Diabetes, Biologic Drugs, and Biosimilar Insulins

Position Statement

The ability of people living with diabetes to obtain appropriate medications at an affordable price and in a fair and timely manner is paramount to optimal disease management. Diabetes Canada is committed to helping patients reduce their risk of complications and improve their health outcomes by advocating for their access to evidence-based, personalized diabetes treatments, including biologic drugs and biosimilar insulins.

Diabetes Canada welcomes that biosimilar insulins offer additional treatment choices for people living with diabetes and may be the preferred option for some. However, we also believe that the decision to use a biologic drug or a biosimilar insulin must be made jointly by patients living with diabetes and their health care providers.

A biosimilar should not be considered as interchangeable with its reference biologic drug with no regard for the person or clinical context. Medical switching should occur only with explicit knowledge and consent from patients and their health care providers. When a patient's characteristics or circumstances contribute to lability in diabetes care, and a switch could exacerbate that lability, a switch in medical treatment may not be advised.

Diabetes Canada recommends that health care providers:

- Consider biosimilar insulins as the first treatment option for insulin-naive patients where these represent a cost-effective advantage.
- Discuss and agree jointly with the person living with diabetes on the appropriate use of biosimilar insulin, providing clear and sufficient information.
- In the absence of clinical or contextual circumstances that compromise a patient's health, and with discussion and consent, consider switching to a biosimilar insulin for patients with sufficient monitoring, if it can be achieved safely and effectively.
- Support patients not to switch if they believe the patients have characteristics or circumstances, temporary or otherwise, that would contribute to some lability in his/her diabetes care or negatively impact other health outcomes.
- Report any adverse reaction to a biosimilar insulin, as for a biologic insulin, to allow for post-market surveillance to take place.
- Facilitate patient access to support services, such as education and counselling, to allow for a positive transition, if required.

- Recommend an increase in the frequency of self-monitored blood glucose (SMBG) testing, review of symptoms, precipitants and treatment of hypoglycemia, and the type and frequency of blood work during the transition period (e.g., Hemoglobin A1c (HbA1c)).
- Work together across the health care team to support patients who transition from a reference biologic drug to a biosimilar insulin, and to track the clinical outcomes associated with switching. This will help inform the safety and effectiveness for future patients.

Diabetes Canada recommends that governments and private insurers:

- Do not implement forced non-medical switching policies that require patients established on treatment to switch from a reference biologic drug to a biosimilar insulin.
- Provide sufficient information and support to patients and request informed consent to switch from a biologic drug to a biosimilar insulin.
- Allow patients who do not wish to switch, the opportunity to continue on established therapy as per the decision made jointly between patient and health care provider.
- Swiftly and diligently respond to submissions requesting an *exceptional Special Authority authorization*, as to not delay patients' access to therapy based on their personal circumstances and needs. In the case of a claim rejection letter, an explanatory statement must be provided for an *exceptional Special Authority* denial.
- Perform ongoing post-market surveillance and safety reporting of biosimilar insulins to establish long-term safety and efficacy profiles in the post-marketing phase.

Diabetes Canada recommends that people living with diabetes:

- Consider biosimilar insulins when initiating treatment with insulin.
- Be informed of all relevant information about the use of biosimilar insulin to have an informed discussion with a health care provider. Accept the responsibility and participate in treatment decisions.
- If needed, provide sufficient detail and context to your provider to request an *exceptional Special Authority authorization*, if that is part of the insurer's policy.
- Request education and support from a provider if required and increase frequency of blood glucose monitoring during a switch to a biosimilar insulin.
- Report any adverse reaction to a biosimilar insulin or reference biologic insulin, to allow for appropriate post-market surveillance to take place.

Why are Policies about Biologic Drugs and Biosimilar Insulins Important to Diabetes Canada?

Diabetes rates have risen significantly in Canada over the past few decades and health care costs have correspondingly skyrocketed. Funding decisions related to health systems and services are increasingly being made in an environment of limited fiscal resources. However, there must be a balance. While considering financial constraints, patients need to remain at the centre of health policy decisions. People with diabetes should be supported to achieve their full health potential, with the appropriate consideration given to the cost of doing so.

With this in mind, insulin-naive patients can be encouraged to initiate treatment with a biosimilar insulin. Non-medical switching occurs when the switching of a patient's medical treatment is for reasons other than the patient's health and safety. Reasons for forced non-medical switching include: reduced costs for a government agency or employer; increased profits for a private insurer; and agreements between the payer and the vendor to favour a specific medical treatment. This position statement is based on a review of the evidence about the roles and impacts of forced non-medical switching policies for biosimilar insulins on people living with diabetes. This statement provides recommendations to health care providers, governments, public and private insurers, and people living with diabetes in their assessment of treatment with biologic drugs and biosimilar insulins within their jurisdictions.

Diabetes Canada developed the present evidence-informed recommendations using a systematic approach and deliberative process. The steps in this process included:

- Identification of priority questions and outcomes;
- Retrieval of the evidence;
- Assessment and synthesis of the evidence;
- Formulation of recommendations;
- Review and input from experts; and
- Planning for communication, dissemination, implementation, evaluation, and updating of the recommendations.

Diabetes

From 2000 to 2015, the prevalence of diagnosed diabetes (type 1 and type 2) in Canada increased from 1.3 million to 3.1 million people (1). In Canada, 11 million people currently live with diabetes or prediabetes, and cost our health care system $3 billion annually in direct health care costs (2).

Diabetes is a condition characterized by an elevation in blood glucose (blood sugar) levels due to either a lack of insulin or a reduced effectiveness of one's own insulin (3). People with diabetes need to manage their glucose levels to achieve their target blood glucose (3). Target blood glucose levels are set for individuals depending on age, treatment methods, and other co-existing health

problems (3). Diabetes is a leading cause of blindness, end-stage renal disease, heart disease, stroke, and non-traumatic amputations in Canadian adults (3).

There are two major types of diabetes. Type 1 diabetes occurs when pancreatic beta cells no longer function leading to insulin deficiency (3). Consequently, glucose builds up in the blood instead of entering the cells to be used as energy (3). Approximately 5-10% of people living with diabetes have type 1 diabetes. Type 1 diabetes usually develops in childhood or adolescents but can develop in adulthood (3). Insulin therapy, which varies in methods of delivery, is required for the treatment of type 1 diabetes and is life sustaining (4).

Type 2 diabetes occurs when the body can not properly use the insulin that is released from the pancreas or does not make enough insulin (3). Consequently, glucose builds up in the blood instead of entering the cells to be used as energy (3). Over 90% of people living with diabetes have type 2 diabetes. Type 2 diabetes generally develops in adulthood, but children are increasingly affected. Various treatment options exist for treating type 2 diabetes including: nutrition guidance and physical activity, glucose lowering medications, and insulin therapy (5). The treatment plan prescribed by a clinician will depend on goals, lifestyle, meal plan, age, and general health (5).

Biologic Drugs and Biosimilars

Biologic drugs are made using biotechnology and come from living organisms or from their cells (6–11). They are large and complex; have a variety of functions that impact disease progression and health outcomes; and are generally administered as injectables (6,12). The complexity of a biologic drug is determined by its chemical, biological, or microbiological properties, which are highly dependent on the manufacturing process (7,8,12). Therefore, each biologic drug is unique, making it impossible to replicate exactly (7–12).

There has been an increase in the availability of biologic drugs in Canada, which present new treatment options for patients. However, the high cost of biologic drugs has been a growing concern for patients, public, and private insurance plans. Biologic drugs make up 26.2% of the Canadian pharmaceutical market; and among Organisation for Economic Co-operation and Development (OECD) countries, Canada has the second highest per capita spending on biologic drugs at $141 dollars (13).

Recently, manufacturers have developed alternative products that are intended to replicate the original reference biologic drugs as closely as possible, these are called biosimilars (6–11). Biosimilars are similar to a reference biologic drug, and are produced after the patent on the reference biologic drug has expired (6–11). Biosimilars are sometimes mistakenly called ‘generic’ versions of reference biologic drugs; however, biosimilars are similar to, but not identical to the reference biologic drug (6–11). This is due to the complexities of their manufacturing

process (6–11). Biosimilars are often less expensive than the reference biologic drugs.

Insulin therapy is a lifesaving treatment for all people living with type 1 diabetes and for some people living with type 2 diabetes (4,5). Insulin preparations, which are proteins, are manufactured using recombinant DNA technology and are formulated as biologic products (e.g., originator insulins and biosimilar insulins) (4,10). The goal of insulin therapy is to help regulate blood glucose and they have been developed to have varying durations of action (4).

Clinical Standards: Safety and Efficacy of Biosimilars

Biologics are more variable and structurally complex than chemically synthesized drugs because they are derived from living organisms (6). Thus, the scientific regulatory approval process for biosimilars differs from that of generic drugs (6). The scientific regulatory approval process for biosimilars by Health Canada requires manufacturers to provide information that demonstrates the similarity of their biosimilar to the reference biologic drug (6). Similarity of the biosimilar to the reference biologic drug is shown using comparative studies via a step-wise approach: beginning with structural and functional studies, and continuing with human clinical studies (6).

To authorize a biosimilar, Health Canada evaluates if the information provided by the manufacturer is complete and whether it shows that: [1] the biosimilar and the reference biologic drug are highly similar; and [2] there are no clinically meaningful differences in efficacy and safety between the biosimilar and the reference biologic drug (6). Once a biosimilar has been authorized for sale, Health Canada issues a Notice of Compliance (NOC) and a unique Drug Identification Number (DIN) (6).

Interchangeability, Automatic Substitution, and Switching

Interchangeability refers to two medical treatments that are therapeutically equivalent and can be safely exchanged in clinical practice; such as the action of replacing a reference biologic drug with a biosimilar (6–9,11,14,15). Automatic substitution refers to replacing one drug with another at the pharmacy level, without consulting the prescribing health care provider (7–9,11,14,15). Health Canada's authorization of a biosimilar for sale is not an indication that it is interchangeable to the reference biologic drug (6). In Canada, each province and territory authorizes whether two products are interchangeable or can be automatically substituted according to their own rules and regulations (6).

Switching refers to a health care provider deciding to exchange one medical treatment with another with the same therapeutic indications (6–9,11,14,15). This results in a change in routine use from a reference biologic drug to a biosimilar, whereby there are no intended clinical differences in the efficacy and safety (6–9,11,14,15).

Policy to Increase the Uptake of Biosimilars

The Canadian Agency for Drugs and Technology in Health (CADTH) reports that in Canada and around the world, various policies at the national or organizational level have been and continue to be implemented, to increase the uptake of biosimilars and enhance the confidence of health care professionals in biosimilars (15). These policies function by employing non-medical forced switching, interchangeability designations, and automatic substitution regulations (15). The increased uptake of biosimilars as a cost-saving alternative to high-cost biologic drugs is intended to maximize savings for local and national health care economies. However, the increased uptake of biosimilars and associated cost savings depends on several factors including: patient and health care provider's knowledge and acceptance of biosimilars, cost of biosimilars, insurer coverage, and policies around interchangeability, automatic substitution, and switching (15).

Impact on Health Care Providers

Some health care providers are largely unfamiliar with biosimilars and/or reluctant to prescribe them in treatment-naïve patients and/or patients currently managed on reference biologic drugs (16). This limits the acceptance of biosimilars by patients, as it is related to the comfort of health care providers educating patients and prescribing biosimilars (16). Other barriers to prescribing biosimilars include: safety and efficacy concerns, patient opinions, and how cost savings from the use of biosimilars are distributed (11,17).

There is a scarcity of data specific to the risks associated with switching from a reference biologic drug to a biosimilar insulin in people living with diabetes who have already been established on a therapy with a biologic drug. The long-term effects of switching from a biologic drug to a biosimilar and back to a biologic drug, if the biosimilar is ineffective for any reason, or between biosimilars, have not been extensively examined in the diabetes population. Thus, post-market surveillance will be essential in ensuring the efficacy and safety of biosimilar insulins, in addition to monitoring for potential increased immunogenicity of the product (9,18). Notably, the effectiveness of biosimilar insulins for diabetes management, as well as any associated adverse outcomes and side effects, can be monitored in 'real time' through glucose monitoring.

Impact on Public and Private Coverage

Biosimilars can be less expensive than reference biologic drugs and may place less of a burden on the health care system, thereby freeing up health care dollars for diabetes and chronic disease treatment, prevention, and care initiatives. Some public plans are beginning to cover biosimilar insulins in place of their reference biologic drugs. The lower cost of biosimilars to provincial drug plans and the opportunity to maximize resources, appears to be a major driver for this switch

(19). Several private plans have been reported to be following suit.

Impact on People Living with Diabetes

There is insufficient information about individuals within sub-populations (e.g., pediatric, pregnant women, frail seniors, and those with a significant history of poor mental health) who may be at risk of harms associated with forced non-medical switching. There is also some evidence to suggest that changing a treatment plan, particularly when a condition is well-managed on this plan, can be highly disruptive and troubling to some patients and can have a negative psychological impact (20). While a negative outcome will not occur for all patients, it must be considered on an individual basis, while taking the patient and contextual factors into consideration.

Conclusion

Diabetes Canada supports an individualized patient-centered approach that prioritizes the needs and safety of people living with diabetes. People living with diabetes should have access to safe and effective treatment options without financial hardship. Health care providers and people living with diabetes need to have an opportunity to make a joint informed decision about treatment options.

Biosimilar insulins are a safe and effective treatment option for all people living with type 1 diabetes and those people living with type 2 diabetes who require insulin. Insulin-naive patients can be encouraged to initiate treatment with a biosimilar insulin. The decision to switch a patient from a reference biologic drug to a biosimilar insulin should be based on joint patient and health care provider decision. Diabetes Canada believes that forced non-medical switching from a reference biologic drug to a biosimilar insulin, without consideration of individual factors is not in the best interest of people living with diabetes.

Diabetes Canada will review this policy statement regularly, to ensure that it continues to be accurate and reflect the most up-to-date evidence.

References

1. Public Health Agency of Canada. Canadian chronic Disease Surveillance System (CCDSS) [Internet]. Public Health Agency of Canada. 2017 [cited 2019 Sep 13]. Available from: https://health-infobase.canada.ca/ccdss/data-tool/

2. Diabetes Canada. 2015 Report on Diabetes – Driving Change. 2015.

3. Diabetes Canada Clinical Practice Guidelines Expert Committee, Punthakee Z, Goldenberg R, Katz P. Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome. Can J Diabetes. 2018 Apr;42 Suppl 1:S10–5.

4. Diabetes Canada Clinical Practice Guidelines Expert Committee, McGibbon A, Adams L, Ingersoll K, Kader T, Tugwell

B. Glycemic Management in Adults With Type 1 Diabetes. Can J Diabetes. 2018 Apr;42 Suppl 1:S80–7.

5. Diabetes Canada Clinical Practice Guidelines Expert Committee, Lipscombe L, Booth G, Butalia S, Dasgupta K, Eurich DT, et al. Pharmacologic Glycemic Management of Type 2 Diabetes in Adults. Can J Diabetes. 2018 Apr;42 Suppl 1:S88–103.

6. Health Canada. Biosimilar biologic drugs in Canada: Fact Sheet [Internet]. Health Canada. 2019 [cited 2019 Sep 13]. Available from: https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/fact-sheet-biosimilars.html

7. McKinnon RA, Cook M, Liauw W, Marabani M, Marschner IC, Packer NH, et al. Biosimilarity and Interchangeability: Principles and Evidence: A Systematic Review. Biodrugs. 2018;32(1):27–52.

8. Wiland P, Batko B, Brzosko M, Kucharz EJ, Samborski W, Świerkot J, et al. Biosimilar switching – current state of knowledge. Reumatologia. 2018;56(4):234–42.

9. White J, Goldman J. Biosimilar and Follow-on Insulin: The Ins, Outs, and Interchangeability. J Pharm Technol JPT Off Publ Assoc Pharm Tech. 2019 Feb;35(1):25–35.

10. Blumer I, Edelman S. Biosimilar insulins are coming: the top 10 things you should know. Postgrad Med. 2014 May;126(3):107–10.

11. James J, Pollom RK, Hadjiyianni I, Buchholz G, Reed BL. Biosimilar insulins: What do you need to know? Int Diabetes Nurs. 2017 Jan 2;14(1):32–5.

12. Vulto AG, Jaquez OA. The process defines the product: what really matters in biosimilar design and production? Rheumatol Oxf Engl. 2017 01;56(suppl_4):iv14–29.

13. Patent Medicine Prices Review Board. Biosimilars in Canada: Current Environment and Future Opportunity [Internet]. Patent Medicine Prices Review Board. 2019 [cited 2019 Sep 16]. Available from: http://pmprb-cepmb.gc.ca

14. Heinemann L. Biosimilar Insulin and Costs: What Can We Expect? J Diabetes Sci Technol. 2015 Sep 8;10(2):457–62.

15. Pant S, de Léséleuc L, Spry C. Environmental Scan: International Policies on the Appropriate Use of Biosimilar Drugs [Internet]. CADTH; 2018 Oct [cited 2019 Sep 16] p. 22. Report No.: 88. Available from: https://www.cadth.ca/sites/default/files/pdf/es0333_international-policies-on-use-of-biosimilar-drugs.pdf

DIABETES CANADA

16. Kaida-Yip F, Deshpande K, Saran T, Vyas D. Biosimilars: Review of current applications, obstacles, and their future in medicine. World J Clin Cases. 2018 Aug 16;6(8):161–6.

17. Chapman SR, Fitzpatrick RW, Aladul MI. Knowledge, attitude and practice of healthcare professionals towards infliximab and insulin glargine biosimilars: result of a UK web-based survey. BMJ Open. 2017 21;7(6):e016730.

18. Dolinar RO, Edelman S, Heinemann L, Home P, Goyal S, Polonsky WH, et al. Impact of Biosimilar Insulins on Clinical Practice. J Diabetes Sci Technol. 2014 Jan;8(1):179–85.

19. Ministry of Health. Biosimilars Initiative for Patients - Province of British Columbia [Internet]. British Columbia. 2019 [cited 2019 Sep 13]. Available from: https://www2.gov.bc.ca/gov/content/health/health-drug-coverage/pharmacare-for-bc-residents/what-we-cover/drug-coverage/biosimilars-initiative-patients

20. Rezk MF, Pieper B. Treatment Outcomes with Biosimilars: Be Aware of the Nocebo Effect. Rheumatol Ther. 2017 Oct 14;4(2):209–18.

Last Updated: January 2020