

# The use of biosimilar insulins in 2023

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## About the Author



Dr. Sarah Monsonego is originally from Montreal and obtained her medical degree at McGill University. She completed her Internal Medicine residency in 2017 at the University of Ottawa and remained in Ottawa for her residency in Endocrinology & Metabolism, which she completed in 2020. After her residency, Dr. Monsonego relocated to Toronto and currently practices as a community Endocrinologist doing both ambulatory and hospital work. Her practice focuses on general endocrinology, and she has a keen interest in type 2 diabetes and obesity, as well as diabetes in pregnancy.

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## Introduction

A biosimilar is a drug that is highly similar to a biologic drug and has been shown to have no clinically meaningful difference from its originator drug despite minor differences in clinically inactive components. In light of the increasing rates of diabetes and costs to the Canadian healthcare system, the use of biosimilar insulins is intended to increase the affordability of biologics. This article will review the available biosimilars approved in Canada (Table 1), safety and efficacy studies, and the advantages and potential concerns regarding the switch to biosimilar insulins.

## Background

The history and development of insulin are continuously evolving. From the initial discovery of insulin in 1921, several milestones have marked its progress, including the use of recombinant technology to enable production of large amounts of insulin in 1977.<sup>1</sup>

This synthetic version of insulin was termed “human insulin” to distinguish it from insulin derived from animal sources. Subsequent landmarks include the development of rapid-acting insulin in the 1990s, followed by the long-acting form of insulin in the early 2000s. Technology to develop insulin at a commercial level has continued to evolve, and the first biosimilar insulin, insulin glargine, was approved in Canada in 2015.

Biologic drugs are large molecules derived from living organisms and are produced using biotechnology.<sup>2</sup> Once the patent for a biologic drug expires, manufacturers may produce a newer version of the drug called a biosimilar. Biosimilars are often mistaken for generic drugs, however, they differ from generics in several ways. Due to the complexities of their manufacturing process, the molecular structure of a biosimilar is not identical to its reference biologic drug, whereas generic drugs contain identical medical ingredients.

The cost savings for biosimilars are somewhat less than those of a generic drug as their cost of development is higher. Prior to authorization, Health Canada must evaluate whether the biosimilar drug is highly similar to its reference drug, as well as ensure that clinical trials demonstrate comparable efficacy and safety.<sup>3</sup> The approval process is stricter than that required for generic drugs, but it is less complex than the process required for the approval of a novel drug.

## An important solution to rising healthcare costs

In Canada, diabetes is the leading cause of blindness, end-stage renal disease, heart disease, stroke, and amputations. There are approximately 11 million people living with prediabetes or diabetes in Canada and the cost of to the national health care system is approximately \$3 billion annually.<sup>3</sup> Fortunately, biologic drugs such as insulin are more

Insulin Molecule	Reference Brand (Manufacturer)	Biosimilar Insulin (Manufacturer)
Insulin glargine 100 u/mL	<b>Lantus®</b> (Sanofi) <ul style="list-style-type: none"> <li>• 10 mL vials</li> <li>• 3 mL prefilled disposable pen 3 mL: Lantus® SoloSTAR®</li> <li>• 3 mL cartridges: should only be used with <ul style="list-style-type: none"> <li>• JuniorSTAR® (0.5 unit dose increments)</li> <li>• ClikSTAR®</li> <li>• AllStar Pro™</li> </ul> </li> <li>• Also available in 300 u/mL concentration as Toujeo® SoloSTAR® and DoubleSTAR®</li> </ul>	<b>Basaglar®</b> (Eli Lilly) <ul style="list-style-type: none"> <li>• Available only in 100 u/mL concentration</li> <li>• 3 mL cartridges</li> <li>• 3 mL prefilled KwikPens®</li> </ul>
		<b>Semglee®</b> (Mylan) <ul style="list-style-type: none"> <li>• Available only in 100 u/mL concentration</li> <li>• 3 mL prefilled disposable pens</li> </ul>
Insulin lispro 100 u/mL	<b>Humalog®</b> (Eli Lilly) <ul style="list-style-type: none"> <li>• 10 mL vials</li> <li>• 3 mL vials</li> <li>• 3 mL prefilled disposable KwikPen®</li> <li>• 3 mL cartridges</li> <li>• Junior KwikPen (0.5 unit dose increments), 3 mL prefilled pen</li> <li>• Also available as Humalog 200 u/mL KwikPen® (3 mL prefilled pen)</li> </ul>	<b>Admelog®</b> (Sanofi) <ul style="list-style-type: none"> <li>• Available only in 100 u/mL concentration</li> <li>• 10 mL vials</li> <li>• 3 mL cartridges</li> <li>• 3 mL disposable prefilled SoloSTAR® pen</li> </ul>
Insulin aspart 100 u/mL	<b>NovoRapid®</b> (Novo Nordisk) <ul style="list-style-type: none"> <li>• 10 mL vials</li> <li>• 3 mL Penfill® cartridges</li> <li>• NovoRapid® FlexTouch® 3 mL disposable pens</li> </ul>	<b>Trurapi®</b> (Sanofi) <ul style="list-style-type: none"> <li>• Trurapi® SoloSTAR® disposable pens</li> <li>• 3 mL cartridges</li> <li>• Trurapi® cartridges should be used only with the following pens: <ul style="list-style-type: none"> <li>• JuniorSTAR® (0.5 unit dose increments)</li> <li>• AllStar PRO® (1 unit dose increments)</li> </ul> </li> </ul>
		<b>Kirsty®</b> (Mylan) <ul style="list-style-type: none"> <li>• 10 mL vials</li> <li>• 3 mL disposable prefilled pen</li> </ul>

**Table 1:** Available biosimilar insulins approved in Canada.

readily available than in the past, however, their cost has become a major concern. The availability of newer versions of a biologics allows for more competition, thereby lowering their cost. Not only will access to biosimilars increase affordability for biologic drugs for patients; when made accessible on a larger scale they would help reduce the financial burden on the Canadian healthcare system and provide opportunity to maximize healthcare resources.

Certain provinces have developed a switching policy to expand the use of biosimilar insulins; Ontario will become the seventh Canadian province to adopt this policy in the near future. Public formularies are beginning to cover biosimilar insulins instead of their reference biologic drugs which, in turn, impacts some private insurance plans. The Ontario Drug Benefit (ODB) program is one of the largest public drug plans in Canada. Biosimilars Canada predicts that implementing

a switching policy in Ontario would result in a cost savings of approximately 160 million dollars annually.<sup>4</sup>

### **Biosimilar insulins are equally safe and effective**

Health Canada implements similar regulatory standards as those of other biologic drugs when authorizing a biosimilar drug. In 2010, Health Canada approved the first biosimilar safety and efficacy pathway.<sup>2</sup> The process is initiated with extensive structural and functional studies followed by human clinical studies. As a general note, the pathway focuses on analytical characterization (in vitro studies); however, there are fewer clinical studies comparing biosimilars to their reference biologic drugs.<sup>5</sup> Clinical study programs and specific data requirements differ according to the individual product. Biosimilar

Study	Study type	Patient characteristics	Sample size	Primary endpoint	Primary outcome
ELEMENT 1 <sup>6</sup>	Prospective, open label, parallel trial	Type 1 DM with HbA1C <11%, treated with basal bolus	N=267 Lantus® N=268 Basaglar®	Change in HbA1C at 24 weeks	Basaglar® was non-inferior to Lantus® in terms of the change in HbA1c from baseline to 24 weeks
ELEMENT 2 <sup>7</sup>	Randomized, double-blind trial	Type 2 DM insulin-naïve, or previously on Lantus® on ≥2 OADs and A1C <11%	N=380 Lantus® N=376 Basaglar®		
SORELLA 1 <sup>8</sup>	Randomized, open-label parallel arm	Adult type 1 DM in combination with insulin glargine	N=253 Admelog® N=254 Humalog®	Change in HbA1c at Week 26	Admelog® was non-inferior to Humalog® in terms of the change in HbA1c from baseline to 26 weeks
SORELLA 2 <sup>9</sup>	Randomized open-label, multicenter, 2-arm parallel study	Adult type 2 DM in combination with insulin glargine	N= 253 Admelog® N= 252 Humalog®		
GEMELLI 1 <sup>10</sup>	Randomized, open-label parallel arm	Adult type 1 or type 2 DM in combination with insulin glargine	N=296 NovoRapid® N=301 Trurapi®	Change in HbA1c at Week 26	Trurapi® was non-inferior to NovoRapid® in terms of the change in HbA1c from baseline to 26 weeks
INSTRIDE 1 <sup>11</sup>	Open-label, randomized, multicentre, parallel-group	Adult type 1 DM in combination with insulin lispro	N=278 Lantus® N=280 Semglee®	Change in HbA1c at Week 24	Semglee® was non-inferior to Lantus® in terms of HbA1C reduction at 24 weeks
INSTRIDE 2 <sup>12</sup>	Open-label, randomized, multicentre, parallel-group	Adult type 2 DM in combination with insulin lispro	N=283 Lantus® N=277 Semglee®	Change in HbA1c at Week 24	

**Table 2:** Safety and efficacy studies.

authorization is based on the entirety of evidence given to Health Canada including comparative structural and functional as well as clinical studies. Health authorities can choose to mandate or reject certain studies in order to establish biosimilar efficacy on a case-by-case basis.

Once authorized, biosimilars are issued a unique Drug Identification Number (DIN). Health Canada monitors the safety of biosimilars by conducting post-marketing surveillance studies and monitoring for adverse reaction reports. Despite their approval by Health Canada, biosimilars are not considered equivalent to their reference drug and their interchangeability varies according to province. Interchangeability of a drug refers to the ability of a pharmacist to change one drug to another without the intervention of the prescriber.<sup>2</sup> In randomized clinical trials, biosimilar

insulins demonstrated similar efficacy and safety to their reference insulin in both patients with type 1 and type 2 diabetes (Table 2).<sup>6-14</sup>

Clinical outcomes were measured in terms of change in A1C from baseline, and no significant difference between the two drugs was observed. Subgroup analyses also demonstrated comparable glycemic control and safety when switching from a reference to a biologic insulin.<sup>6-14</sup> The risk of hypoglycemia, immunogenicity and other adverse reactions with biosimilars was comparable to that of their reference insulins. When exposed to a biologic drug, there is a theoretical risk of an immune system response and the development of antibodies which may have the ability to reduce the drug's efficacy. In reality, the presence of antibodies has no actual clinical impact; however, it is still important to note and requires

monitoring. Studies that demonstrate no anticipated clinically meaningful differences in immunogenicity are required. Health Canada also requires a 'Risk Management Plan' by manufacturers for monitoring once a biosimilar has been authorized which includes strict pharmacovigilance parameters. In a systematic review of biosimilar insulin vs reference insulins, all of the drugs studied demonstrated a similar proportion of patients developing antibodies between the biosimilar and reference groups.<sup>15,16</sup>

### **Clinical considerations and practical guidelines**

The product monographs of biosimilars state similar indications to those of their reference insulins. This is supported by the clinical studies cited above (Table 2). However, there is insufficient data on special sub-populations including pregnant women and the pediatric population.<sup>3</sup> Biosimilar insulins have demonstrated comparable safety in insulin pumps,<sup>17</sup> but currently only Admelog® (Sanofi, Bridgewater, New Jersey) is available in vial format for pumps in Canada, whereas the use of Trurapi® (Sanofi, Bridgewater, New Jersey) is not yet indicated in pump form.

Theoretical concerns regarding safety and immunogenicity exist because of the small difference in the structure of the biosimilar molecule. Despite favourable studies demonstrating comparable efficacy and safety, there may be hesitation among physicians and patients when switching to a biosimilar. The uncertainty of biosimilars as non-identical molecules are limiting their extensive use.<sup>18</sup> In response to this, increasing awareness regarding biosimilar insulins among patients and providers can help reduce misconceptions, increase prescribers' comfort level, and enable patients in their treatment decisions.<sup>19</sup>

Diabetes Canada supports biosimilar insulins as the first treatment option for insulin-naïve patients when a cost advantage is present. However, they do not recommend mandatory switching policies initiated at the governmental level. Switching to a biosimilar insulin should be a joint decision made between the patient and their healthcare provider.<sup>3</sup> Diabetes Canada recommends supporting patients who are at risk of increased lability in their glycemic control with a change in their insulin. There is evidence in the literature that altering an effective treatment plan can be disruptive to patients, causing psychological impact. Clinical studies have demonstrated that the nocebo effect (when negative expectations of the patient regarding a treatment causes the treatment to have a more negative effect than it otherwise would have) can impact a patient's perspective of a drug

and its outcomes. Patients may associate non-specific symptoms with the new drug which may lead to a perceived lack of efficacy, resulting in higher rates of discontinuing the medication.<sup>19</sup> Therefore, prior to switching to a biosimilar insulin, it is important for prescribers to discuss the topic of switching with the patient, and to provide support and counselling to allow for a positive transition.

When switching insulins, glucose levels should be carefully monitored. In theory, dosing and titration of insulin is the same when initiating or switching to a biosimilar insulin. Any adverse reaction to a biosimilar insulin should be reported for post-marketing surveillance to take place.

Use of the device should be reviewed prior to switching a patient to a biosimilar (e.g., prefilled pens vs cartridges). Biosimilar insulin devices are available in the manufacturer's format, rather than that of its reference insulin. Patients may have a preference in the type of device used, which can affect their level of comfort in its use.

Additionally, prescribing and dispensing errors are more likely to occur when there is increased availability of various versions of an insulin. Prescribing brand name products is important in order to avoid automatic substitution or confusion on the part of dispensing pharmacists.<sup>20</sup>

### **Summary**

Biosimilar insulins are similar but not identical to their reference insulin and are not necessarily interchangeable. Safety and efficacy studies have demonstrated that they are comparable to their reference insulin and that their dosing regimens are identical. Biosimilars provide improved patient access and affordability to biologic therapy. Many provincial payers have initiated biosimilar policies in order to increase the use of biosimilar insulins and reduce healthcare costs. Involuntary switching to a biosimilar can impact the patient's perspective of their glycemic control. Therefore, awareness of biosimilars, and effective conversations to address individual patients' needs are essential.

### **Financial Disclosures**

The author has no financial interests to disclose.

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