.046; 32%, p=0.002; respectively) compared with NPH insulin in the last 12 weeks of treatment, mainly attributable to a reduction in nocturnal hypoglycemia in the insulin detemir breakfast/bedtime group (p<0.001). Few severe hypoglycemic episodes were recorded, with no statistical differences between the groups. The NPH group gained weight during the study, but there was no clinically significant change in weight in either of the insulin detemir groups (-0.8 kg, p=0.006; -0.6 kg, p=0.04, respectively).

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A multinational, open-label, parallel-group trial studied 505 patients with type 2 diabetes.[167] 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%; NPH insulin, 7.5%). 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 2 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.[168] HbA1c was comparable among the 3 groups after 16 weeks, with reductions of 0.39% to 0.49% (p=0.64). Lower FPG was observed with insulin detemir morning/dinner and insulin detemir morning/bedtime compared with NPH groups (9.8 mmol/L and 9.1 mmol/L versus 11.1 mmol/L, p=0.006), but the insulin detemir groups did not differ significantly (p=0.15). Within-person variation in self-measured FPG was significantly lower for both insulin detemir regimens than for NPH (SD: insulin detemir morning/dinner 2.5, insulin detemir morning/bedtime 2.6, NPH 3.1 mmol/L, p<0.001) but was comparable between the 2 insulin detemir groups (p=0.48). Ten-point plasma glucose profiles were lower between dinner and breakfast in the insulin detemir morning/dinner group (p=0.043) compared with the 2 other groups. Risk of overall and nocturnal hypoglycemia was similar for the 3 groups.

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

In 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.[169] Glycemic control with insulin detemir/insulin aspart was improved in comparison with NPH insulin/regular human insulin (HbA1c: 7.88% versus 8.11%; p<0.001). Lower postprandial plasma glucose levels were seen in the insulin detemir/insulin aspart group (p<0.001), as well as lower within-person day-to-day variation in plasma glucose (SD: 2.88 versus 3.12 mmol/L; p<0.001). Risk of overall and nocturnal hypoglycemia was 21% (p=0.036) and 55% (p<0.001) lower in the insulin detemir/insulin aspart group than in the NPH insulin/regular human insulin group, respectively.

A 22-week, multinational, open-label, randomized, parallel-group trial enrolled 395 patients with 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.[170] At 22 weeks, HbA1c was comparable between treatments (insulin detemir group: 7.46%, NPH group: 7.52%, p=0.515) with decreases from baseline of 0.65% and 0.58%, respectively. The insulin detemir group was associated with a significantly lower within-person variation in self-measured FPG (SD: 1.2 versus 1.54 mmol/L, p<0.001), as well as a lower body weight gain (0.51 kg versus 1.13 kg, p=0.038) than with the NPH group. The risk of nocturnal hypoglycemia was 38% lower with the insulin detemir group compared to the NPH group (p=0.14). The overall safety profile was similar between the 2 treatments.

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insulin glargine 100 U/mL (Lantus) versus 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.[171] NPH insulin patients maintained their regimen of either once daily or twice daily injections whereas insulin glargine patients received once daily injections at bedtime. All patients continued to administer individually titrated insulin lispro before meals. Insulin glargine patients had lower self-reported fasting blood glucose concentrations. More patients achieved a fasting blood glucose concentration of less than 119 mg/dL in the insulin glargine group (29.6%) than in the NPH insulin group (16.8%). No differences were noted in the HbA1c or hypoglycemic episodes between the groups. Less variability of blood glucose concentrations was noted in the insulin glargine group. More injection site pain was reported in the insulin glargine group (6.1%) than in the NPH group (0.3%).

In a multicenter, randomized, open-label, parallel-group study, 534 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.[172] A small decrease in HbA1c levels was noted with both insulin glargine (-0.16%) and NPH insulin (-0.21%; p>0.05). Significant reductions in median FPG levels from baseline (-1.67 versus -0.33 mmol/L with NPH insulin, p=0.0145) were achieved with insulin glargine compared to NPH insulin. After the 1-month titration phase, significantly fewer subjects receiving insulin glargine experienced symptomatic hypoglycemia (39.9% versus 49.2%; p=0.0219) or nocturnal hypoglycemia (18.2% versus 27.1%; p=0.0116) compared with subjects receiving NPH insulin.

Patients with 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.[173] A greater mean decrease in FBG was achieved at endpoint with insulin glargine compared with NPH insulin (-21 versus -10 mg/dL; p=0.015), and a greater percentage of patients treated with insulin glargine reached the target FBG (32.6% versus 21.3%; p=0.015). Similar percentages of patients in both treatment groups achieved HbA1c values of 7% or less at endpoint. After the 1-month titration phase, the percentage of patients who reported at least 1 symptomatic hypoglycemic event confirmed by a blood glucose value of less than 50 mg/dL was significantly lower with insulin glargine than with NPH insulin (73.3% versus 81.7%; p=0.021). Severe hypoglycemia was also significantly reduced in insulin glargine patients.

In an open-label, 24-week, multicenter trial, 765 patients with type 2 diabetes on 1 or 2 oral medications with inadequate glycemic control (HbA1c greater than 7.5%) were randomized to either bedtime insulin glargine 100 U/mL or NPH insulin once daily and also continued their prestudy medications.[174] Mean FPG at end point was similar with insulin glargine and NPH (117 versus 120 mg/dL), as was HbA1c (6.96% versus 6.97%). A majority of patients (approximately 60%) attained HbA1c less than 7% with each insulin type. However, nearly 25% more patients attained this without documented nocturnal hypoglycemia (≤ 72 mg/dL) with insulin glargine (33.2% versus 26.7%; p<0.05). Rates of other categories of symptomatic hypoglycemia were 21% to 48% lower with insulin glargine.

A total of 518 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.[175] The treatment groups showed similar improvements in HbA1c from baseline to end point on intent-to-treat analysis. The mean change in HbA1c from baseline to endpoint was similar in the insulin glargine group (-0.41% ± 0.1%) and the NPH group (-0.59% ± 0.1%). The treatments were associated with similar reductions in

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fasting glucose levels. Overall, mild symptomatic hypoglycemia was similar in insulin glargine subjects (61.4%) and NPH insulin subjects (66%). However, nocturnal hypoglycemia in the insulin glargine group was reduced by 25% more than the NPH group during the treatment period after the dose-titration phase (26.5% versus 35.5%, p=0.0136). Patients in the insulin glargine group experienced less weight gain than those in the NPH group (0.4 versus 1.4 kg, p<0.0007).

In an open-label, randomized, controlled trial, 695 patients with 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.[176] HbA1c levels improved by -1.24% with morning insulin glargine, -0.96% with bedtime insulin glargine, and -0.84% with bedtime NPH insulin. HbA1c improvement was more pronounced with morning insulin glargine than with NPH insulin (p=0.001) or bedtime insulin glargine (p=0.008). Baseline to endpoint fasting blood glucose levels improved similarly in all 3 groups. Nocturnal hypoglycemia was less frequent with morning (17%) and bedtime insulin glargine (23%) than with bedtime NPH insulin (38%, p<0.001).

In a multicenter, open-label, randomized study, 570 patients with type 2 diabetes were treated with insulin glargine 100 U/mL or NPH insulin given once daily at bedtime.[177] Previous oral antidiabetic therapy was continued throughout the study. At 52 weeks, there was a trend toward a decrease in HbA1c values from baseline to endpoint with both drugs (insulin glargine: -0.46%; NPH insulin: -0.38%; p=0.415). Over the entire treatment period, NPH insulin-treated patients (41%) and insulin glargine-treated patients (35%) experienced a similar level of symptomatic hypoglycemia, but there was a statistically significant difference in the percentage of patients that experienced nocturnal hypoglycemia in NPH patients compared with those treated with insulin glargine in the overall population (24% versus 12%,respectively p=0.002). The incidence of adverse events was similar for the 2 treatments.

Glycemic control and symptomatic hypoglycemia rates with insulin glargine 100 U/mL versus NPH were studied in 125 poorly controlled type 1 diabetes patients.[178] 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% for the insulin glargine versus NPH groups, but HbA1c was lower in the insulin glargine versus NPH group at study initiation (9.2% versus 9.7%). Adjusted least-squares mean change from baseline was -1.04% versus -0.51%, a significant treatment benefit in favor of insulin glargine (p<0.01). The mean values for end-point FBG were 7.9 versus 9 mmol/L in favor of insulin glargine (p<0.05). Significantly fewer moderate or severe nocturnal hypoglycemic episodes were observed in the insulin glargine group (p=0.04 and p=0.02).

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.[179] Patients with poorly controlled type 2 diabetes on oral antidiabetic agents (HbA1c 7.5% to 10.5%) 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%; p<0.01).

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insulin glargine 100 U/mL (Lantus) versus human insulin 70/30

In a 24-week, multinational, multicenter, open-label, parallel-group clinical trial, 371 insulin-naïve patients with type 2 diabetes and poor glycemic control on a sulfonylurea plus metformin were randomized to daily morning insulin glargine 100 U/mL plus glimepiride and metformin or to insulin 70/30 twice daily without oral antidiabetic agents.[180] Mean HbA1c decrease from baseline was significantly more pronounced (-1.64% versus -1.31%, p=0.0003), and more patients reached HbA1c less than 7% without confirmed nocturnal hypoglycemia (45.5% versus 28.6%, p=0.0013) with the insulin glargine arm than with insulin 70/30. Similarly, FBG decrease was greater in the insulin glargine group (adjusted mean difference -17 mg/dL; p<0.0001), and more patients reached target FBG under 100 mg/dL with insulin glargine than with insulin 70/30 (31.6% versus 15%, p=0.0001). Insulin glargine patients had fewer confirmed hypoglycemic episodes than insulin 70/30 patients (4.07 versus 9.87 episodes/patient-year, p<0.0001).

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

In a 52-week multinational, open-label, parallel-group, treat-to-target, 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% 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.[181] 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% with or without a major hypoglycemic episode in the last month of treatment and FBG. Results after 52 weeks showed no significant differences in mean HbA1c between insulin detemir and insulin glargine groups (7.57% and 7.56%, respectively; mean difference, 0.01%; 95% CI, -0.13 to 0.16). Additionally, there was no significant difference in the proportion of patients receiving insulin detemir and insulin glargine in achieving an HbA1c value equal to or lower than 7% without major hypoglycemia (31.9% and 28.9%, respectively). In addition, there were no significant differences in estimated mean FPG (8.58 and 8.81 mmol/L; mean difference, -0.23 mmol/L; 95% CI, -1.04 to 0.58) or in basal insulin doses. The relative risks for total and nocturnal hypoglycemia were not significantly different between insulin detemir and insulin glargine (0.94 and 1.12, respectively; p=NS).

In a 24-week, multinational, open-label, treat-to-target trial, 973 insulin-naïve patients with type 2 diabetes and an HbA1c of 7% to 10.5% were randomized to insulin detemir twice daily or insulin glargine 100 U/mL once daily.[182] Patients in this study had been treated with metformin for 3 months or greater prior to the study. The primary outcome was the percentage of patients reaching an HbA1c of less than 7% without symptomatic hypoglycemia. In the insulin glargine and insulin detemir groups, 27.5% and 25.6% of patients, respectively, reached HbA1c of less than 7%. It was demonstrated that insulin glargine once-daily is non-inferior to insulin detemir twice-daily regarding the percentage of patients who achieve a target HbA1c without hypoglycemia. Insulin detemir-treated patients had less weight gain and more often achieved HbA1c of less than 6.5% (p=0.017). However, the drop-out rate and daily insulin doses were lower in the insulin glargine group.

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

In a 26-week, multicenter, open-label, parallel-group trial, 320 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.[183] After 26 weeks, HbA1c decreased from 8.8% to 8.2% in the insulin detemir group and from 8.7% to 8.2% in the insulin glargine group. The overall risk of hypoglycemia was similar; however, the risk of severe and nocturnal hypoglycemia was 72% and 32% lower, respectively, with insulin detemir than with insulin glargine ($p<0.05$). Body weight gain was not significantly different between treatment arms.

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

The 28-week parallel-group study randomized 233 insulin-naive patients on more than 1,000 mg daily metformin alone or in combination with other oral antidiabetic agents to receive biphasic insulin aspart twice daily or insulin glargine 100 U/mL at bedtime and titrated to target blood glucose.[184] At study end, the mean HbA1c value was lower in the biphasic insulin aspart group than in the insulin glargine group (6.91% versus 7.41%, $p<0.01$). The HbA1c reduction was greater in the biphasic insulin aspart group than in the insulin glargine group (-2.79% versus -2.36%, $p<0.01$), especially for subjects with baseline HbA1c greater than 8.5% ($p<0.05$). Minor hypoglycemia was greater in the biphasic insulin aspart group than in the insulin glargine group (3.4 and 0.7 episodes/year; $p<0.05$), and weight gain at study end was greater for biphasic insulin aspart-treated subjects than for insulin glargine-treated subjects (5.4 versus 3.5 kg, $p<0.01$).

In the randomized, open-label, parallel study, biphasic insulin aspart plus metformin twice daily were compared with insulin glargine 100 U/mL plus glimepiride daily in 255 insulin-naïve patients.[185] The primary endpoint was the difference in absolute change in HbA1c between groups after 26 weeks of treatment. HbA1c change was significantly greater in the insulin aspart group than the insulin glargine group (between-group difference: -0.5%; $p=0.0002$). During the maintenance phase, 1 major hypoglycemic episode occurred in each group; 20.3% and 9% of patients experienced minor hypoglycemic episodes in the insulin aspart and insulin glargine groups, respectively ($p=0.0124$). Insulin glargine patients experienced significant weight gain of 1.5 kg ($p<0.0001$); the weight change with insulin aspart patients of +0.7 kg was not statistically significant ($p=0.0762$).

In a 26-week, open-labeled, randomized, parallel-group, multinational, treat-to-target trial, 480 insulin-naïve 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.[186] A total of 433 patients completed the trial. At the end of treatment, biphasic insulin aspart and insulin glargine reduced the mean HbA1c levels by -1.41% and 1.25%, respectively (95% CI, -0.3 to -0.02; $p=0.029$). After 26 weeks, the mean HbA1c levels were 7.1% for the biphasic insulin aspart group and 7.3% for the insulin glargine group. The relative risk for a nocturnal hypoglycemic episode was greater in the biphasic insulin aspart group than for insulin glargine (relative risk: 2.41; 95%CI, 1.34 to 4.34; $p=0.003$), although hypoglycemic rates were overall low with 3 major episodes occurring in each group.

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

In an open-label, multicenter study, 418 patients with 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 3 times daily (n=210).[187] The primary efficacy endpoint

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was the change in HbA1c from baseline to endpoint (week 44). There was no significant difference between the 2 treatment groups relative to mean reduction in HbA1c. The percentage of patients that reached HbA1c of 7% or less was 57% in the glargine group and 69% in the lispro group. However, the mean change in fasting blood glucose was significantly greater in the insulin glargine group (-4.3 mmol/L) compared to the insulin lispro group (-1.8 mmol/L; p<0.0001). Patients treated with insulin glargine were also shown to have greater reductions in nocturnal blood glucose compared with patients treated with insulin lispro (-3.3 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.

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

Patients with type 2 diabetes (n=374) were randomly assigned to insulin lispro mix 50/50 3 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.[188] Investigators could replace insulin lispro mix 50/50 with 75/25 at the evening meal if the fasting plasma glucose target was unachievable. At week 24, HbA1c was lower with insulin glargine (6.78% versus 6.95%, p=0.021), but HbA1c was reduced significantly from baseline for both therapies (p<0.0001). Non-inferiority of insulin lispro mix to insulin glargine was not demonstrated based on the prespecified noninferiority margin of 0.3%. The percentages of patients achieving target HbA1c varied depending on the specific target; statistically significant differences did occur in favor of insulin glargine at HbA1c less than 7% and HbA1c less than 6.5%. Rates of hypoglycemia were similar for both groups.

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

EDITION 4: In a 26-week open-label study, 546 adults with 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).[189] 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%, respectively) that met the pre-specified non-inferiority margin of 0.4%. Patients treated with insulin glargine 300 U/mL used 17.5% more basal insulin than patients treated with insulin glargine 100 U/mL. There were no clinically important differences in glycemic control when insulin glargine 300 U/mL was administered once daily in the morning or in the evening. Hypoglycemia was similar between the groups, except for during the first 8 weeks, when nocturnal confirmed or severe hypoglycemia was lower with insulin glargine 300 U/mL (rate ratio 0.69; 95% CI, 0.53 to 0.91).[190] There were no clinically important differences in body weight between treatment groups.

EDITION 1: 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.[191,192] 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% compared to insulin glargine 100 U/mL. Patients treated with insulin glargine 300 U/mL used 11% more basal insulin compared to those treated with insulin glargine 100 U/mL. A lower percentage of patients experienced at least 1 confirmed (≤ 70 mg/dl) or severe hypoglycemic event with the 300 U/mL concentration than the 100 U/mL concentration at any time of day (86% versus 92%; relative risk [RR],

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0.94; 95% CI, 0.89 to 0.99) and during the night (54% versus 65%; RR, 0.84; 95% CI, 0.75 to 0.94), although the annualized rates of such hypoglycemic events were similar. There were no clinically important differences in body weight between treatment groups.

In two 26-week, open-label studies, 1,670 adults with 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.[193] At the time of randomization, 808 patients were treated with basal insulin for more than 6 months (EDITION 2) and 862 patients were insulin-naïve (EDITION 3). At week 26, treatment with insulin glargine 300 U/mL provided a mean reduction in HbA1c that met the pre-specified non-inferiority margin of 0.4% compared to insulin glargine 100 U/mL. A lower percentage of patients experienced nocturnal hypoglycemia in the 300 U/mL groups than in the 100 U/mL groups (EDITION 2: RR 0.86 (95% CI, 0.73 to 1.01); EDITION 3: RR 0.76 (95% CI, 0.59 to 0.99).[194,195] When annualized, the EDITION 2 study reported a 37% relative reduction in nocturnal confirmed or severe hypoglycemic events with glargine 300 U/mL versus 100 U/mL, while the EDITION 3 study reported similar event rates in the 2 groups. Patients treated with insulin glargine 300 U/mL used 12% (EDITION 2) and 15% (EDITION 3) more basal insulin than patients treated with insulin glargine 100 U/mL. There were no clinically important differences in body weight between treatment groups.

insulin glulisine (Apidra) versus 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.[196] Changes in mean HbA1c were -0.26%, -0.11%, and -0.13% in the pre-meal insulin glulisine, post-meal insulin glulisine, and regular insulin groups, respectively. The reduction in HbA1c was greater for the pre-meal insulin glulisine group in comparison with the regular insulin group (p=0.02) and the post-meal insulin glulisine group (p=0.006); no significant difference was found between post-meal insulin glulisine versus regular insulin. Overall, blood glucose profiles were similar in all 3 treatment groups but were significantly lower for pre-meal insulin glulisine post-breakfast and post-dinner measurements. Severe hypoglycemic episodes were comparable for all groups. Body weight increased (+0.3 kg) in the regular insulin and pre-meal insulin glulisine groups; however, weight decreased in the post-meal insulin glulisine group (-0.3 kg; p=0.03).

Patients with type 2 diabetes who had received at least 6 months of continuous insulin therapy were randomized in a multinational, controlled, open-label, parallel group, 26-week study.[197] Patients (n=890) received NPH insulin twice daily and either insulin glulisine or regular insulin at least twice daily. There were no differences in HbA1c reductions (insulin glulisine: -0.32%; regular insulin: -0.35%; p=0.57). Insulin glulisine lowered plasma glucose significantly more versus regular insulin at 2 hours (14.14 mmol/L versus 15.28 mmol/L; p=0.0025). Nocturnal hypoglycemia from the fourth month to the end of treatment was less frequent with insulin glulisine versus regular insulin (9.1% versus 14.5%; p=0.029).

insulin glulisine (Apidra) versus insulin lispro (Humalog)

The objective of the multinational, multicenter, controlled, open-label, randomized, parallel-group study was to compare the efficacy and safety of insulin glulisine to that of insulin lispro in adults diagnosed with type 1 diabetes.[198] 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

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from baseline -0.14% in both groups). The basal insulin dose was relatively unchanged from baseline in the insulin glulisine group but increased in the insulin lispro group (insulin glulisine: 0.12 units versus insulin lispro: 1.82 units; p=0.0001). There was no relevant difference between the 2 groups in the reporting of symptomatic hypoglycemia (overall, nocturnal, or severe).

insulin lispro (Humalog) versus 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.[199] Two-hour post-breakfast and 2-hour post-supper blood glucose levels were significantly lower for insulin lispro than for regular human insulin at the end point (p=0.02 in both cases). HbA1c improved from 10.5% (insulin lispro) and 10.3% (regular human insulin) to 8% in each treatment arm. Hypoglycemia rates were similar during the day with a trend towards a reduced incidence in the night hours with insulin lispro (0.08 episodes/month versus 0.16 episodes/month, p=0.057).

Inhalation insulin

insulin inhalation powder (Afrezza) versus insulin aspart (Novolog) 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.[200] During a 4-week run-in period, subjects were converted to mealtime insulin aspart using a 1:1 unit conversion and titrated their basal insulin dosage to achieve a fasting plasma glucose (FPG) 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 units (equivalent to approximately 7.7 units SC insulin) and for insulin aspart by 1.6 units. The mean daily basal insulin dose was also higher in the inhaled insulin group than the insulin aspart group, 37.1 units versus 31.6 units, respectively. At week 24, treatment with basal insulin plus mealtime inhaled insulin provided less HbA1c reduction than insulin aspart (-0.21 versus -0.4%, respectively), and the difference (-0.19%) 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%. A greater proportion of patients in the insulin aspart group achieved the HbA1c target of less than or equal to 7% (30.7% versus 18.3%; p=0.0158). Patients treated with insulin inhalation powder experienced a mean decrease in weight of 0.39 kg, while those treated with insulin aspart showed a mean increase of 0.93 kg. Severe hypoglycemia was experienced in 18.4% of subjects on inhaled insulin and 29.2% of those on insulin aspart; the incidence of mild to moderate hypoglycemia was similar between the groups (96% and 99.6%, respectively). The most common respiratory adverse reaction was cough, which was reported in 31.6% of subjects in the inhaled insulin group and 2.3% for the insulin aspart group. Cough was generally mild and intermittent, but led to study discontinuation in 5.7% of patients that received inhaled insulin and 0% subjects on insulin aspart.

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In a 52-week, open-label trial, 539 patients with type 1 diabetes were randomized to insulin glargine 100 U/mL (basal) plus either insulin inhalation powder or insulin aspart.[201] Dose titration was permitted during the entire trial based on pre-meal and postprandial blood glucose levels. This trial did not meet its primary efficacy endpoint of noninferiority margin of 0.4% for insulin inhalation powder compared with insulin aspart. At Week 52 mean change in HbA1c was -0.13% and -0.37% for insulin inhalation powder and insulin aspart, respectively (difference 0.24; 95% CI, 0.08 to 0.404). A similar proportion of patients achieved HbA1c less than or equal to 7% in both groups (16.3% versus 16%, respectively). Patients treated with insulin inhalation powder reported a mean decrease in weight of 0.5 kg, while those treated with insulin aspart showed a mean increase of 1.4 kg. Incidence of hypoglycemia was reported in 0.08 events/subject-month for the inhaled insulin group and 0.1 events/subject-month for the insulin aspart group.

insulin inhalation powder (Afrezza) versus placebo for type 2 diabetes mellitus

A 24-week double-blind, placebo-controlled trial, enrolled adults with type 2 diabetes inadequately controlled on optimal or maximally tolerated doses of metformin monotherapy, or at least 2 oral antidiabetic agents.[202] Following a 6-week run-in period, 353 patients were randomized (1:1) to add-on therapy with insulin inhalation powder or an inhaled placebo powder. Insulin doses were titrated for the first 12 weeks and remained stable thereafter. Oral antidiabetic doses remained unchanged. Open-label rescue therapy (insulin glargine 100 U/mL or glimepiride) in addition to the study treatment was allowed in patients who experienced persistent or worsening hyperglycemia greater than pre-specified thresholds. At Week 24, the insulin group reported statistically significantly greater mean reduction in HbA1c compared to the placebo group (0.82% versus 0.42%; p<0.0001). A greater proportion of patients in the insulin group achieved the HbA1c target of less than or equal to 7% (32.2% versus 15.3%, respectively; p=0.0005). Patients in the insulin group experienced a mean increase in weight of 0.5 kg, while those in the placebo group reported a mean decrease of 1.1 kg. Severe hypoglycemia was reported in 5.7% of patients on inhaled insulin and 1.7% of those who received placebo. Cough was reported in 24% of the active treatment group and 20% of the placebo group.

insulin inhalation powder (Afrezza) plus insulin glargine 100 U/mL (Lantus) versus human insulin 70/30 for type 2 diabetes mellitus

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.[203] For patients assigned to insulin glargine plus inhaled insulin, half of the total daily pre-randomization insulin dose was replaced with mealtime inhaled insulin and the remaining was replaced by basal insulin glargine. Dose titration was permitted throughout the study. At Week 52, mean change in HbA1c were -0.59% and -0.71% for insulin glargine/inhaled insulin and biphasic insulin, respectively. Non-inferiority (margin 0.4%) of inhaled insulin plus basal insulin was demonstrated compared to biphasic insulin (difference 0.12%; 95% CI, -0.05 to 0.29). A greater proportion of patients in the biphasic insulin group achieved the HbA1c target of less than or equal to7% (26.8% versus 22.1%, 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%, 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.

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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.[204] The outcomes examined included fasting glucose, postprandial glucose, HbA1c, and weight gain. Mortality data are scant. Of the 45 studies, 43 were randomized controlled trials. The studies included a total of 14,603 patients with a mean age of 59 years, a median HbA1c of 8.7%, and a mean body mass index (BMI) of 29.4 kg/m2. 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) 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). 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 [219.2 mg/dL; 95% CI, 225.9 to 212.5]). 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, fasting plasma glucose, 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% to 0.2%, decrease the incidence of hypoglycemia episodes by about 20%, decrease nocturnal hypoglycemic episodes by 25% to 50%, and decrease fasting plasma glucose levels compared to human insulins. Insulin glulisine studies show an additional decrease in HbA1c of about 0.1%, as well. All of these products may be administered with a meal rather than the 30 to 60 minutes prior to a meal for regular human insulin. Insulin aspart vials and cartridges are latex-free, and the solution contains less metacresol than insulin lispro, 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 patient with diabetes. Both insulin lispro and insulin aspart combinations have a faster onset of activity and shorter duration of action than biphasic human insulin. Insulin glulisine is not available in such a combination.

Insulin degludec (Tresiba), insulin detemir (Levemir), and insulin glargine (Lantus, Toujeo) have changes in the insulin amino acid sequence. They produce a longer duration of action with minimal peak effect and are used as basal insulins. All 3 agents may be used in type 1 diabetics as basal insulin, and in

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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%, decrease nocturnal hypoglycemic episodes by 25% to 33%, and generally have lower fasting plasma glucose 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.

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