

Insulin degludec (Tresiba®): Ultra-long basal insulin with less nocturnal hypoglycemia than glargine

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Diabetes mellitus is a group of chronic metabolic conditions characterized by hyperglycemia and formally diagnosed with any of four options: (1) HbA_{1c} ≥6.5%; (2) fasting plasma glucose ≥126 mg/dL; (3) two-hour post-meal glucose ≥200 mg/dL; or, (4) random plasma glucose ≥200 mg/dL in patients with symptoms of hyperglycemia or hyperglycemic crisis. From 2010 to 2012, the prevalence of diabetes and prediabetes increased from 25.8 to 29.1 million people and 79 to 86 million people, respectively.¹ The incidence in this time frame has decreased from 1.9 to 1.7 million people, suggesting improvements in avoidance and identification of warning signs that lead to metabolic disorders.² Nevertheless, diabetes costs approach ~\$245 billion annually in the United States, with roughly three-quarters of the cost attributed to direct medical costs. The average medical expenditures for diagnosed diabetics are 2.3 times higher than in non-diabetic patients.² Complications of diabetes can be either acute, such as diabetic ketoacidosis or hyperosmolar coma, or chronic, including thromboembolic disorders, kidney disease, retinopathy, or neuropathy.²

While the majority of patients (~69%) with diabetes are not treated with insulin,³ most patients will eventually require exogenous insulin administration as the disease progresses. Exogenous insulin is derived from either pork pancreas or through genetic recombination and is available in a variety of formulations with different durations of action, from rapid-acting to long-acting formulations and agents. The purpose of this article is to highlight a new “ultra-long acting” insulin, degludec, and summarize the differences between degludec and other insulins. This article will also summarize the clinical trials evaluating degludec, describe adverse effects and precautions, and discuss possible economic factors related to its use.

CLINICAL PHARMACOLOGY

Insulin regulates blood glucose through stimulation of GLUT4 transporters in the periphery and inhibition of hepatic gluconeogenesis. Through formation of multi-hexamers in the subcutaneous tissue, insulin degludec induces a depot effect that prolongs absorption similar to insulin detemir. The steady-state concentration of degludec is reached in 3-4 days of repeated use with a plasma protein binding of >99% and a half-life of 25 hours, independent of dose. Clinical studies have revealed no clinically significant differences in metabolism with regard to older age, gender, race and ethnicity, or hepatic impairment. **Table 1** below highlights pharmacokinetic properties of existing insulins, including degludec.

Endogenous insulin is cleared through a combination of hepatic metabolism and renal elimination with some additional clearance through peripheral tissues.^{6,7} In contrast, exogenous insulin is primarily cleared by the kidney through glomerular filtration and subsequent metabolism in the proximal convoluted tubules by insulin degrading enzyme. Consequently, impaired renal function can lead to decreased clearance and an increased risk of hypoglycemia in patients administering insulin exogenously. In patients with end-stage renal disease (ESRD), insulin degludec maintains its pharmacokinetic parameters even in patients undergoing hemodialysis.⁸

PHASE III TRIALS

The BEGIN series of trials evaluated non-inferiority of insulin degludec to insulin glargine in adults with confirmed type 1 or 2 diabetes mellitus.⁹⁻¹¹ The primary endpoint for all trials was change in HbA_{1c} with secondary endpoints related to glucose control, including fasting plasma glucose, change in insulin dose required to maintain adequate glucose levels, and quality of life. These trials are summarized in **Table 2**.

BEGIN Once Long

The international BEGIN Once Long trial assessed the non-inferiority of insulin degludec and glargine, each combined with daily metformin, over 52 weeks.⁹ Patients were eligible if they were aged ≥18 years with type 2 diabetes for ≥6 months, had an HbA_{1c} between 7% and 10%, and a BMI ≤40 kg/m². Exclusion criteria included use of thiazolidinediones, exenatide, or liraglutide in the 3 months prior to screening, clinically significant cardiovascular, hepatic, renal, or oncologic disease, recurrent severe hypoglycemia or hypoglycemia unawareness, or proliferative retinopathy. Patients were randomly assigned to receive insulin degludec once daily with their evening meal or insulin glargine once daily at a time chosen by the patient and investigator. Patients were directed to discontinue all oral antidiabetic drugs (OADs) at the start of trial with the exception of metformin and a dipeptidyl peptidase-4 (DPP-4) inhibitor if they were already taking those



IN THIS ISSUE

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Table 1 | Pharmacokinetics of existing insulins.^{4, 5}

Type of Insulin	Generic (Brands in US)	Onset	Peak	Duration
Rapid	Aspart (Novolog), Glulisine (Apidra), Lispro (Humalog)	15 min	30 – 90 min	3 – 5 hours
Short	Humulin R, Novolin R	30 – 60 min	2 – 4 hours	5 – 8 hours
Intermediate	NPH (Humulin N, Novolin N)	1 – 3 hours	8 hours	12 – 16 hours
Long-acting	Detemir (Levemir), Glargine (Lantus)	1 hour	Peakless	20 – 26 hours
Ultra-long acting	Degludec (Tresiba)	1 hour	Peakless	42 hours
Pre-mixed NPH (intermediate-acting) and regular (short-acting)	Humulin 70/30, Novolin 70/30, Humulin 50/50	30 – 60 min	Varies	10 – 16 hours
Pre-mixed insulin lispro protamine suspension (intermediate-acting) and insulin lispro (rapid-acting)	Humalog Mix 75/25, Humalog Mix 50/50	10 – 15 min	Varies	10 – 16 hours
Pre-mixed insulin aspart protamine suspension (intermediate-acting) and insulin aspart (rapid-acting)	Novolog Mix 70/30	5 – 15 min	Varies	10 – 16 hours

agents. During the trial, insulin was titrated to achieve a prebreakfast plasma glucose of 3.9 to 4.9 mmol/L (70 to 88 mg/dL). After 52 weeks, participants were switched to NPH insulin with OADs for 1 week to ensure accurate assessment of anti-insulin antibody levels.

No significant differences were observed between the two treatment groups with regard to baseline characteristics. Following 52 weeks of therapy, patients assigned to degludec had, on average, a 4.08% reduction in HbA_{1c} compared with a 4.10% reduction in patients assigned to glargine (treatment difference, 0.09% [95% CI, -0.04 to 0.22]), thus demonstrating non-inferiority on the primary outcome. No significant difference was observed between treatment groups in rates of hypoglycemia or self-monitored blood glucose serum concentration. Similar percentages of patients experienced reduction of HbA_{1c} to below 7% without confirmed hypoglycemia (degludec, 42% vs. glargine, 46%; $p=0.34$) and without nocturnal confirmed hypoglycemia (degludec, 53% vs. glargine, 54%; $p=0.68$) in the last 12 weeks of treatment. Patients receiving degludec had significantly greater reduction in fasting plasma glucose (estimated treatment difference between degludec and glargine of -0.43 mmol/L [95% CI, -0.74 to -0.13 ; $p=0.005$]), patient reported improvements in “over-all physical” and “physical functioning,” (1.0 [95% CI, 0.1 to 2.0; $p=0.033$] for “overall physical” and 1.4 [95% CI, 0.3 to 2.4; $p=0.016$] for “physical functioning”) and confirmed reduction of nocturnal hypoglycemic episodes ($p=0.038$).⁹

BEGIN Basal-Bolus (Type 1 Diabetes)

The BEGIN Basal-Bolus study assessed non-inferiority of 52 weeks of treatment with insulin degludec and glargine, each combined with insulin aspart for mealtime therapy, in patients with type 1 diabetes mellitus.¹⁰ Similarly to the BEGIN Once Long study, patients were eligible if they were aged ≥ 18 years, with a diagnosis of type 1 diabetes mellitus at least 1 year prior to enrollment, an HbA_{1c} $< 10\%$, and a BMI ≤ 35 kg/m². Major exclusion criteria included use of antidiabetic medications other than insulin in the past 3 months, active cardiovascular disease, impaired liver or renal function, cancer, or previous recurrent hypoglycemia.

Patients on previous basal insulin therapy were randomly assigned to either glargine or degludec, at the same dose as their total daily basal regimen prior to study entry. Basal insulin was then titrated to meet a pre-breakfast plasma glucose concentration of 3.9 to < 5.0 mmol/L (78 to < 90 mg/dL). Bolus insulin was replaced with insulin aspart at a 1:1 unit conversion for all patients. At the end of the trial, basal insulin therapies were substituted with NPH insulin for detection of insulin antibodies.

Baseline characteristics and withdrawal patterns between both groups were similar. After 52 weeks of therapy, a comparison of HbA_{1c} reduction between glargine and degludec patients revealed no statistical difference in efficacy between the basal insulins (0.40% HbA_{1c} reduction for insulin degludec vs. 0.39% for glargine; estimated treatment difference, -0.01% [95% CI, -0.14 to 0.11 ; $p < 0.0001$]). Additionally, no significant differences were observed between groups with regard to laboratory-reported fasting plasma glucose (95% CI, -1.03 to 0.36 ; $p=0.35$) and mean weight gain (1.8 kg with insulin degludec vs. 1.6 kg with insulin glargine; $p=0.62$). Notably, degludec was associated with nocturnal hypoglycemia less often than glargine (3.91 vs. 5.22 episodes per patient-year [hazard ratio 0.73; 95% CI, 0.56 to 0.96]). There were no significant differences between treatment groups in health-related quality of life assessments or other physical examination findings.¹⁰

BEGIN Basal-Bolus (Type 2 Diabetes)

An additional BEGIN Basal-Bolus study was conducted for patients diagnosed with type 2 diabetes mellitus.¹¹ Selection parameters were slightly different from the aforementioned type 1 study; patients were eligible if they were aged ≥ 18 years with a diagnosis of type 2 diabetes for ≥ 6 months prior to enrollment and a BMI ≤ 40 kg/m². Exclusion criteria included current use of GLP-1 agonists or rosiglitazone. Participants were randomly assigned to glargine or degludec once daily with aspart for mealtime insulin. Randomization was stratified according to previous insulin regimen (basal only versus basal-bolus) or delivery system (pump versus other). All OADs aside from metformin or pioglitazone were discontinued at trial start. Basal insulins were titrated to

Table 2 | Summary of clinical trials for insulin degludec.

Trial	Design	Treatments	Endpoint(s)	Results	Authors' Conclusions
BEGIN Once Long⁹ (2012)	1 year, RCT, OL, PG, TTG, non-inferiority (n=1030)	<ul style="list-style-type: none"> • Degludec QD • Glargine QD • Both groups given metformin 	<ul style="list-style-type: none"> • <u>Primary</u>: change in HbA_{1c} • <u>Secondary</u>: FPG, SMBG, HbA_{1c} <7% responders, functional health status 	Comparable glucose control (4.08% reduction with degludec, 4.10% reduction with glargine), reduced nocturnal hypoglycemia with degludec (p=0.038)	Degludec provides similar improvements in long-term glycemic control for type 2 diabetic patients uncontrolled by oral antidiabetic drugs
BEGIN Basal-Bolus Type 1¹⁰ (2012)	1 year, RCT, OL, PG, TTG, non-inferiority (n=629)	<ul style="list-style-type: none"> • Degludec QD • Glargine QD • Both groups given aspart for meal-time insulin 	<ul style="list-style-type: none"> • <u>Primary</u>: change in HbA_{1c} • <u>Secondary</u>: FPG, SMBG, HRQoL 	Comparable glucose control (0.40% reduction with degludec, 0.39% with glargine), reduced nocturnal hypoglycemia with degludec (p=0.024)	Degludec might be a useful basal insulin in type 1 diabetic patients with reduced risk of nocturnal hypoglycemia
BEGIN Basal-Bolus Type 2¹¹ (2012)	1 year, RCT OL, PG, TTG, non-inferiority (n=992)	<ul style="list-style-type: none"> • Degludec QD • Glargine QD • Both groups given aspart for meal-time insulin 	<ul style="list-style-type: none"> • <u>Primary</u>: change in HbA_{1c} • <u>Secondary</u>: FPG, SMBG, prandial plasma glucose increment, time to SMBG target before breakfast, HRQoL 	Comparable glucose control (-1.10% with degludec, -1.18% with glargine), reduced hypoglycemia with degludec	Degludec has a lower risk of hypoglycemia than glargine

FPG = fasting plasma glucose; HRQoL = health-related quality of life; OL = open label; PG = parallel-group; QD = once daily; RCT = randomized controlled trial; SMBG = self-monitored blood glucose; TTG = treat-to-target.

prebreakfast glucose concentrations of 3.9 to <5.0 mmol/L (78 to <90 mg/dL) as with the other trial.

Baseline characteristics were similar between both groups at the beginning of the study. Similarly to the type 1 study, degludec was determined to be non-inferior to glargine for reduction of HbA_{1c}. Using similar insulin doses in each group, the estimated mean HbA_{1c} reduction from baseline was 1.10% with insulin degludec compared to 1.18% with insulin glargine, for an estimated treatment difference of 0.08% (95% CI, -0.05 to 0.21). Participants who used insulin degludec reported improved quality of life and experienced reduced hypoglycemia, both overall (estimated rate ratio, 0.82; 95% CI, 0.69 to 0.99) and for nocturnal rates only (estimated rate ratio, 0.75; 95% CI, 0.58 to 0.99). Adverse events, including weight gain, were not different between groups.¹¹

DEVOTE

DEVOTE is an ongoing trial comparing cardiovascular safety of insulin degludec to glargine, which began in October 2013 and will continue for up to 5 years.¹² This study is a multinational, randomized, double-blind, parallel-group trial evaluating time-to-first occurrence of a major adverse cardiovascular event (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke). Secondary outcomes include the number of severe hypoglycemic episodes and change in HbA_{1c}. This trial is limited to patients with type 2 diabetes and excludes patients with New York Heart Association Class IV heart failure or recent coronary or cerebrovascular events.¹²

ADVERSE EFFECTS AND PRECAUTIONS

Table 3 lists the most common side effects experienced during clinical trials. Notably, the incidence of nasopharyngitis in patients treated with insulin degludec was almost twice as high in patients with type 1 diabetes compared to those with type 2 diabetes. Depending on definitions of hypoglycemia, the reported incidence of hypoglycemia episodes during degludec therapy differed greatly, from 11% to 95%.

Contraindications for degludec are few and include hypersensitivity to components of degludec or use during an acute episode of hypoglycemia. Precautions noted by the manufacturer include unexpected changes in blood glucose, hypersensitivity reactions, hypokalemia, and fluid retention and congestive heart failure exacerbations when used with a peroxisome proliferator-activated receptor (PPAR)- γ agonists, such as thiazolidinediones. For patients taking PPAR- γ agonists who will be treated with insulin, observation for signs and symptoms of congestive heart failure is recommended. Reduction or discontinuation of PPAR- γ agonists should also be considered, as appropriate.

Major drug interactions with degludec are primarily concerned with symptoms and exacerbation of hypoglycemia. These interactions can be separated into 4 categories: drugs that may increase risk of hypoglycemia (e.g., ACE inhibitors, fibrates, MAO inhibitors, salicylates); drugs that may decrease blood glucose lowering effect of degludec (e.g., atypical antipsychotics, corticosteroids, oral contraceptives, sympathomimetic agents); drugs

Table 3 | Adverse events occurring in ≥5% of degludec-treated patients with diabetes mellitus in trials up to 1 year in duration.

Adverse Reaction	Type 1 Diabetes Patients (Tresiba) (n=1102)	Type 1 Diabetes Patients (Lantus) (n=1257)	Type 2 Diabetes Patients (Tresiba) (n=2713)	Type 2 Diabetes Patients (Lantus) (n=849)
Hypoglycemia	10.4 – 12.7% ^a 93.0 – 99.4% ^b	6.5 – 23.0% ^c	0 – 80.9% ^a 28.5 – 80.9% ^b	0.4 – 7.8% ^c
Nasopharyngitis	23.9%	NR	12.9%	NR
URTI	11.9%	22.4%	8.4%	11.4%
Headache	11.8%	5.5%	8.8%	NR
Sinusitis	5.1%	NR	NR	NR
Gastroenteritis	5.1%	NR	NR	NR
Diarrhea	NR	NR	6.3%	NR

NR = not reported.

^aDefined as “an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.”

^bDefined as “a severe hypoglycemia episode or an episode where a laboratory or a self-measured glucose calibrated to plasma was less than 56 mg/dL or where a whole blood glucose was less than 50 mg/dL (i.e., with or without the presence of hypoglycemic symptoms).”

^cDefined as “an event with symptoms consistent with hypoglycemia requiring the assistance of another person and associated with either a blood glucose below 50 mg/dL (≤56 mg/dL in the 5-year trial and ≤36 mg/dL in the ORIGIN trial) or prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration.”

that may increase or decrease blood glucose lowering effect of degludec (e.g., beta-blockers, clonidine, lithium); and, drugs that may obscure signs of hypoglycemia (e.g., beta-blockers, clonidine, guanethidine, reserpine). Some medications, such as beta-blockers and clonidine, appear in multiple categories and caution is advised with concurrent use of these agents with degludec.⁵

DOSING AND ADMINISTRATION

Insulin degludec is administered by a FlexTouch[®] pen with commercially-available strengths of both 200 units/mL and 100 units/mL. The starting dose for degludec with insulin-naïve patients is 0.2 to 0.4 units per kilogram body weight for type 1 diabetic patients and 10 units daily for type 2 diabetic patients based off clinical trials and dosing recommendations for other basal insulins. Patients already on insulin therapy can be transitioned to degludec from glargine or detemir at a 1:1 ratio of the total daily dose of basal insulin.⁵ Degludec can be injected subcutaneously in the back of upper arms, abdomen, or outer side of thighs. There are no special instructions for select patient populations. A trend was observed between patients with increasing BMI and reduced glucose-lowering effect for degludec among both type 1 and 2 diabetics.⁵ However, the clinical significance of this observation remains unclear and no recommendations have been made regarding dosing adjustments based on BMI.⁵ Insulin degludec should be refrigerated at 2 to 8 °C, but not frozen.

COSTS

Table 4 lists pricing for insulin degludec and two other basal insulins. Novo Nordisk currently provides a savings card to reduce the cost of degludec to \$15 per month for a maximum of 24 months or \$500 per prescription maximum. Patients cannot be enrolled in government, state, or federally funded medical or prescription benefit programs to be eligible for this savings card. For more information about the program, prescribers and patients can contact Novo Nordisk at 1-855-834-3466.

SUMMARY

Insulin degludec is a new “ultra long-acting” basal insulin with a greater duration of action compared with other available basal insulins and a reduced incidence of nocturnal hypoglycemia compared to glargine. Degludec produces similar control of blood glucose in patients with type 1 and 2 diabetes mellitus with similar adverse effects and contraindications in both patient populations. However, based on a sample of cash prices in the Gainesville, FL area, degludec appears to be modestly more expensive than glargine or detemir; costs and coverage may differ for patients with prescription insurance. Additional information concerning potential cardiovascular risk in type 2 diabetic patients with high risk for cardiovascular safety will be available upon completion of the DEVOTE trial (expected in 2018), which may help further elucidate the place in therapy for insulin degludec.

Table 4 | Average cash prices for basal insulins in Gainesville, FL.¹³

Basal Insulin	Quantity	Price
Degludec (Tresiba)	5 x 3-mL FlexTouch pens (100 units/mL)	\$475.00
Degludec (Tresiba)	3 x 3-mL FlexTouch pens (200 units/mL)	\$557.00
Glargine (Lantus)	5 x 3-mL SoloSTAR Pens (100 units/mL)	\$392.00
Glargine (Toujeo)	5 x 1.5-mL SoloSTAR Pens (300 units/mL)	\$619.00
Detemir (Levemir)	5 x 3-mL FlexTouch pens (100 units/mL)	\$423.00

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The ROCKET-AF study found that rivaroxaban, when compared to warfarin, was non-inferior in preventing thromboembolic events without increasing bleeding risk in patients with atrial fibrillation. According to a recently published report in the *BMJ*, the faulty devices may have made the results from the warfarin arm appear worse than they actually were.² Accordingly, these devices called into question the apparent safety results of rivaroxaban, because rivaroxaban may appear safer than it actually was in regards to bleeding risk.

In response, the authors of the ROCKET-AF study published results of a *post-hoc* analysis investigating the effect of these faulty devices on study results.³ The authors identified study patients with “recall conditions” and compared outcomes in the treatment subgroups. The analysis found that the primary efficacy and safety findings in patients with the “recall conditions” were consistent with the original study results. The authors concluded that the faulty devices likely did not have a “significant clinical effect” on the primary outcomes of the study.

Despite the response from the ROCKET-AF study authors, several questions still remain, such as whether other patient groups may have been affected by the faulty devices. An independent review of the results may help shed further light into whether the results of the study still remain valid. However, the implication of this situation has also put into question the transparency of the information provided by study investigators regarding INR devices utilized in other studies, as little public information is currently being disseminated.

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EDITOR'S CORNER

Validity of ROCKET-AF Study Questioned Due to Faulty INR Devices

The findings from the pivotal ROCKET-AF study, which were published in 2011, are being scrutinized after information regarding the use of faulty point-of-care (POC) INR devices in the warfarin arm have surfaced. These devices were suspected to deliver results that were “clinically significantly lower” than the laboratory method; resulting in unnecessary increases in warfarin doses and potentially placing patients at a higher risk for bleeding. According to the FDA, the issue appears to affect patients with certain conditions such as anemia with abnormal hematocrit levels and conditions that raise fibrinogen levels.¹

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