Therapeutic Class Overview
Insulins

Therapeutic Class

- **Overview/Summary:** This review will focus on the antidiabetic insulins, including human insulin products and synthetic insulin analogs.[1-18] Insulin products are Food and Drug Administration (FDA)-approved improve glycemic control in patients with diabetes mellitus (DM) type 1 and type 2. DM is a group of metabolic disorders with types 1 and 2 being the broadest categories. All categories of DM ultimately results in hyperglycemia, but the etiologies for each are distinct and may include reduced insulin secretion, decreased glucose utilization, or increased glucose production. Due to the metabolic dysregulation of DM, secondary pathophysiologic changes in multiple organ systems occur. Examples of severe complications that may occur include end-stage renal disease (ESRD), nontraumatic lower extremity amputation, and adult blindness. Additionally, it also predisposes the patient to cardiovascular disease.[19] Overall, there are a variety of oral and injectable antidiabetic agents currently available to treat diabetes. Available insulin products are summarized in Table 1. Insulin therapy is usually administered by subcutaneous injection, which allows for prolonged absorption and less pain compared to intramuscular injection.[1-18,20] Additionally, regular insulin is also formulated as an inhalation.[4] At least one formulation of all insulin products are supplied in multidose vials, with the exception of insulin degludec.[1-18] Inhaled insulin powder is formulated in disposable, single-use cartridges, known as Technosphere® which provided a more efficient inhalation device than what has been used in the past.[4] Another inhaled formulation of regular insulin, Exubera®, was previously FDA-approved; however, this agent was removed from the market in 2007 due to low patient and provider acceptance.[21] All insulin products have at least one formulation with a concentration of 100 units/mL (U-100). Several agents are also formulated with a higher concentration, regular insulin as 500 units/mL (U-500; Humulin® R U-500), and insulin glargine as 300 units/mL (U-300; Toujeo® SoloSTAR) and insulin degludec (Tresiba®) and insulin lispro (Humalog U-200®).[1-18]

Table 1. Current Medications Available in the Therapeutic Class[1-18]

Generic (Trade Name)	FDA-Approved Indications	Dosage Form/Strength	Generic Availability
Single Entity Products			
Insulin aspart (NovoLog®, NovoLog® FlexPen, NovoLog® PenFill)	To improve glycemic control in diabetes mellitus*	Cartridge: 100 units/mL Pen: 100 units/mL Vial: 100 units/mL	-
Insulin degludec (Tresiba®)	To improve glycemic control in diabetes mellitus*	Pen: 100 units/mL 200 units/mL	-
Insulin detemir (Levemir®, Levemir® FlexTouch)	To improve glycemic control in diabetes mellitus*	Pen: 100 units/mL Vial: 100 units/mL	-
Insulin glargine (Lantus®, Lantus® SoloSTAR, Toujeo® SoloSTAR)	To improve glycemic control in diabetes mellitus*	Pen: 100 units/mL (Lantus® SoloSTAR) 300 units/mL	-

Generic (Trade Name)	FDA-Approved Indications	Dosage Form/Strength	Generic Availability
		(Toujeo® SoloSTAR) Vial: 100 units/mL	
Insulin glulisine (Apidra®, Apidra® SoloSTAR)	To improve glycemic control in diabetes mellitus*	Pen: 100 units/mL Vial: 100 units/mL	-
Insulin lispro (Humalog®, Humalog® KwikPen, Humalog® U-200 KwikPen)	To improve glycemic control in diabetes mellitus*	Cartridge: 100 units/mL Pen: 100 units/mL 200 units/mL Vial: 100 units/mL	-
Insulin NPH (isophane), (Humulin® N, Humulin® N KwikPen, Novolin® N, Novolin® N ReliOn)	To improve glycemic control in diabetes mellitus*	Pen: 100 units/mL Vial: 100 units/mL	-
Insulin regular (Afrezza®, Humulin® R, Humulin® R U-500, Humulin® R U-500 KwikPen, Novolin® R)	To improve glycemic control in diabetes mellitus* Treatment of diabetic patients with marked insulin resistance*,†	Inhalation powder (Afrezza®): 4 units/cartridge Inhalation powder pack (Afrezza®): 4 units-8 units 8 units-12 units Vial: 100 U/mL 500 U/mL (Humulin® R U-500, Humulin® R U-500 KwikPen)	-
Combination Products			
Insulin aspart/insulin aspart protamine (NovoLog® Mix 70/30, NovoLog® 70/30 Flex Pen)	To improve glycemic control in diabetes mellitus*	Pen: 70/30 units/mL Vial: 70/30 units/mL	-
Insulin lispro/insulin lispro protamine (Humalog® Mix 50/50, Humalog® Mix 75/25, Humalog® Mix 50/50 KwikPen, Humalog® Mix 75/25 KwikPen)	To improve glycemic control in diabetes mellitus*	Pen: 50/50 units/mL 75/25 units/mL Vial: 50/50 units/mL 75/25 units/mL	-
Insulin, regular/insulin, NPH (Humulin® 70/30, Humulin®	To improve glycemic control in diabetes mellitus*	Pen: 70/30 units/mL	-

Generic (Trade Name)	FDA-Approved Indications	Dosage Form/Strength	Generic Availability
70/30 KwikPen, Humulin® 70/30 Pen, Novolin® 70/30, Novolin® 70/30 ReliOn)		Vial: 70/30 units/mL	

FDA=Food and Drug Administration
*Includes diabetes mellitus type 1 and type 2. Generally, these agents have not been studied for the treatment of type 2 diabetes in pediatric patients. Additionally, some agents may carry an indication for use in pediatric patients, but have never been studied in that population.
†Humulin® R U-500 only

Evidence-based Medicine

- There are numerous clinical trials demonstrating the safety and efficacy of insulin products in the management of diabetes type 1 and 2.[22-157] Of note, only head-to-head or active-comparator trials have been included as insulin is a well-established treatment.
- The efficacy and safety of insulin degludec was evaluated in the BEGIN clinical trial program. This included multiple 26-week and 52-week clinical trials with several trials being extended to 78 or 104 weeks in order to gather additional long-term safety and efficacy data. Insulin degludec once-daily injection was evaluated in both insulin-naïve and insulin-experienced adults with type 1 and 2 diabetes who had inadequate blood sugar control at trial entry.[13,47-49,75-81]
    - Hemoglobin A1c (HbA1c) reduction was in line with reductions achieved with insulin glargine and insulin detemir (-0.3 to -0.6% decrease from baseline in type 1 DM and -1.0% to -1.5% decrease from baseline in type 2 DM).[13,47-49,75-81]
    - In addition, the agent was associated with a lower risk of hypoglycemia compared to insulin glargine.[13,47-49,75-81]
    - A meta-analysis of four of these trails demonstrated a lower rate of overall and nocturnal hypoglycemia in type 1 and 2 DM.[82]
    - A concentrated formulation of insulin degludec (200 units/mL) was compared to the standard formulation of insulin glargine with similar results.[83]
- The safety and efficacy of inhaled regular insulin (Afrezza®) in both diabetes type 1 and type 2. Clinical trials were 24 weeks each.[4,156,157]
    - For type 1 diabetes, inhaled regular insulin was non-inferior to insulin aspart for mean reduction in HbA_{1c}. However, it provided less HbA_{1c} reduction than insulin aspart (-0.4% vs -0.21%). On the other hand, there was a reduction in the rate of hypoglycemia (9.8 vs 14.0 events per subject month; P<0.0001) and less weight gain (−0.39 kg vs 0.93 kg; P=0.0102) with inhaled regular insulin.
    - For type 2 diabetes, mean reduction in HbA_{1c} was significantly greater in the insulin group compared to the placebo group (-0.82% vs -0.42%; 95% confidence interval [CI]: −0.57 to −0.23; P<0.0001).
- The safety and efficacy of insulin glargine U-300 (Toujeo®) was evaluated in four clinical trials. Each study compared insulin glargine U-300 to insulin glargine U-100 in an open label design over 26 weeks of therapy.
    - In all studies, insulin glargine U-300 was shown to be non-inferior to insulin glargine U-100. Additionally, the dose of basal glargine insulin required was higher in all studies for U-300 (requiring 11% to 17.5% more units). Generally, both U-100 and U-300 had similar rates of adverse events, including hypoglycemia and all three studies showed similar changes in weight.[12,84-86]
- Differences in safety and efficacy of insulin preparations are modest with slightly better improvement in in HbA_{1c} with the rapid-acting analogues compared to regular insulin.[45,46]
- Long-acting insulin analogs have been shown to be at least as effective as NPH insulin in HbA_{1c} reduction, with some studies showing a significant improvement associated with the long-acting insulin analogs compared with NPH insulin with similar rates of side effects.[68,115,116,118]

- When comparing the long-acting analogs head-to-head, several trials have demonstrated non-inferiority between the products in the same outcomes when used in the management of type 1 diabetes and as add-on therapy in type 2 diabetics.[50,51,88-90]
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Key Points within the Medication Class

- According to Current Clinical Guidelines:[158-168]
    - The goal of treatment for both type 1 and type 2 DM is to control hyperglycemia and reduce the risk of long-term complications.
    - For patients with type 1 DM, insulin therapy is required due to pathogenesis of the disease. The standard approach to therapy is a regimen that includes long-acting basal insulin and rapid-acting prandial insulin tailored to the individual.
    - For type 2 DM, there are many more options for therapy, including the insulin products, oral antidiabetic agents, and other injectable antidiabetic agents.
        - Metformin remains the cornerstone of most antidiabetic treatment regimens.
        - Patients with a high HbA_{1c} will likely require combination or triple therapy in order to achieve glycemic goals.
        - At this time, uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered.
    - For both conditions, the trend in treatment is toward a patient-centered approach focusing on patient needs, preferences and tolerances, individualized treatment, and flexibility in the choice of drugs, the over-riding goal being to improve glycemic control while minimizing adverse effects.
- Other Key Facts:[1-18]
    - Insulin therapy is usually administered by subcutaneous injection. Regular insulin is also formulated as an inhalation. At least one formulation of all insulin products are supplied in multidose vials with only regular insulin not being formulated in a prefilled pen or syringe.[1-18]
    - All insulin products have at least one formulation with a concentration of 100 units/mL.[1-18]
    - A Risk Evaluation and Mitigation Strategy (REMS) is required for this inhaled regular insulin and includes requirements for patient evaluation and testing prior to initiating therapy in order to ensure appropriate patient selection (e.g., avoiding this agent in patients with underlying chronic lung disease).
    - There are currently no generic formulations of insulin; however, there are several products available over-the-counter.

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