Update on New Insulin Formulations

PES D&T Committee

**Basaglar**

Basaglar (insulin glargine) launched by Eli Lilly on December 15, 2016: Basaglar, a brand of insulin glargine marketed by Eli Lilly, was FDA approved in 2015 and became available in the United States on December 15, 2016. Following its launch, many insurers are limiting coverage for Lantus and requesting that patients change to Basaglar. Although not approved as a "biosimilar," Basaglar has an identical amino acid sequence to Lantus and very similar pharmacokinetic and pharmacodynamic profiles (Linnebjerg et al., Diabetes Care, 2015, 38:2226-2233; Linnebjerg et al., Diabetes Obes Metab, 2017, 19:33-39). It is FDA approved for use in Types 1 and 2 diabetes, following trials showing non-inferiority in both conditions (Type 2: Rosenstock et al., Diabetes Obes Metab, 2015, 17:734-741; Type 1: Blevins et al., Diabetes Obes Metab, 2015, 17:726-733). Basaglar is available in the KwikPen® delivery device. In the pediatric population, the prescribing information states that safety and effectiveness are established in patients age 6 to 15 years, but not in patients younger than age 6 years.

**Insulin Degludec**

Insulin degludec, marketed by Novo Nordisk as Tresiba, was approved for use in the pediatric population in mid-December, 2016. Approval is for children age 1y and older; of note, however, prescribing information indicates that degludec is not recommended for those receiving less than 5 units of basal insulin daily. The following summarizes the current prescribing information and studies upon which approval was based:

- **How is insulin degludec different than glargine?** After SC injection, degludec forms soluble multihexamers that slowly release insulin, reportedly resulting in a smoother pattern of release into the circulation and a long half life of about 25 hours in adults, which is about twice the half-life of glargine. Heise et al. report that degludec has 4 times lower pharmacodynamic variability than glargine in adults with Type 1 Diabetes under euglycemic clamp conditions (2012, Diabetes Obes Metab 14(9):859-864), suggesting lower intra-individual day-to-day variability in glucose lowering action. Phase 2¹ and Phase 3² studies in adults with T1D showed about 25% less nocturnal hypoglycemia with degludec compared to glargine, with no differences in HbA1c.

- **How is degludec dosed in pediatrics?** In children with both Type 1 and Type 2 diabetes switching from glargine, the prescribing information currently recommends starting with 80% of the glargine dose and then titrating to glycemia. The prescribing information recommends administration once daily at the same time of day in children. Compared to glargine, there is potentially more leeway in timing of administration due to long half-life, and the adult prescribing information recommends administration “once-daily at any time of day.”

- **What are the data in pediatrics?** The Phase 3b BEGIN: Young 1 trial³ randomized 350 children aged 1-17yo with Type 1 diabetes to receive degludec once daily vs. detemir once or twice daily (according to local labeling). Aspart was also administered in both
regimens. Over 90% of randomized children completed the 26-week main phase of the trial, which was followed by a 26 week extension phase during which subjects continued on the treatment assigned during the main phase. The primary endpoint was change from baseline in HbA1c after 26wk of treatment. The degludec and detemir groups had clinically similar HbA1c values at 26 and 52 weeks, establishing non-inferiority of degludec. There was no difference between groups in rates of hypoglycemia. There was a significantly lower rate of hyperglycemia with ketosis in the degludec group compared to the detemir group (0.7 vs. 1.1 events per year).

**Insulin Degludec References:**

**Toujeo**

Toujeo was FDA approved in 2015 for use in adults with type 1 or type 2 diabetes; it is not yet approved for use in the pediatric population. Toujeo is insulin glargine in a concentration of 300 units/mL. Approval of Toujeo was based on the EDITION series of clinical trials\(^1\)-\(^4\), which demonstrated in adults with both Type 1 and Type 2 diabetes that Toujeo had similar safety and efficacy compared to glargine 100 units/mL. Additionally, trials in adults with Type 2 diabetes suggested lower risk of hypoglycemia with Toujeo compared to glargine 100 units/mL\(^1\)-\(^3\). A euglycemic clamp study in adults with Type 1 diabetes suggested a longer duration of action for Toujeo compared to glargine 100 units/mL, as well as a more even steady-state pharmacokinetic profile\(^5\). Toujeo comes in the SoloStar® prefilled pen.

**Toujeo References:**
4. New insulin glargine 300 Units/mL versus glargine 100 units/mL in people with Type 1 Diabetes: a randomized, Phase 3a, open-label clinical trial (EDITION 4). Home et al., 2015, *Diabetes Care* 38:2217-2225. [https://www.ncbi.nlm.nih.gov/pubmed/26084341](https://www.ncbi.nlm.nih.gov/pubmed/26084341)
5. New insulin glargine 300 units·ml⁻¹ provides a more even activity profile and prolonged glycemic control at steady state compared with insulin glargine 300 Units·ml⁻¹. Becker et al., 2015, *Diabetes Care* 38:637-643. https://www.ncbi.nlm.nih.gov/pubmed/25150159