FOCUS ON INTERCHANGEABLE BIOSIMILAR INSULINS

This resource provides a summary for practicing pharmacists on recent developments of interchangeable biosimilar insulins in the treatment of diabetes. Information is included to prepare pharmacists to educate patients and answer questions about biosimilars and the availability of interchangeable biosimilar insulins.

Introduction

In 2020, the Centers for Disease Control and Prevention (CDC) published the National Diabetes Statistics Report that estimated 26.9 million people of all ages, or 8.2% of the United States (US) population, are diagnosed with diabetes.[1] Approximately 10.9% (2.9 million) of US adults aged 20 years or older have reported using insulin within a year of their diagnosis. Insulin is notoriously expensive in the United States; according to the American Diabetes Association, the total cost of diagnosed diabetes was estimated to be $327 billion in 2017.[2] A patient with diabetes living in the United States has an average expenditure cost that is 2.3 times higher than a patient without diabetes[3]. Many patients are forced to choose between purchasing their medications and other day-to-day necessities.[2,3]

Insulin glargine is a synthetic, long-acting basal insulin that is typically used once daily for the treatment of diabetes in children and adults. It is available as many different brands and formulations and varies in price. In July 2021, the US Food and Drug Administration (FDA) approved the first interchangeable biosimilar insulin product, insulin glargine-yfgn, which is interchangeable for the reference product, Lantus (insulin glargine).[4,5] The introduction of interchangeable biosimilar insulins may create better access and lower costs for patients with type 1 or type 2 diabetes mellitus.[6]

What Is a Biologic?

The rise of biologics on the market has become increasingly noticeable over the past several decades—but what are they? A biologic is a medication or product that is synthesized from a living organism or consists of cells obtained from living organisms through highly complex processes.[7,8] Insulin is considered a biologic because it is derived from the cells of bacteria and yeast. Since living cells are genetically variable, it is difficult to yield perfect exact copies of the product.[9] Biologics are comprised of unstable chemical bonds that are more sensitive to changes in environment than chemically and synthetically made medications. Because of their unpredictability and complexity, insulin and other biologics undergo an FDA approval process that is different from small-molecule drugs to ensure safety and efficacy.[10-11] The **Purple Book** is an FDA database that contains information on all biological products approved by the agency, including biosimilars, interchangeable products, and their reference products. There are biologics used to treat cancer, rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, psoriasis, diabetes, and more. Examples of biologics for the treatment of diabetes include insulin aspart, lispro, degludec, detemir, and glargine.

What Is a Biosimilar?

On March 23, 2020, the FDA officially reclassified insulin as a biologic and thus shifted its regulatory framework. Owing to the structural complexity of a biosimilar, the manufacturer must submit their product for review and approval through the 351(k) pathway while small-molecule generics may be submitted through an abbreviated new drug application (ANDA).[11] An original biologic is referred to as the "reference product" and a product that is highly comparable to the original is called a "biosimilar". Since it is impossible to create an exact copy of a biologic, biosimilars cannot be recognized as a true generic.[11,13] In comparison, small-molecule drugs undergo a simpler chemical process that ensures uniformity, and each manufactured batch is identical.

As expected, the complex process of developing and manufacturing biologics is rigorous and expensive. Thus, biologics are generally more costly products for patients.

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To help address this cost burden for patients, the FDA developed a separate approval pathway for biosimilars through the Biologics Price Competition and Innovation Act (BPCIA). Its intent is to increase competition and patient access to the products.[12] Biosimilars have the same potential for side effects, routes of administration, strengths or concentrations, and dosage forms. Regardless of the product's similarity, pharmacists are required to contact the prescriber to receive authorization to substitute a reference biologic for a biosimilar.[14] Pharmacists should review their state's laws to ensure the pharmacy is compliant with all rules and regulations.

The FDA designates a "Proper Name" to biosimilars and interchangeable biosimilars to distinguish them from the reference product. The Proper Name, sometimes referred to as the nonproprietary name, includes a unique suffix of four lower case letters attached with a hyphen to the core name.[15] The purpose of the additional four letters is to assist with differentiating between the products.

What Is an Interchangeable Biosimilar?

According to the FDA, an interchangeable biosimilar is a product that meets the safety requirements to be substituted without the intervention of the prescriber.[16] In a situation where patients may go without their medication due to various factors, having an immediate and less expensive option may lead to better outcomes.[16] Interchangeable biosimilars save the pharmacy team time and effort in contacting the prescriber for an alternative therapeutic agent and increase patient access to the medication.

In order for an FDA-approved biosimilar to be recognized as an interchangeable biosimilar, the manufacturer must specifically apply for the product to be designated as an alternative therapy for a specific reference biologic in practice. Safety is assessed through additional data that measure the interchangeability against the reference product. Generally, the manufacturers implement studies in which patients will alternate between the interchangeable biosimilar and the reference product and the results must show equivalence, with no differences in efficacy or safety.[17]

SPOT THE DIFFERENCE: INSULIN GLARGINE

To confirm whether a product is an interchangeable biosimilar, pharmacists can use the Advanced Search function in the Purple Book. This will display all products related to the searched term in a detailed chart. The chart shows all the features of the biologics including the reference product and indicates whether it is an approved interchangeable biosimilar. This information is located under the column labeled "License Type" and will display "351(k) Interchangeable". It is important to identify which proprietary reference product may be substituted with the interchangeable biosimilar as not all the products may be used as a substitution.

There are several insulin glargine biologics available on the market (Table 1). Toujeo and Basaglar are biologics but are not considered to be a biosimilar to the reference product Lantus via the 351(k)-application pathway. Rezvoglar (insulin glargine-aglr) has been FDA-approved as a biosimilar and requires a prescription written specifically for the product to be dispensed.

Unbranded insulin glargine-yfgn and *branded* insulin glargine-yfgn (Semglee) are currently the only interchangeable biosimilar insulins available on the market. Their reference product is Lantus (insulin glargine). This means that if state law authorizes a pharmacist to substitute interchangeable biosimilars, unbranded insulin glargine-yfgn, Semglee (insulin glargine-yfgn), and Lantus (insulin glargine) can be dispensed interchangeably without contacting a health care provider for a new prescription. However, neither the unbranded nor branded biosimilars can be interchanged with any of the other insulin glargine biologics on the market.[18] The prices may vary greatly. When comparing products, consideration should include insurance and manufacturer rebates.[19,20,21]

Table 1. Insulin Glargine Biologics and Biosimilars[18]

Proprietary Name	Proper Name	License Type	Reference Product Proper Name	Reference Product Proprietary Name
Lantus	Insulin glargine	351(a)	N/A	N/A
Basaglar	Insulin glargine	351(a)	N/A	N/A
Toujeo	Insulin glargine	351(a)	N/A	N/A
Rezvoglar	Insulin glargine-aglr	351(k) Biosimilar	Insulin glargine	Lantus
Semglee	Insulin glargine	351(a)	N/A	N/A
Semglee	Insulin glargine-yfgn	351(k) Interchangeable	Insulin glargine	Lantus
Insulin glargine-yfgn	Insulin glargine-yfgn	351(k) Interchangeable	Insulin glargine	Lantus

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What is the Clinical Evidence that Supports Use of the Interchangeable Biosimilar Insulin Glargine?

INSTRIDE 1 was a non-inferiority, open-label study that evaluated the safety and efficacy of insulin glargine-yfgn compared with the reference product Lantus in patients with type 1 diabetes mellitus. Participants received either insulin glargine-yfgn or the reference product once-daily in combination with mealtime insulin lispro. At 24 weeks, participants who received glargine-yfgn had a mean change in hemoglobin A1C of 0.14% from baseline, while those who received the reference product observed a 0.11% change. The difference between each arm's change was minimal at 0.03% (SE 0.046; 95% CI, 0.066 to 0.117) and met the criteria for non-inferiority of insulin glargine-yfgn. Safety results indicated there were no clinically meaningful differences between groups in incidence of overall and nocturnal hypoglycemia, systemic reactions, and immunogenicity.[22] INSTRIDE 2 found similar results in patients with type 2 diabetes.[23]

With the efficacy and safety of insulin glargine-yfgn well understood, the aim of INSTRIDE 3 was to demonstrate equivalence. The study was a continuation of INSTRIDE 1; participants who successfully completed 52 weeks of reference insulin in INSTRIDE 1 were eligible to be randomized in INSTRIDE 3.[24]

STUDY DESIGN:

INSTRIDE 3 was a multicenter, open-label, randomized, parallel-group, phase 3 study comparing the efficacy and safety of insulin glargine-yfgn compared with reference insulin glargine (Lantus) in patients with type 1 diabetes mellitus to determine equivalence.[24,25]

Participants were randomized into one of two treatment sequences. The reference insulin group continued to use the reference insulin for the duration of the 36-week study period. The treatment-switching group received insulin glargine-yfgn for weeks 0-12, reference insulin of weeks 12-24, then insulin glargine-yfgn for weeks 24-36 (Figure 1). After week 36, both treatment groups resumed the reference insulin until week 40 for a safety follow-up visit.[24,26,27]

The primary endpoint was to assess the change in A1C from baseline to week 36 to demonstrate equivalence

between the two treatment sequence groups. The data are described as least squares (LS) mean change in A1C.[24,26] This statistical method provides the opportunity for a better correlation of the drug therapies and change in A1C, taking into account numerous variables, such as gender, weight, or other baseline measures, that may be imbalanced between treatment groups.[28] Fasting plasma glucose (FPG), self-monitored blood glucose (SMBG), daily insulin doses, rate of hypoglycemia and adverse events (AE) were also measured.[24,26]

RESULTS:

A total of 127 participants were randomized starting in December 2015, with 64 in the glargine-yfgn (identified as MYL-1501D in the study) treatment sequence and 63 in the reference insulin treatment sequence. Of those, 119 participants completed the study.[24]

Efficacy Endpoints:

At week 36, the LS mean (standard error) change in A1C from baseline was –0.05 (0.032) in the glargine-yfgn group and –0.06 (0.034) for reference insulin (Figure 2). The LS mean difference between the two sequence groups was 0.01 (95% CI, –0.085 to 0.101). This data indicates equivalence between the two treatment sequences as the 95% CI is within the established equivalence limits. A1C remained stable for both groups with no statistically significant changes ($p > 0.05$). During the study, there were no significant changes in FPG and SMBG from baseline.[24]

Figure 1. INSTRIDE 3 Study Design[24]

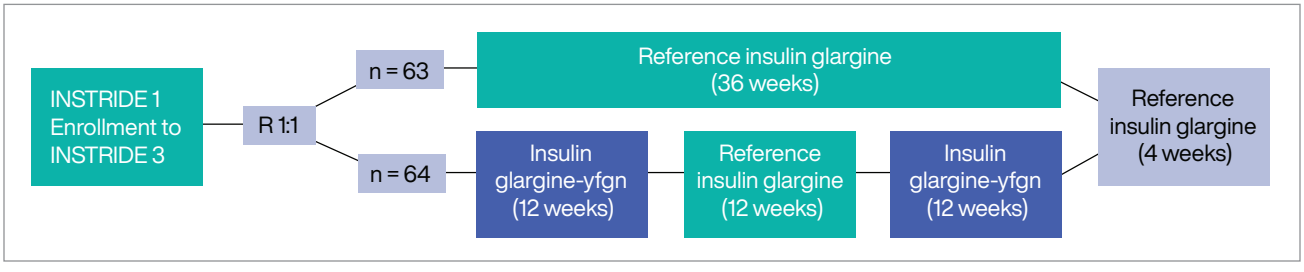

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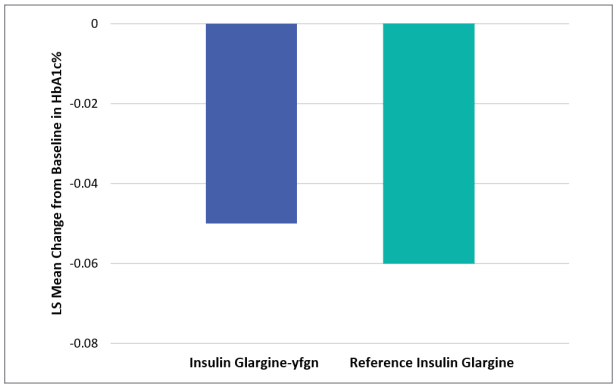
Figure 2. Change in A1C From Baseline at Week 36 of the INSTRIDE 3 Study[24]



Safety Endpoints:

The overall rate of hypoglycemia events was similar in both treatment sequence groups, with no statistically significant difference. A total of 41 participants (64.1%) in the insulin-yfgn and 42 (66.7%) in the reference insulin group experienced one or more AEs. The most common AEs reported were infections such as upper respiratory tract infections, nasopharyngitis, and influenza.[24]

STUDY CONCLUSION:

With no statistically significant differences when comparing changes in A1C, FPG, SMBG, and AEs when participants were switched back and forth between the two therapies in comparison to someone who remained on the reference product, this study supports that insulin glargine-yfgn would be an equivalent and interchangeable alternative for Lantus (insulin glargine). It may also be considered for initiation of basal insulin.

What are Key Points to Remember?

When navigating and counseling on biosimilar insulins in pharmacy practice, it is important to consider the following points:

- All biosimilars and interchangeable biosimilars meet the FDA's high standards of approval.
- Biosimilar insulin products are considered *highly similar* compared with an existing insulin biologic, also known as the reference product.
- There can be multiple biosimilar insulins for the same reference product.
- Biosimilar insulin products are as safe and effective as the reference product with no clinically meaningful difference. However, pharmacists *cannot* dispense or change between biosimilars without a prescription specifically written for it.
- An *interchangeable biosimilar insulin* meets requirements set forth by the federal Biologics Price Competition and Innovation Act (BPCIA), allowing pharmacists to independently substitute an interchangeable product with its reference product if state law permits.
    - Be mindful that interchangeable biosimilar insulins are only approved to be substituted with the reference product that it was studied against in the 351(k)-application process.
    - Additional clinical studies are required to show that safety and effectiveness is maintained when switching back and forth between the interchangeable biosimilar and reference product.
- Refer to the FDA **Purple Book** for more information regarding biologics, biosimilars, and interchangeable biosimilars.
- Pricing may vary depending on the patient's insurance and rebates offered by the manufacturer.
- Counseling on appropriate use, dosing, and storage requirements should occur and be reiterated when dispensing all insulin products.

The high costs of insulin continue to be a barrier for many patients. Interchangeable biosimilar insulin products have the potential to reduce costs and increase accessibility for patients in the United States. By doing so, these life-saving alternatives may reduce the incidence of patients forgoing or rationing their prescribed insulin and prevent further disease complications. The interchangeable designation of a biosimilar can also decrease the administrative time required from the pharmacy staff to seek approval from the prescriber for substitution. These therapies not only improve the patient's overall health outcomes and quality of life, but they can also have a significant impact along the entire continuum of health care.

If your patients are having trouble staying adherent to medications due to costs, there are several strategies that pharmacists can take to help. This may occur when patients do not have commercial insurance or have trouble paying their copay or coinsurance. Pharmacists may consider the following:

- If state law permits, investigate to see whether the insulin or biologic can be readily substituted to an equivalent biosimilar
- Discuss with the patient the use of manufacturer rebates or coupons available on the company's website
    - Advise that some discounts are readily available for download while some may require calling a patient assistance program. Provide the appropriate toll-free number for the patient.
- Assist the patient with comparing prices
- Contact the prescriber for an alternative medication or biosimilar, when appropriate
- Educate patients on the critical importance of maintaining their insulin regimen
- Encourage patients to reach out to a pharmacist or the prescriber regarding any medication or supply access issues

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