



INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: Long-acting Insulins & Biosimilars
-October 2021-



Background:

In October 2021, the Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) provided a drug class review of long-acting insulins and biosimilars for Type 2 Diabetes Mellitus (T2DM). The insulin class was last reviewed in 2017. Insulin detemir (Levemir®) is currently named to the National Core Formulary (NCF) as the sole long-acting insulin. Following clinical review and analysis, and with the FDA approval of the first interchangeable insulin glargine biosimilar product (Semglee®) in July 2021¹, the NPTC voted to **ADD any “interchangeable” insulin glargine product (Semglee® or Lantus®)** to the NCF.

Discussion:

American Indian and Alaskan Native adults have a higher prevalence (16%) of diabetes than any other race or ethnicity and the healthcare costs associated with managing this complex medical condition are significant². A biosimilar is a biologic product, highly similar to an FDA-approved reference product with no differences in safety, purity, and potency³. Since biologic products are complex molecules, they may have minor differences in inactive components and are not exact replicas of the original reference product³. Insulin glargine (Lantus®) is an example of a reference product and was used for comparison in the insulin glargine biosimilar (Semglee®) clinical trials. A biologic must undergo additional switching studies showing the impact of alternating between the reference product and the biologic to obtain “interchangeable” status³. Once a biologic becomes interchangeable, it can be substituted for the reference product by the pharmacist without the intervention of the provider³. More descriptive information further explaining the differences between biological, biosimilar, and interchangeable products can be found on the FDA’s website at: <https://www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products>.

Basal, long-acting insulins are typically administered as a single daily dose and are preferred over NPH insulin because they provide a relatively flat serum insulin concentration for nearly 24 hours, which may confer a lower hypoglycemia risk⁴. Long-acting insulins should be tailored to the patient based on glycemic goals⁴.

Clinical studies:

A Cochrane review and meta-analysis in 2011 compared insulin’s detemir (Levemir®) and glargine (Lantus®) in 2,250 patients with T2DM for up to 52 weeks and showed no significant differences in (1) hemoglobin A1c \leq 7% with or without hypoglycemia and (2) no significant differences in overall, nocturnal and severe hypoglycemia between treatment groups⁶. Treatment with insulin glargine did result in a lower daily basal insulin dose and a lower number of injection site reactions. Additionally, there was no significant difference in the variability of fasting plasma glucose or glucose values in 24-hour profiles between treatment groups and no clinically-relevant differences in efficacy or safety between insulins for targeting hyperglycemia. However, to achieve the same glycemic control, insulin detemir was often injected twice-daily in a higher dose but resulted in less weight gain, whereas insulin glargine was more commonly injected once-daily, with somewhat fewer injection site reactions⁶.

A 2018 systematic review and network meta-analysis compared the benefits and harms of basal insulins in 39 trials (N = 26,195) of patients with T2DM. The study, labeling its evidence as low quality due to use of mostly indirect comparisons, suggested that basal insulins for T2DM do not substantially differ in their glucose lowering effect⁷. No differences in the incidence of hypoglycemia among basal insulin regimens were noted except with insulin degludec, which was associated with a lower incidence of any hypoglycemia compared with insulin glargine (OR 0.64, 95% CI: 0.43 to 0.96)⁷.

Key trials to insulin glargine (Semglee®) receiving the designation of biosimilar interchangeability include the INSTRIDE 1 trial in 558 patients with type 1 diabetes and the INSTRIDE 2 trial in 560 patients with type 2 diabetes^{8,9}. These studies showed non-inferiority for mean change in hemoglobin A1c at week 24, indicating that Semglee® was non-inferior to the reference insulin glargine in INSTRIDE 1. Non-inferiority was also demonstrated between Semglee® and reference insulin glargine for reduction of HbA1c during 24 weeks of treatment in INSTRIDE 2⁹. The mean change in hemoglobin A1c from baseline to week 24 was -0.60% (95% CI: -0.78 to -0.41) and -0.66% (95% CI: -0.84 to -0.48) for Semglee® and reference insulin glargine, respectively. The two treatment groups were similar in secondary endpoints, including hypoglycemia and nocturnal hypoglycemia, local and systemic reactions, other safety variables, and immunogenicity in both studies. Switching participants between Semglee® and reference insulin glargine in the INSTRIDE 3 trial demonstrated equivalent efficacy and similar safety and immunogenicity¹⁰.

Both the American Diabetes Association and American Association of Clinical Endocrinology clinical practice guidelines currently recommend therapy with long-acting basal insulin as the initial choice in most T2DM cases when non-insulin antihyperglycemic therapy fails to achieve target glycemic control or when a patient, whether drug naïve or experienced, has symptomatic hyperglycemia^{4,11}. The United Kingdom's National Institute for Health and Care Excellence 2021 guidelines for insulin use in T1DM recommends starting an insulin for which a biosimilar is available, and using the product with the lowest acquisition cost¹².

Findings:

- No clinically significant differences in glucose lowering between insulins degludec, detemir, and glargine
- No clinically significant differences in pharmacokinetic and/or pharmacodynamic data between Semglee® and the reference insulin glargine product
- No clinically relevant difference in efficacy or safety between insulin detemir and insulin glargine for targeting hyperglycemia
- There were no clinically meaningful differences between Semglee® and reference insulin glargine in incidence of overall and nocturnal hypoglycemia, local or systemic reactions, safety or immunogenicity

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the [NPTC website](#).

References:

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