Long-Acting Human Insulin Analogs

Created: June 2014

Endogenous insulin is a hormone secreted by the beta cells of the pancreatic islets of Langerhans. Insulin acts via specific membrane-bound receptors on target tissues to regulate metabolism of carbohydrates, proteins and fats. Exogenous insulin, manufactured for pharmacologic use through recombinant DNA technology using either E. coli or Saccharomyces cerevisiae is used as replacement therapy in the management of diabetes mellitus. It supplements deficient levels of endogenous insulin and temporarily restores the ability of the body to properly utilize carbohydrates, fats and proteins. Insulin therapy is indicated in all cases of type 1 diabetes mellitus and in patients with type 2 diabetes mellitus when weight reduction, proper dietary regulation, and/or oral antidiabetic agents have failed to maintain satisfactory concentrations of blood glucose in both the fasting and postprandial state. In addition, insulin is indicated in the treatment of diabetic ketoacidosis and hyperosmolar hyperglycemic states, and in otherwise stable, type 2 diabetic patients in the presence of major surgery, fever, severe trauma, infections, serious renal or hepatic dysfunction, hyperthyroidism or other endocrine dysfunction, gangrene, Raynaud’s disease, or pregnancy.

Insulin aspart (NovoLog®), insulin lispro (Humalog®) and insulin glulisine (Apidra®) are rapid-acting insulin analogs indicated for treatment of type 1 and type 2 diabetes mellitus. Their pharmacokinetic parameters as reported in the product information are very similar. A number of small clinical trials have been performed comparing insulin aspart and insulin lispro pharmacokinetic and pharmacodynamic profiles, which suggest that few meaningful differences exist between the products. Insulin glulisine is effective when compared to other short- and rapid-acting insulins, demonstrating either; non-inferiority, no significant difference, or superiority in primary endpoints in studies involving patients with type 1 and type 2 diabetes. Insulin glulisine appears to be more rapidly absorbed compared to the other two agents, although this is likely insignificant from a clinical standpoint.

The long-acting insulin products currently on the market include insulin glargine (Lantus®) and insulin detemir (Levemir®). Based on clinical trials, both glargine and detemir offer more predictable glycemic control with less risk of hypoglycemia when compared to shorter acting insulin analogues. In addition, these agents are FDA approved and may be used for once daily dosing in many patients as a result of a 24-hour absorption profile and extended duration of action.

**Class/Pharmacologic Category:** Long-acting recombinant human insulin analogs

**Mechanism of Action:** Regulation of glucose metabolism through binding to insulin receptors and facilitating cellular uptake of glucose into skeletal muscle and adipose tissue, and by decreasing glucose output from the liver. Inhibits lipolysis and proteolysis, and enhances protein synthesis.
FDA Approved Indications:

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Indication/Dose</th>
<th>Dose</th>
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</thead>
<tbody>
<tr>
<td>Insulin detemir (Levemir®)</td>
<td>To improve glycemic control:</td>
<td>Dose should be individualized** and may be administered subcutaneously once or divided doses twice daily</td>
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<tr>
<td>Approved 2005</td>
<td>in adults and *<em>children ≥2 years of age with type 1 diabetes mellitus</em></td>
<td>Initiation in insulin naïve type 2 diabetics or inadequately controlled on oral antidiabetic agents – 10 units (or 0.1-0.2 units/kg) daily in the evening or in divided doses twice daily</td>
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<tr>
<td>Novo Nordisk</td>
<td>in adults with type 2 diabetes mellitus</td>
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<tr>
<td>Insulin glargine (Lantus®)</td>
<td>To improve glycemic control:</td>
<td>Dose should be individualized** and be administered subcutaneously once daily at the same time every day</td>
</tr>
<tr>
<td>Approved 2000</td>
<td>in adults and *<em>children ≥6 years of age with type 1 diabetes mellitus</em></td>
<td>For insulin naïve patients with type 2 diabetes – 10 units (or 0.2 units/kg) once daily and adjust to patient response</td>
</tr>
<tr>
<td>Sanofi-Aventis</td>
<td>in adults with type 2 diabetes mellitus</td>
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</table>

*In type 1 diabetes, long-acting insulin analogues must be used in combination with rapid- or short-acting insulin

**Converting from other insulin products may require dose and timing adjustment

Dose adjustments (renal and hepatic):

Dosage adjustment may be required and should be based on carefully monitored blood glucose levels

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Detemir</td>
<td>Some studies have shown increased circulating insulin concentrations</td>
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<tr>
<td>Glargine</td>
<td>Not recommended during periods of rapidly declining renal or hepatic function</td>
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<td></td>
<td>May require dose reduction due to reduced gluconeogenesis and insulin metabolism</td>
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</table>

Special populations:

- **Pregnancy** – Carefully monitor glucose control, as it may vary with progression of pregnancy. Glargine use should only occur if the potential benefits outweigh the potential fetal risk given the limited human data. Detectable detemir levels were evident in the cord blood of 25% of infants; no difference in pregnancy outcomes or fetal/newborn health compared to NPH.
- **Nursing Mothers** – It is unknown whether detemir or glargine are excreted in human milk, use caution is nursing women. Glargine is compatible with breastfeeding.
- **Pediatrics** – Neither agent has been studied in children with type 2 diabetes. Detemir has not been studied in type 1 diabetes <2 years of age. Glargine has not been studied in type 1 diabetes <6 years of age.
• Geriatrics – Dosing should be conservative to avoid hypoglycemic reactions. Some older patients may be more sensitive to insulin therapy.

Pharmacodynamics: Detemir has a relatively constant time-action profile with no pronounced peak as a result of slowed systemic absorption due to self-association of the drug molecules and slowed distribution to peripheral target tissues because of binding to albumin. In type 1 diabetes, at doses of 0.2 to 0.4 units/kg, insulin detemir exerts more than 50% of its maximum effect from 3 to 4 hours up to approximately 14 hours after dose administration. The time-action profile of detemir is less variable than NPH, but varies with dose.

Glargine has a relatively constant 24-hour glucose-lowering profile with no pronounced peak. Microprecipitates, formed after injection, slowly release small amounts of glargine into circulation. In type 1 diabetes, the onset of action was slower and the duration of action was prolonged compared to NPH insulin.

Pharmacokinetics: The table below compares pharmacokinetic parameters of insulin formulations after subcutaneous injection. The values are approximate since many factors can affect the pharmacokinetics of insulin.

<table>
<thead>
<tr>
<th>Table 5: Pharmacokinetic Comparison</th>
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<tr>
<td>Parameters</td>
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<tr>
<td>Absorption</td>
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<td>Bioavailability</td>
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<td>Cmax</td>
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<td>AUC</td>
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<td>Elimination half-life</td>
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<td>Vd</td>
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<td>Protein binding</td>
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<td>Onset of action</td>
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<td>Peak effect</td>
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<td>Duration of effect</td>
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Glargine – metabolized to two active metabolites with in vitro activity similar to insulin.

Contraindications: Hypersensitivity to the medication or any of its excipients. Insulin products are also contraindicated during episodes of hypoglycemia.

Warning and precautions: Dermatologic and sensitivity reactions at the injection site may develop in patients receiving insulin. These reactions are relatively minor and usually resolve within a few days to a few weeks. Localized reactions and generalized myalgias have been reported with the use of cresol, which is included in formulations of glargine and detemir as an excipient.

Drug interactions:
• Corticosteroids, niacin, danazol, diuretics, sympathomimetic agents, glucagon, isoniazid, phenothiazines, somatropin, thyroid hormones, estrogens, protease inhibitors and atypical antipsychotics may decrease the blood glucose-lowering effects of insulin
• Oral antidiabetic agents, pramlintide, ACEIs, disopyramide, fibrates, fluoxetine, MAOIs, pentoxifylline, salicylates, somatostatin analogs, GLP-1 receptor agonists and sulfonamide antibiotics may increase the blood glucose lowering effect of insulin
• Disopyramide and lithium may increase or decrease the blood glucose lowering effect of insulin
• Clonidine, beta-blockers, guanethidine and reserpine may increase or decrease the blood glucose-lowering effect of insulin, and may diminish the signs and symptoms of hypoglycemia
• Concomitant thiazolidinedione therapy may result in fluid retention and heart failure

**Drug – Food/Nutrition interactions:** The amount and type of food intake may alter blood glucose levels and impact insulin requirements.

**Pregnancy Category:** Detemir – category B; Glargine – category C; use only if potential benefit outweighs potential risk.

**Adverse Effects:** Hypoglycemia is the most common adverse reaction of insulin therapy – the risk increases with intensive glycemic control. Lower rates of severe hypoglycemia were reported with detemir compared to glargine and NPH. The adverse effect profiles of both insulin glargine and insulin detemir are similar and include allergic reactions, injection site reactions, lipodystrophy, rash, pruritus, edema and weight gain.

**Monitoring:** Blood glucose, HgA1c

**Look alike, Sound alike:**
- Lantus and Lente
- Levemir and Lente
- Levemir and Lantus

**Summary of Clinical Trial Results:**

**Type 1 diabetes:**
- Overall, a 21 to 39% lower once daily dose of glargine was seen compared to combined once and twice daily detemir dosing regimens
  - Once daily dosages of glargine and detemir are similar
  - Up to a 42% higher detemir dose is required when administered twice daily compared with detemir once daily
- Reduction in A1C was similar with glargine and detemir when treating to target
- Reduction in fasting plasma glucose was similar with glargine and detemir
- Glargine was associated with a non-significant, but greater incidence of severe hypoglycemia
- Weight gain was similar with glargine and detemir
- Higher twice daily detemir doses do not appear to be associated with improved glycemic control

**Type 2 diabetes:**
- Overall, a 8 to 77% lower once daily dose of glargine was seen compared to combined once and twice daily detemir dosing regimens
  - Once daily dosages of glargine were 7 to 18% lower than once daily dosages of detemir; one small crossover trial reported no difference
  - Detemir twice daily dosages were also shown to be 11 to 92% higher than detemir once daily
- In general, the reduction in A1C was similar with glargine and detemir when treating to target
  - Two trials in insulin naïve patients each showed significant A1C differences at specific targets; one favoring glargine to an A1C < 7% and 6.5% vs. detemir once daily and one favoring detemir twice daily to an A1C < 6.5% vs. glargine
- Reduction in fasting plasma glucose was similar with glargine and detemir in all but one trial
Two trials noted significant differences in individual plasma glucose levels around lunch, dinner and bedtime; one trial favoring each agent
Detemir was associated with similar or significantly lower rates of hypoglycemia
Weight gain was significantly greater with glargine
- Less weight gain is seen with once daily vs. twice daily detemir
Lower glargine and detemir doses were required by insulin naïve patients compared to those previously receiving insulin
Co-administration with metformin compared to other oral antidiabetic agents, as reported in one trial resulted in lower A1C levels

**Type 1 and Type 2 diabetes:**
- Detemir exhibits significantly lower within-subject variability in glucose-lowering effects compared to both glargine and NPH
  - Glargine exhibits lower variability than NPH
### Summary of Clinical Trials:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Trial Overview</th>
<th>Primary efficacy endpoint</th>
<th>Outcomes</th>
<th>Author's conclusion</th>
<th>Comments/Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparing dosing of basal insulin analogues detemir and glargine: Is it really unit-per-unit and dose-per-dose? 2014 Wallace JP, et al.</td>
<td>Meta-analysis 7 large, RCTs (n = 319-973), 24-52 weeks Type 1 and 2 diabetes</td>
<td>Total daily insulin dose Achieved A1C</td>
<td><strong>Type 1 diabetes:</strong> (Pieber) Similar A1C achieved, higher daily detemir BID dose vs. glargine QD, similar mean total daily aspart doses (Heller) Similar A1C achieved, higher daily detemir BID dose, similar detemir QD dose vs glargine QD</td>
<td>When converting, higher doses of detemir may be required; a conservative dose increase may be appropriate when converting to detemir; a dose reduction when converting to glargine may minimize hypoglycemia risk Consider BID detemir dosing if glucose control declines after 12 hours or when using low doses (≤0.4 units/kg/day) in type 1 diabetes Definite trend toward a higher dose requirement with detemir vs. glargine - average 38% higher detemir dose for comparable glycemic control Larger dose differences seen in insulin naïve patients</td>
<td>Trials show no clinically relevant efficacy differences; dosing and frequency remain controversial Significant heterogeneity between trials Varying dosage protocols may have introduced bias due to lack of standardized dosing frequency Bolus insulin and nonsulin antidiabetic therapies may have impacted basal insulin dosing Little evidence exists for conversion from detemir to glargine Majority of trials have potential commercial bias, were open-label or non-blinded BID dosing may have been the reason for higher detemir dose requirement (similar results seen when glargine administered BID) BID detemir doses not consistently associated with improved glycemic control</td>
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<td>Pharmacokinetics: (Plank) Small, 24-hour, isoglycemic clamp study in type 1 diabetes (n=11) – detemir duration of action is dose dependent Type 2 diabetes – PK data conflicting; glargine duration longer than detemir</td>
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<td><strong>Type 2 diabetes:</strong> Adjunct to oral therapy, insulin naïve (Rosenstock) Similar A1C achieved, higher mean detemir QD and BID doses vs. glargine QD, 55% in detemir group required BID dosing (Swinnen) A1C result not reported, significantly higher detemir BID dose requirement vs. glargine QD (Meneghini) Lower A1C achieved with glargine (7.13% vs. 7.48%), significantly higher detemir QD dose requirement vs. glargine QD Basal-bolus therapy (Hollander) No significant difference in A1C, higher but non-significant (calculation unclear) mean detemir (QD, BID) dose requirement vs. glargine QD based on “basal dose comparison,” higher total daily detemir BID dose requirement and weight gain vs. detemir QD without improved glycemic control (Raskin) Mean basal insulin doses and mean achieved A1C not significantly different between detemir and glargine, similar mean daily insulin doses with detemir QD and BID</td>
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<td>Once-daily initiation of basal insulin as add-on to metformin: a 26-week, randomized, treat-to-target trial comparing insulin detemir with insulin glargine in patients with type 2 diabetes 2013 Meneghini L, et al.</td>
<td>Multinational, randomized, open-label, treat-to-target trial Insulin-naïve adults 26-weeks n=457 Type 2 diabetes (≥ 6 months) Baseline A1C 7-9% Prior concomitant metformin monotherapy or dual therapy with another agent Once daily detemir or glargine</td>
<td>Change in A1C from baseline Safety: Change in weight or BMI from baseline Incidence of hypoglycemia and adverse events</td>
<td>A1C decreased by a mean of 0.48% to 7.48% with detemir QD and 0.74% to 7.13% with glargine QD 38% in detemir group and 53% in glargine group achieved A1C ≤7% (p=0.026); without hypoglycemia (32% vs. 38%, respectively) (NS) 11% in detemir group and 21% in the glargine group achieved A1C ≤6.5% (p=0.011); without hypoglycemia (8.6% vs. 15.2%, respectively) (NS) Greater percent of patients receiving metformin (62%) at baseline achieved A1C ≤7% compared to other oral antidiabetic medications; higher percent in glargine group, similar rates without hypoglycemia At study end: Lower, but non-significant difference in fasting plasma glucose between insulins Self-monitored plasma glucose levels with glargine significantly lower before and after lunch and dinner Significantly lower within-subject variation of fasting self-monitored plasma glucose in detemir group Mean total daily dose (units) and weight-based dose (units/kg) statistically significantly lower in glargine group: Detemir – 57 units; 0.70 unit/kg Glargine – 51 units; 0.61 unit/kg Significantly lower rate of all hypoglycemic episodes with detemir vs. glargine; no difference in nocturnal hypoglycemia rate; rate of additional adverse events similar between groups Slight weight decrease with detemir and increase with glargine; statistically significant difference favoring detemir</td>
<td>Non-inferiority of detemir QD vs. glargine QD could not be confirmed: detemir cannot be concluded as inferior; can infer statistically greater A1C reduction with glargine Similar fasting plasma glucose values achieved, although not stabilized in the detemir group A1C reductions not as great as anticipated; postprandial glucose control may not have been optimized after discontinuation of oral agents Detemir was associated with less hypoglycemia Both insulins were well tolerated Detemir provides a weight change advantage over glargine</td>
<td>Higher baseline fasting plasma glucose levels in detemir group previously taking thiazolidindiones may have contributed to the non-stabilized levels at study end Discontinuing sulfonylureas may highlight differences in duration of basal insulins Low baseline A1Cs in this study may account for limited reductions in A1C at study end Discontinuing oral antidiabetic drugs while not adjusting the metformin dose may be considered a study limitation Funded by Novo Nordisk</td>
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<tr>
<td>Study</td>
<td>Design</td>
<td>Outcome Measures</td>
<td>Results</td>
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<td>Non-inferiority of insulin glargine versus insulin detemir on blood glucose variability in type 1 diabetes patients: A multicenter, randomized, crossover study 2011 Renard E, et al.</td>
<td>Multicenter, randomized, crossover trial 32-weeks n=88 Type 1 diabetes (≥3 years) Baseline A1C ≤8.5% Prior intensive glargine basal-bolus therapy (≥6 months) Once daily glargine; once or twice daily detemir; glulisine as mealtine insulin</td>
<td>Coefficient of variation (CV) of fasting blood glucose</td>
<td>CV of fasting and pre-dinner blood glucose was not significantly different between therapies; remained non-significant when corrected for period or sequence of treatment. Mean amplitude of glucose excursions and mean of daily differences were similar between groups Changes in A1C (≤0.20%) and body weight were small and similar Median daily glargine doses (0.28 unit/kg) were lower than daily detemir doses (0.39 unit/kg); glulisine doses were similar for both groups 60% of detemir patients required BID dosing to achieve pre-dinner blood glucose target Adverse events were similar between groups Median monthly rate of symptomatic hypoglycemia was similar between groups Severe symptomatic hypoglycemia tended to be higher with glargine (NS)</td>
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<td>Non-inferiority of insulin glargine on fasting blood glucose variability as part of a basal-bolus regimen was demonstrated</td>
<td>Glargine also not inferior in other measurements of glucose variability Glucose variability was high in both groups compared to other trials (potentially contributed to by short-acting insulin analog) There was wide inter-individual variation in CV (6.3% vs. 66.9%) Both basal insulins were well tolerated with similar rates of hypoglycemia, and comparable A1C and weight variations</td>
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<td>A 24-week, randomized, treat-to-target trial comparing initiation of insulin glargine once-daily with insulin detemir twice-daily in patients with type 2 diabetes inadequately controlled on oral glucose-lowering drugs 2010 Swinnen SG, et al.</td>
<td>Multicenter, open-label, randomized trial 24-weeks n=973 Randomized 1:1 Type 2 diabetes, Insulin-naïve Baseline A1C 7-10.5% Prior, stable oral antidiabetic agent (≥3 months) Once daily glargine; twice daily detemir TZD discontinued</td>
<td>Percent of patients reaching A1C &lt;7% without symptomatic hypoglycemia</td>
<td>Significantly more glargine patients completed the study (95.4% vs. 89.9%) – discontinuation due to adverse events 27.5% in glargine group and 25.6% in detemir group achieved A1C &lt;7% without symptomatic hypoglycemia Mean A1C improvement was similar between groups Percent of patients achieving A1C &lt;7% was similar between groups; significantly more detemir patients achieved an A1C &lt;6.5% (p=0.017) Glargine produced significantly greater decreases in fasting plasma glucose, while plasma glucose reductions around lunch, dinner and at bedtime were significantly greater with detemir Approximately 30% of patients in each group experienced symptomatic hypoglycemia Weight gain was significantly higher with glargine Daily insulin dose was significantly lower with glargine than detemir (43.5±29 units/day vs. 76.5±50.5 units/day)</td>
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<tr>
<td>Non-inferiority of glargine QD to detemir BID was demonstrated</td>
<td>Glargine and detemir result in similar A1C improvements and risk of hypoglycemia Both basal insulins were well tolerated with similar rates of hypoglycemia, and comparable A1C and weight variations</td>
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<td>Detemir BID dosing, as seen in other trials may result in higher dose requirements than detemir QD: literature also shows detemir QD doses are higher than NPH QD and glargine QD</td>
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<td>Limitations – patients treated with detemir as basal insulin were excluded, 25% of included patients were not randomized</td>
<td>Detemir BID dosing, as seen in other trials may result in higher dose requirements than detemir QD: literature also shows detemir QD doses are higher than NPH QD and glargine QD</td>
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<td>More recent recommendation is to initiate detemir using a QD regimen</td>
<td>Detemir BID dosing, as seen in other trials may result in higher dose requirements than detemir QD: literature also shows detemir QD doses are higher than NPH QD and glargine QD</td>
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<table>
<thead>
<tr>
<th>No higher dose requirements with insulin detemir than glargine in type 2 diabetes: A crossover, double-blind, and randomized study using continuous glucose monitoring. 2010 King AB. (See also 2009 reference by King)</th>
<th>Single-center, randomized, double-blind, crossover trial n=29 Type 2 diabetes Baseline A1C 7.1 ± 0.9% Once daily glargine; once daily detemir administered at 8pm Prior anti-diabetic medications</th>
<th>Daily basal insulin dose to achieve basal glucose &lt;120 mg/dL, but less than 5% of readings &lt;70 mg/dL (24-hour glucose response)</th>
<th>No difference in 24-hour glucose control between agents Mean duration of treatment/titration was 3.8 ± 1.3 days for detemir and 3.5 ± 1.8 days for glargine Mean basal insulin doses (0.26 unit/kg) not significantly different between groups; individual dosage requirements varied by patient 16/29 patients did not require dosage change at crossover 26/29 patients required ≤0.4 units/kg Mean pre-dinner glucose levels and midnight-6am basal glucose levels not significantly different between groups</th>
<th>Mean basal insulin dose of 0.26 units/kg is low compared to other trials; possibly due to more sensitive glucose monitoring, timing of evening meal, not treating postmeal glucose and short trial duration Fasting morning glucose may be influenced by timing of the prior evening’s meal</th>
<th>Target plasma glucose was ≤108 mg/dL 4.8% of glargine patients received glargine BID off-protocol – included in ITT analysis Literature shows higher dose requirement with glargine BID compared to glargine QD Funded and supported by Novo Nordisk</th>
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<tbody>
<tr>
<td>Comparison of insulin detemir and insulin glargine in a basal-bolus regimen, with insulin aspart as the mealtime insulin, in patients with type 1 diabetes: A 52-week, multinational, randomized, open-label, parallel-group, treat-to-target noninferiority trial. 2009 Heller S, et al.</td>
<td>Multinational, randomized, open-label, parallel-group, treat-to-target, noninferiority trial 52-weeks n=443 Randomized 2:1 to detemir and glargine Type 1 diabetes (&gt;12 months) Baseline A1C ≤11.0% Prior basal-bolus insulin regimen Once daily glargine; Once daily detemir, but could transition to BID; aspart administered at main meals</td>
<td>To determine whether detemir is noninferior to glargine based on glycemic control (A1C) after 52-weeks</td>
<td>At study end: Glycemic control was not significantly different between treatment groups; A1C change of -0.53% to 7.57% for detemir and -0.54% to 7.56% for glargine A1C for detemir QD and BID was similar, 7.59% and 7.60% 33% of detemir patients and 30.4% of glargine patients achieved an A1C ≤7% (NS); without major hypoglycemia 31.9% and 28.9%, respectively (NS) Similar estimated mean fasting plasma glucose between therapies Mean 10-point self-monitored plasma glucose profiles were lower at study end with no significant difference between groups at any time point. Basal doses not significantly different; 0.40 unit/kg for detemir and 0.33 unit/kg for glargine Basal-bolus doses: Detemir QD – 0.33 unit/kg: 0.37 unit/kg Detemir BID – 0.47 unit/kg: 0.30 unit/kg Glargine QD – 0.33 unit/kg: 0.31 unit/kg Mean change in body weight, percentage of patients experiencing hypoglycemia, rate of all hypoglycemic episodes per patient-year and severe hypoglycemic episodes not significantly different between groups</td>
<td>Noninferiority of detemir to glargine was demonstrated for the primary endpoint Clinically significant and statistically similar improvements in glycemic control seen with both treatments Reductions in A1C were not associated with an increase in mean rate of hypoglycemic episodes Detemir BID no better than QD at improving A1C compared to glargine Switching from detemir QD to BID resulted in an increased insulin dose requirement without additional improvement in glycemic control Similar proportions of patients in each group met the requirements to convert to a BID regimen of their respective basal insulin product – potential support for similar duration of action</td>
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</table>
### A 52-week, multinational, open-label, parallel-group, noninferiority, treat-to-target trial comparing insulin detemir with insulin glargine in a basal-bolus regimen with mealtime insulin aspart in patients with type 2 diabetes.

<table>
<thead>
<tr>
<th>2009</th>
<th>Raskin P, et al.</th>
<th>Multicenter, randomized, open-label, parallel-group, treat-to-target trial 26-weeks n=385 Randomized 2:1 to detemir and glargine Type 2 diabetes Baseline A1C 7 to 11% Prior oral antidiabetic agent or insulin therapy Once daily glargine; Once daily detemir, but could transition to BID; aspart administered at main meals Oral insulin secretagogues discontinued</th>
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<td>To determine whether detemir is noninferior to glargine based on glyemic control (A1C) after 26-weeks Safety: Incidence of hypoglycemia and adverse events</td>
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<td>At study end: Similar mean basal insulin doses; 0.81 ± 0.456 unit/kg for detemir and 0.75 ± 0.324 unit/kg for glargine (p=0.100) 87.4% of detemir patients remained on QD regimen Detemir BID mean daily dose 0.89 ± 0.429 unit/kg compared to 0.80 ± 0.460 unit/kg for detemir QD Insulin-naïve patients required lower mean daily doses of detemir and glargine than non-insulin-naïve patients Significant A1C decrease from baseline in both groups (p&lt;0.001) 43% of detemir patients and 57% of glargine patients achieved target A1C &lt;7% overall; without hypoglycemic episodes, 41% and 56%, respectively (p=0.035 between groups) Comparable decreases in fasting plasma glucose: Detemir – 174 mg/dL to 130 mg/dL Glargine – 172 mg/dL to 134 mg/dL Mean pre-dinner and self-monitored plasma glucose levels not significantly different between groups Detemir treated patients gained significantly less weight than glargine treated patients – 1.37kg Rates of hypoglycemic and adverse events were comparable between groups</td>
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<td>Noninferiority of baseline-adjusted HgA1C for detemir to glargine was met; Inconclusive using LOCF based on CONSORT reporting guideline Significant improvements in glycemic control was seen with both regimens The greater than 1% point improvement in A1C is clinically significant in reducing diabetes-related mortality and complications Majority of patients did not achieve recommended glycemic treatment target The detemir group had a higher rate of non-compliance When only considering patients that completed the study, there was no clinical difference in efficacy between groups</td>
</tr>
<tr>
<td></td>
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<td>Greater percentage of males and Caucasians in the glargine group Failure to achieve treatment target due to possible advanced stage of beta-cell function deterioration Low rates of hypoglycemia suggest titration could have been more aggressive Other studies have not seen a significant difference in achieving target A1C between groups Patients completing the study had lower A1C levels than non-completers Results including LOCF must be interpreted carefully due to potential bias A limitation was the lack of ability for blinding due to different product devices Funded and monitored by Novo Nordisk</td>
</tr>
<tr>
<td>2008</td>
<td></td>
<td>Multinational, open-label, parallel-group, noninferiority, treat-to-target trial 52-weeks n=319 Randomized 2:1 to detemir and glargine Type 2 diabetes (≥12 months) A1C at 52-weeks 2-hour postprandial target plasma glucose ≤162 mg/dL</td>
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<td>At study end: A1C was clinically significantly lower than baseline and similar between groups, 7.19% for detemir and 7.03% for glargine Estimated mean A1C decrease from baseline was similar between groups; glargine treated patients had a numerically greater decrease than both detemir QD or BID treated patients Patients achieving A1C ≤7.0% (and achieving without hypoglycemia) was not significantly different between groups Fasting plasma glucose and mean change from baseline was not significantly different between groups</td>
</tr>
<tr>
<td></td>
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<td>Detemir was noninferior to glargine with regard to absolute mean A1C values and mean decrease from baseline Both regimens showed comparable effectiveness in improving overall glycemic control Detemir resulted in significantly less weight gain than glargine Detemir doses were numerically higher than glargine at 52-weeks BID detemir resulted in higher insulin doses without additional</td>
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<td>A higher percentage of males were randomized to the detemir group Similar percentage of patients in each group met criterion to switch to BID dosing however, only 57.2% of detemir patients switched Detemir reportedly has less inter-patient variation than NPH or glargine (Heise, 2004) BID basal therapy tends to lead to an increase in basal insulin dose greater than the reduction in bolus insulin dose</td>
</tr>
</tbody>
</table>
| Hollander P, et al. | Baseline A1C 7.0% to ≤11.0%
Prior oral antidiabetic agent or insulin therapy
Once daily glargine; Once daily detemir, but could transition to BID; aspart administered at main mealtimes
Oral insulin secretagogues & α-glucosidase inhibitors discontinued | Mean within-subject variation and coefficients of variation for prebreakfast and predinner plasma glucose were not significantly different between groups
Mean weight gain was significantly lower in the detemir group by 1.04kg; less weight gain was also seen with detemir QD than BID
Mean weight gain was significantly lower in the detemir QD group by 0.64kg; less weight gain was seen with detemir QD than BID
Detemir - 0.78 unit/kg; 0.82 unit/kg; 0.95 unit/kg
Glargine - 0.59 unit/kg; 0.32 unit/kg
(Hypoglycemic and adverse events occurred at a similar rate in each group
Mean weight gain was significantly lower in the detemir group by 1.04kg; less weight gain was also seen with detemir QD than BID
Detemir - 0.78 unit/kg; 0.82 unit/kg; 0.95 unit/kg
Glargine - 0.59 unit/kg; 0.32 unit/kg
(Hypoglycemic and adverse events occurred at a similar rate in each group
| improvement in glycemic control and a reduced weight advantage over glargine compared to QD detemir
The clinical significance of a 1kg weight gain difference between groups remains to be determined
BID dosing with glargine has also been shown to require higher doses than once daily therapy
Literature in type 2 diabetes has shown that time-action profiles and duration of action between detemir and glargine are not significantly different
The open-label design could have introduced bias; specifically in switching patients to BID detemir
Supported by Novo Nordisk |

| A randomized, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naïve people with type 2 diabetes. 2008 Rosenstock J, et al. | Multinational, randomized, open-label, parallel-group, noninferiority trial
52-weeks
n=582
Randomized 1:1
Type 2 diabetes (≥12 months)
Baseline A1C 7.5 to 10.0%
Insulin-naïve, prior oral antidiabetic agents
Once daily glargine; Once daily detemir, but could transition to BID | At study end:
55% of detemir patients completed the trial on a BID regimen
Mean daily detemir dose was 0.78 unit/kg (0.52 unit/kg for QD; 1.00 unit/kg for BID) and 0.44 unit/kg for glargine
A1C decreased by 1.5% to 7.2% with detemir (7.1% for both QD and BID) and to 7.1% with glargine
Fasting and self-monitored plasma glucose were comparable
Overall, 52% of patients achieved an A1C ≤7.0%; without hypoglycemia – 33% with detemir and 35% with glargine
Achievement of fasting and pre-dinner plasma glucose targets were not significantly different; significance was achieved for pre-breakfast target favoring glargine and pre-dinner target favoring detemir
Risk of hypoglycemia per patient-year was low and comparable between groups; major hypoglycemic episodes were rare
Weight gain was significantly lower with detemir (3.0kg vs. 3.9kg); weight gain with QD detemir 2.3kg vs. 3.7kg with BID (significance not reported) | Non-inferiority criteria for detemir to glargine was met
Similar, clinically significant improvements in glycemic control achieved with both agents
Higher overall detemir doses partly due to inclusion of BID regimen
Higher withdrawal rate with detemir partly due to adverse events
Weight advantages favoring detemir primarily due to QD dosing; eating patterns not accounted for
Detemir administered earlier in the evening than glargine
Study design does not allow for definitive conclusions between QD and BID detemir regimens
Further study comparing only QD detemir to QD glargine are needed to better define differences
Funded and monitored by Novo Nordisk |
Serious adverse events less frequent with detemir although few considered to be possibly or probably related to therapy

Injection-site, allergic reactions and skin disorders reported more frequently with detemir

<table>
<thead>
<tr>
<th>Lower within-subject variability of insulin detemir in comparison to NPH insulin and insulin glargine in people with type 1 diabetes.</th>
<th>Single-center, parallel group, double-blind trial</th>
<th>Within-subject variability in pharmacodynamics and pharmacokinetic end points of detemir, glargine and NPH</th>
<th>Significantly lower within-subject variability for glucose infusion rate (GIR)-AUC (0-12, 0-24 and 2-24 hour) and maximum with detemir compared to glargine and NPH (p&lt;0.001); glargine lower than NPH</th>
<th>Detemir has a more predictable glucose-lowering effect and significantly lower within-subject variability than NPH and glargine</th>
<th>Age and percent of males between groups differed</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>Heise T, et al.</td>
<td>Type 1 diabetes Baseline A1C 7.5 ± 1.2% Four single doses (0.4 unit/kg) of one of the three basal insulins</td>
<td>Lower mean GIR-AUC and maximum with glargine compared with detemir and NPH</td>
<td>GIR over four dosing days generally more consistent with detemir than NPH or glargine</td>
<td>Limitation - use of an insulin infusion during initiation of the clamp procedure (GIR-AUC differences seen in 0-24 and 2-24 hour periods)</td>
</tr>
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<td>Ongoing metabolic activity beyond 24 hours occurred in 39% of glargine patients, 24% of detemir patients and 14% of NPH patients</td>
<td>Variability with NPH may be due to inconsistent re-suspension by patients prior to injection</td>
<td>Limitation – fixed single dose however, data indicate no substantial difference in pharmacodynamics effect between steady-state and single-dose conditions</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Within-subject variability of serum insulin concentration-AUC and Cmax generally lower with detemir than with NPH or glargine</td>
<td>Variable crystal dissolution in subcutaneous tissue may contribute to variability with NPH and glargine</td>
<td>Two authors employed by Novo Nordisk</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>All therapies generally well tolerated</td>
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</tbody>
</table>

**Additional data reported in the meta-analysis above:**

ADAPT trial, type 1 diabetes, detemir QD vs. BID, basal-bolus regimen - similar A1C achieved, significantly lower detemir QD doses, significantly higher aspart doses → similar efficacy, loss of glycemic control with QD

Small retrospective, observational study evaluated conversion from glargine to detemir in type 1 and 2 diabetes (Bryant) – Type 1 diabetes - daily detemir doses similar to prior glargine doses, significantly more patients required BID dosing with detemir than glargine, no A1C change, 22.6% discontinued detemir; Type 2 diabetes - significantly higher basal dose and bolus dose requirement with detemir vs. glargine

Small retrospective, observational study in type 1 diabetes (Kadabi) – significantly worse glycemic control with detemir while requiring higher doses

Small randomized, crossover study in type 2 diabetes (King) – similar and low (0.26 units/kg/day) mean daily dose requirements of detemir QD vs. glargine QD with adjunctive noninsulin therapy, patients were well controlled at baseline – mean A1C 7.1% ± 0.9%

Small, crossover pharmacokinetic study in type 1 diabetes (Porcellati) – higher total daily insulin dose requirement with detemir, but similar basal dose requirement; similar activity profiles to 12 hours, but rapid decline with detemir after 12 hours

Trial in type 2 diabetes (Klein) – comparable activity profile with similar increase in duration with increased unit/kg dose

Crossover, isoglycemic clamp study in type 2 diabetes using 0.4 unit/kg (Lucidi) – glargine appears to provide better glucose control (up to 32 hours) compared to detemir

Crossover, once-daily doses trial in type 1 and 2 diabetes (Kato) – significantly higher post-dinner glucose values with detemir; significantly lower bedtime glucose levels in type 1 diabetes and predinner glucose levels in type 2 diabetes

Several observational studies compare "daily average consumption" of insulin based on units dispensed by a pharmacy – may over- or underestimate use, or have obtained data using questionnaires from non-randomly selected providers

LOCF – last observation carried forward, RCT - randomized, controlled trial, PK – pharmacokinetic, NS – Not Significant, ITT – intent to treat

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PROPRIETARY
**Patient Education:** Patients should be instructed to not change their insulin regimen without consulting a healthcare provider. Patients should be made aware of the signs and symptoms of hypoglycemia and other adverse effects. Appropriate administration technique and monitoring should be discussed.

**Preparation, Administration, and Storage:** Long-acting insulin products should not be diluted or mixed with any other insulin or solution. These agents are only for subcutaneous injection and injection site should be rotated. Insulin devices must not be shared between patients.

Detemir – once daily administration should be administered with the evening meal or at bedtime. Glargine – once daily administration may be given at any time of day, but should be at the same time every day.

Store unopened vials/pens in the refrigerator at 2-8 degrees Celsius until expiration date. Once opened, the vial can be stored in the refrigerator or at room temperature (room temperature only for FlexPen and FlexTouch) and be used within 28 days (Glargine), 42 days (Detemir).

**Product Availability and Cost:**

<table>
<thead>
<tr>
<th>Insulin detemir 100 unit/mL</th>
<th>Insulin detemir Cost (WAC)</th>
<th>Insulin glargine 100 unit/mL</th>
<th>Insulin glargine Cost (WAC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mL FlexPen®</td>
<td>$79.94</td>
<td>3 mL SoloSTAR®</td>
<td>$79.94</td>
</tr>
<tr>
<td>3 mL FlexTouch®</td>
<td>$79.94</td>
<td>10 mL vial</td>
<td>$266.50</td>
</tr>
<tr>
<td>10 mL vial</td>
<td>$266.50</td>
<td>10 mL vial</td>
<td>$266.50</td>
</tr>
</tbody>
</table>

**Potential Cost Saving Strategies:**

1. Convert to the least costly product
   a. Acquisition cost – is the alternate product available at a lower cost?
   b. Location of administration – inpatient vs. outpatient
   c. Hospital status (340B/disproportionate share) – if administration will occur in locations other than inpatient, consider cost impact to non-inpatient areas
   d. Contract pricing – align insulin products from a single manufacturer if possible to maximize market share discounts (consider pen needle cost impact if currently using Novofine® needle)

2. Convert to a lower volume product if using 10mL vials
   a. Insulin pen device – either for the current formulary product or the alternate product
   b. Ensure appropriate administration and safety training is provided

3. Dispense patient specific doses
   a. Ensure sterile products area meets regulatory requirements
   b. Determine ability of sterile products staff to take on additional workload of drawing up doses
c. Consider potential waste associated with returned doses due to dose change or discharge

4. Dispense standard doses
   a. Ensure sterile products area meets regulatory requirements
   b. Determine ability of sterile products staff to take on additional workload of drawing up doses
   c. Assess nursing accountability for squirting out excess insulin or obtaining additional syringes to administer appropriate dose
   d. Consider reduction in RCRA waste associated with vial/pen disposal
   e. Ensure appropriate training

**Pipeline:**

**Insulin degludec** (Novo Nordisk) is an ultra-long acting basal insulin product currently available in Europe, Japan and Mexico for the treatment of type 1 and 2 diabetes in patients 18 years of age and older. Novo Nordisk submitted an NDA for degludec to the U.S. FDA in September 2011. In November 2012, the FDA’s Endocrinologic and Metabolic Drugs Advisory Committee voted 8-4 in support of degludec, with a 12-0 vote in support of a cardiovascular outcomes trial (a majority favoring a post-marketing trial) due to a potential signal in a meta-analysis of major trials of an increased risk for major adverse cardiovascular events (MACE). In February 2013, the FDA declined to approve degludec and issued a “complete response letter” requesting additional cardiovascular outcomes data from a dedicated trial based on the FDA advisory panel’s November 2012 recommendation. “A Trial Comparing Cardiovascular Safety of Insulin Degludec Versus Insulin Glargine in Subjects with Type 2 Diabetes at High Risk of Cardiovascular Events (DEVOTE)” is currently enrolling patients and has an estimated completion date of November 2018. Details of the trial can be found at [http://clinicaltrials.gov/show/NCT01959529](http://clinicaltrials.gov/show/NCT01959529)

Following subcutaneous injection, degludec forms a depot of soluble and stable multihexamers which slowly dissociate for absorption into the circulation. In circulation, degludec has strong, but reversible albumin binding (>99%). Degludec exhibits a linear dose-response curve with a peak after 8 to 12 hours, a half-life of 25-hours and duration of effect greater than 42-hours. Degludec is available outside the U.S. in 100 unit/mL (U-100) and 200 unit/mL (U-200) formulations and data supports the ability to mix with aspart.

Company sponsored comparative clinical trials have primarily been against glargine and have demonstrated non-inferiority with regard to glycemic control and A1C reduction in both type 1 and type 2 diabetes. In type 1 diabetes, these effects have been achieved using similar total daily insulin doses. And, similar to detemir, degludec demonstrates lower day-to-day variability in total glucose-lowering effect compared to glargine. Degludec appears to produce less nocturnal hypoglycemia than glargine, but is similar in overall and severe hypoglycemia, as well as rate and type of adverse events. With
regard to cardiovascular safety, initial data presented to the FDA showed no increased risk of cardiovascular events, however subsequent analysis using different definitions of cardiovascular events at the request of the FDA resulted in an increased hazards ratio for MACE.

Additional data with degludec dosing three times a week is available, but has not been submitted to the FDA for approval. To date, degludec has not been directly compared to NPH.

Conclusion:
The ongoing release of data from clinical trials comparing the efficacy and safety of detemir and glargine continues to provide a greater understanding of key points and patient specific factors to consider when initiating therapy and more importantly when switching between these agents. While switching between agents may not necessarily be routine practice in outpatient diabetes management, this continues to be a great focus for hospitals and health systems working to manage a formulary and control costs. Beyond safety and efficacy, dosing, conversion and duration of effect have gained the most attention.

From an efficacy standpoint, when used as a treat to target therapy, the majority of data shows similar reductions in A1C and fasting plasma glucose levels with glargine and detemir. There is some conflicting data in type 2 diabetes that has shown significantly greater efficacy in reducing A1C to <7% or <6.5% with each product however, much of the data shows non-significant differences. The use of non-insulin therapies and potential variation in endogenous insulin production must also be considered in type 2 diabetes. The effect of metformin specifically, as seen in one trial resulted in lower A1C levels when combined with insulin than other oral antidiabetic agents combined with insulin.

Safety between these agents was also found to be similar with the exception of one trial in type 2 diabetes showing significantly lower rates of hypoglycemia with detemir and one trial in type 1 diabetes showing a higher, but non-significant rate of severe hypoglycemia with glargine.

When comparing dosing and duration of effect of glargine and detemir to determine a conversion factor between agents, there are several factors to consider. First, while detemir exhibits more of a peak effect than glargine and activity tends to decline after 12 hours, these parameters may be impacted by the insulin dose administered. Literature shows that in type 1 diabetes, detemir has a shorter duration of effect at doses ≤0.4 u/kg/day potentially requiring twice daily administration, but at doses >0.4 u/kg/day, duration may be sufficient for daily dosing. This effect has been seen with both agents in type 2 diabetes. Next, the type of diabetes must be considered as it appears to impact comparative doses between insulin regimens. In the summary data above, the percent difference between regimens was greater in patients with type 2 diabetes than type 1 diabetes when comparing glargine to combined daily/twice daily detemir, daily doses of each agent, and daily to twice daily doses of detemir. Interestingly, the
comparison of daily and twice daily regimens of detemir in both type 1 and 2 diabetes resulted in increased insulin dose requirement without additional improvement in glycemic control. Reportedly, glargine dosed twice daily has also been shown to require higher doses than once daily therapy in type 2 diabetes. Finally, prior exposure to insulin therapy should be considered, as lower glargine and detemir doses were required by insulin naïve patients compared to those previously treated with insulin.

Detemir was found to exhibit significantly lower within-subject variability in glucose-lowering effect than glargine or NPH in type 1 and type 2 diabetes, thus increasing the predictability of effect. Variability with glargine is lower than NPH. It is thought that this may partially be due to incomplete resuspension of NPH before injection and the time variation for formation and dissolution of microprecipitates with glargine.

Of note, weight gain can be anticipated with any insulin therapy. In the literature reviewed, there was similar weight gain associated with both agents in type 1 diabetes, however, in type 2 diabetes weight gain was significantly greater with glargine than detemir. The weight gain advantage over glargine is reduced when using detemir twice daily compared to once daily in type 2 diabetes.

Based on this data and when converting between products it is reasonable to consider a dose-to-dose conversion in patients with type 1 diabetes, especially in patients with higher daily dose requirements. Similarly, it is reasonable to anticipate the need to make conservative adjustments in insulin dose when converting between products in patients with type 2 diabetes. Switching from a once to twice daily dosing regimen may be required in patients with low daily insulin dose requirements or when an adequate duration of effect is not achieved, keeping in mind that this will likely result in a higher total daily insulin dose.

Adherence to therapy is critical for efficient management of diabetes and an interchange may cause some compliance issues if insulin is used twice daily as compared to once a day.

References:

1. Lantus Prescribing Information, December 2013
2. Levemir Prescribing Information, October 2013


15. www.novonordisk.com
17. www.fda.gov

About Amerinet
As a leading national healthcare solutions organization, Amerinet collaborates with acute and non-acute care providers to create and deliver unique solutions through performance improvement resources, guidance and ongoing support. With better product standardization and utilization, new financial tools beyond contracting and alliances that help lower costs, raise revenue and champion quality, Amerinet enriches healthcare delivery for its members and the communities they serve. To learn more about how Amerinet can help you successfully navigate the future of healthcare reform, visit www.amerinet-gpo.com.

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