DIABETES CANADA

# BILL C-64

## Comparision of Non-Insured Health Benefits (NIHB) and Diabetes Canada Clinical Practice Guidelines with Bill C-64

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Diabetes Canada's evidence-based clinical practice guidelines are rigorously developed to inform general patterns of care; reduce inappropriate variation in practice; promote efficient use of health-care resources; identify gaps in knowledge; and inform public policy to improve the quality of care and health-care outcomes for people in Canada who live with diabetes.

Based on values that respect the individuality of people living with diabetes and their clinical and social context, Diabetes Canada's clinical practice guidelines also empower people living with diabetes and promote the importance of individualized care through the principles of inclusion, diversity, equity, and accessibility.

All people living with diabetes in Canada should have the opportunity to manage their diabetes to the best of their ability and achieve their optimal health through equal access to person-centered care and support. Every person is unique, and their diabetes management should be tailored to meet their specific needs, including collaborative care that addresses gender identity, sexual orientation, ethnicity, geographical location, culture, and social class. The clinical practice guidelines respect and welcome patient autonomy, and recognize that optimal care for the population (by addressing social determinants of health and inequities in access to care) is as important as defining optimal care for individuals living with diabetes.

While Bill C-64 shows a commitment to helping people live well with diabetes and to reducing risk and/or delaying complications of the condition, its limited drug formulary is lacking several pharmacological treatments that should be offered for consideration to individuals living with diabetes. The limited list opposes the main principles of the clinical practice guidelines which advocates for people to have access to individualized care that is determined through shared decision-making between the individual affected by diabetes and the diabetes health-care team. Not having access to a comprehensive medication formulary that is fulsome and inclusive is detrimental to individuals who cannot tolerate certain therapies and those who need to choose medications and therapies not included in the proposed list.

Unlike the NIHB plan, which offers coverage of all diabetes medications (including cardiorenal protective and prioritized glucose-lowering therapies which support weight-management and are not, on their own, affiliated with hypoglycemia), as well as supplies and technology, Bill C-64 includes only a small number of pharmacologic therapies. This is inconsistent with the clinical practice guidelines which recommend use of the agent/therapy that is best suited to an individual's unique circumstances. The list is also glycemic-centric and neglects to include key medications for cardiorenal protection that are recommended in the clinical practice guidelines, including statins, ACE/ARBs, anti-platelet agents (when indicated), and medications to manage hypertension. The clinical practice guidelines look beyond the glucocentric approach and seek to support each person based on their current health status, including recommending preventative therapies when appropriate according to an individual's level of risk of health outcomes, and supporting the person's desired health-care goals.

## Concerns and inconsistencies with Diabetes Canada Clinical Practice Guidelines

| Drug | Concerns and inconsistencies |
|---|---|
| **SGLT2 Inhibitors** | • Forxiga (dapagliflozin) is included in the proposed list, but canagliflozin and empagliflozin (single entity agents) are not included.<br>• Synjardy (empagliflozin/metformin) is included in the proposed list, but combination Invokamet (canagliflozin/metformin) and Xigduo (dapagliflozin/metformin) are not included.<br>• This limited list is contrary to Diabetes Canada's clinical practice guidelines which support the appropriate use of cardiorenal protective agents when indicated. Further, this discordance is impractical from a clinical care perspective in that it would require a clinician to change a person's medication within a class, i.e. change from empafliflozin to dapafliflozin, in the event that that clinician is simply aiming to adjust the dose of metformin.<br>• The following is a list of the SGLT2 inhibitors that are indicated in the recommendations of the Diabetes Canada clinical practice guidelines: canagliflozin, dapagliflozin, and empagliflozin.*<br>**Note: *See Appendix A*** for the recommendations from the 2020 update of the *Pharmacologic Glycemic Management of Type 2 Diabetes* in *Adults* chapter. The level of evidence is listed for each. |
| **DPP4 Inhibitors** | • Saxagliptin is included in the proposed list in the form of Komboglyze (saxagliptin/metformin), but sitagliptin (neither single entity nor combination product) is not included.<br>• Linagliptin is included in the proposed list in the form of Jentadueto (linagliptin/metformin), but linagliptin (single entity) is not included.<br>• This limited list is very restrictive to the clinician who would be able to use a DPP4 inhibitor only in combination with metformin. Metformin is contraindicated, and/or not tolerated, in a number of individuals with diabetes, requiring that the DPP4 inhibitor be available as a single entity product.<br>• The following is a list of the DPP4 inhibitors that are indicated in the recommendations of the Diabetes Canada clinical practice guidelines: saxagliptin.* Of note, due to a higher risk of heart failure, saxagliptin is not recommended in people with a history of heart failure, a recognized complication of diabetes.<br>**Note: *See Appendix A*** for the recommendations from the 2020 update of the *Pharmacologic Glycemic Management of Type 2 Diabetes* in *Adults* chapter. The level of evidence is listed for each. |

| Drug | Concerns and inconsistencies |
|---|---|
| **GLP1-RA/dual GIP/GLP-1 RA** | • No incretin mimetics (neither GLP-1 RA nor dual GIP/GLP-1 RA) are included in the proposed list.<br>• Again, this is contrary to the guidelines. Access and equity in diabetes care need to look beyond the glucocentric approach and follow the guidelines for GLP1-RA, at least for those with cardiorenal complications. In clinical practice, not everyone is a candidate for SGLT2 inhibitors or can tolerate these medications. These options are not only important, but necessary.<br>• The following is a list of the GLP1-RAs that are indicated in the recommendations of the Diabetes Canada clinical practice guidelines: liraglutide, dulaglutide, and semaglutide.*<br><br>**Note: *See Appendix A*** for the recommendations from the 2020 update of the *Pharmacologic Glycemic Management of Type 2 Diabetes* in *Adults* chapter. The level of evidence is listed for each. |
| **Insulins** | • Biosimilar insulin glargine u100 and detemir are included in the proposed list, but neither insulin degludec nor insulin glargine U300 are included.<br>• There are concerns that many of the insulins on this list would not be "commonly used" (i.e. Entuzity, Hypurin Regular Insulin Pure, Hypurin NPH Insulin Isophane Pork, and even Humulin R and Novolin ge Toronto). According to a 2007 CADTH report, a very small percentage - approximately 0.1% of the Canadian insulin market - uses animal products, which represents 400 people using animal insulin out of approximately 382,000 insulin-dependent Canadians[1]. Access to these particular insulins is important to this small population, however, the majority of insulin users in Canada use synthetic insulins, the majority of which are not included in the proposed list.<br>• With respect to the premixed insulins, Novolin ge 30/70 and Humulin 30/70 are included in the proposed list, but the premixed insulins that are affiliated with comparably less hypoglycemia (i.e. NovoMix 30, Humalog 25, and Humalog 50) are not included.<br>• The following is a list of insulins that are indicated in the recommendations of the Diabetes Canada clinical practice guidelines: glargine U-100, glargine U-300, detemir, degludec, and aspart.* For a complete list of insulins listed in the Diabetes Canada clinical practice guidelines, please see Table 1, available at: https://guidelines.diabetes.ca/GuideLines/media/Images/cpg/Ch13-2020-Tbl1b-Antihyperglycemic-agents-for-use-in-type-2-diabetes.png<br><br>**Note: *See Appendix B*** for the insulin-related recommendations from the 2020 update of the *Pharmacologic Glycemic Management of Type 2 Diabetes* in *Adults* chapter. The level of evidence is listed for each. |

* These are the pharmacologic therapies indicated in the recommendations of the 2020 update of the *Pharmacologic Glycemic Management of Type 2 Diabetes in Adults* chapter.

**It is important to note, however, that ALL antihyperglycemic agents are listed in the chapter preamble, along with their class, mechanism of action, cost, their effect on primary CVD outcomes, risk of hypoglycemia, and other therapeutic considerations. It is also specifically stated that the choice of agent should be individualized as per the unique circumstances of the individual living with diabetes.**

1 Canadian Agency for Drugs and Technologies in Canada. Efficacy and Safety of Human versus Animal Insulins. August 3, 2007

## Conclusion

While a significant step forward for diabetes health-care support in Canada, Bill C-64 needs to expand its formulary to not only ensure more diverse coverage, but to support collaborative and individualized care which is the cornerstone of the clinical practice guidelines. The limited formulary makes individualized care nearly impossible and may negatively impact our health-care system and the health of people living with diabetes by offering sub-optimal therapies (i.e. prioritizing management options that increase a person's risk of hypoglycemia and weight gain). Also, a national pharmacare program with a limited formulary has the potential to impact choice; health-care providers may look to the formulary as a definitive list without collaborating with the person living with diabetes and discussing all theraputic options.

***Diabetes is a complicated condition with a constantly expanding compendium of new therapies and new technologies, and they should all be available and covered as options for care.***

# Appendix A: Recommendations for the advancement or adjustment of treatment in people with type 2 diabetes*

* Taken from the 2020 update to the *Pharmacologic Glycemic Management of Type 2 Diabetes* in *Adults* chapter. This chapter is currently being revised based on newly published evidence, so the recommendations may change.

**1.** In adults with type 2 diabetes **with ASCVD, HF and/or CKD, treatment should include agents from the following classes with** demonstrated **CV or renal benefits** (see Figures 2A, 2B and Table 2).

- **a.** In adults with **type 2 diabetes and ASCVD**, a GLP1-RA or SGLT2i with CV or renal benefit should be used to reduce the risk of:
  - **i.** MACE [Grade A, Level 1A (6,10) for liraglutide and dulaglutide; Grade B, Level 2 for subcutaneous semaglutide (7); Grade A, Level 1A (12) for empagliflozin; Grade B, Level 2 (15) for canagliflozin].
  - **ii.** HHF [Grade B, Level 2 (12,15,17) for empagliflozin, canagliflozin and dapagliflozin].
  - **iii.** Progression of nephropathy [Grade B, Level 2 (44,15,17) for empagliflozin, canagliflozin and dapagliflozin].
- **b.** In adults with type 2 diabetes and **a history of HF** (reduced ejection fraction ≤40%):
  - **i.** An SGLT2i should be used to reduce the risk of HHF or CV death, if the eGFR is >30 mL/min/1.73m$^2$ [Grade A, Level 1A (19) for dapagliflozin; Grade A, Level 1 (18) for empagliflozin and canagliflozin].
  - **ii.** TZD and saxagliptin should be avoided due to their higher risk of HF [Grade A, Level 1A (21,45,46)].
- **c.** In adults with type 2 diabetes and **CKD and an estimated eGFR >30 mL/min/1.73m$^2$**:
  - **i.** An SGLT2i should be used to reduce the risk of:
    - **1.** Progression of nephropathy [Grade A, Level 1A (16) for canagliflozin; Grade A, Level 1 (18) for empagliflozin and dapagliflozin].
    - **2.** HHF [Grade A, Level 1 (18) for canagliflozin, dapagliflozin and empagliflozin].
    - **3.** MACE [Grade B, Level 2 for canagliflozin (16), Grade C, Level 3 (12) for empagliflozin].
  - **ii.** A GLP1-RA may be considered to reduce the risk of MACE (Grade B, Level 2 (6,7) for liraglutide and semaglutide).

**2.** In adults with type 2 diabetes requiring treatment advancement or adjustment to improve glycemic control, the choice of antihyperglycemic medication should be individualized according to clinical priorities (see Figure 2A and Table 1 for therapeutic considerations and cautions) [Grade B, Level 2 (26)].

- **a.** In adults with type 2 diabetes **aged 60 years or older with at least 2 CV risk factors** (see Table 3), inclusion of the following classes in glycemic management should be considered:
  - **i.** A GLP1-RA with proven CV outcome benefit to reduce the risk of MACE [Grade A, Level 1A (10) for dulaglutide; Grade B, Level 2 (6) for liraglutide and Grade C, Level 2 (7) subcutaneous semaglutide]; OR
  - **ii.** An SGLT2i with proven cardiorenal outcome benefit if estimated GFR is >30 mL/min/1.73m$^2$ to reduce the risk of
    - **1.** HHF [Grade B Level 2 (15,17) for dapagliflozin and canagliflozin].
    - **2.** Progression of nephropathy [Grade C, Level 3 (15,17) for canagliflozin and dapagliflozin].
- **b.** If reducing risk of hypoglycemia is a priority: Incretin agents (DPP4i or GLP1-RA), SGLT2i, acarbose and/or pioglitazone should be considered as add-on medication to improve glycemic control with a lower risk of hypoglycemia than other agents [Grade A, Level 1A (26,28,29,47,48,49,74)]. (See Table 1.)
- **c.** If weight loss is a priority: A GLP1-RA and/or SGLT2i should be considered as add-on medication to improve glycemic control with more weight loss than other agents [Grade A, Level 1A (26,28,29,30,47,48,49]. (See Table 1.)

# Appendix B: Recommendations for initiating insulin treatment in individuals with type 2 diabetes*

* Taken from the 2020 update to the *Pharmacologic Glycemic Management of Type 2 Diabetes* in *Adults* chapter. This chapter is currently being revised based on newly published evidence, so the recommendations may change.

**1.** In people not achieving glycemic targets on existing noninsulin antihyperglycemic medication(s), the addition of a basal insulin regimen should be considered over premixed insulin or bolus-only regimens, if lower risk of hypoglycemia and/or preventing weight gain are priorities [Grade B, Level 2 (50)].

**2.** In adults with type 2 diabetes treated with basal insulin therapy, if minimizing risk of hypoglycemia is a priority:

- **a.** Long-acting insulin analogues (insulin glargine U-100, glargine U-300, detemir, degludec) should be considered over NPH insulin to reduce the risk of nocturnal and symptomatic hypoglycemia [Grade A, Level 1A (51-56)].
- **b.** Insulin degludec or insulin glargine U-300 (57) may be considered over insulin glargine U-100 to reduce overall and nocturnal hypoglycemia [Grade B, Level 2 for individuals with ≥1 risk factor for hypoglycemia (58,59)]; [Grade C, Level 3 for other individuals without risk factors for hypoglycemia (56)]; and severe hypoglycemia in patients at high CV risk [Grade C, Level 3 (60)]

### Treatment Advancement or Adjustment for People With Type 2 Diabetes Treated With Insulin

**1.** In adults with type 2 diabetes receiving insulin, doses should be adjusted and/or additional antihyperglycemic medication(s) should be added if glycemic targets are not achieved [Grade D, Consensus].

- **a.** A GLP1-RA should be considered as add-on therapy [Grade A, Level 1A (61,62)], before initiating bolus insulin or intensifying insulin to improve glycemic control with potential benefits of weight loss and lower hypoglycemia risk compared to single or multiple bolus insulin injections [Grade A, Level 1A (63-71)].
- **b.** An SGLT2i should be considered as add-on therapy to improve glycemic control with potential benefits of weight loss and lower hypoglycemia risk compared to additional insulin [Grade A, Level 1A (72-74)].
- **c.** A DPP4i may be considered as add-on therapy to improve glycemic control with potential benefits of less weight gain and lower hypoglycemia risk compared to additional insulin [Grade B, Level 2 (72,75-77)].

**2.** When bolus insulin is added to antihyperglycemic agents, rapid-acting analogues may be considered over short-acting (regular) insulin for greater improvement in glycemic control [Grade B, Level 2 (78,79) for aspart].

**3.** Bolus insulin may be initiated using a stepwise approach (starting with 1 injection at 1 meal and additional mealtime injections as needed) to achieve similar A1C reduction with lower hypoglycemia risk compared to initiating bolus injections at every meal [Grade B, Level 2 (80)].

# Appendix C: Comparison of Diabetes Canada Clinical Practice Guidelines (CPG), NIHB, and Bill C-64 Formulary Listings

| SGLT2 Inhibitors | | | |
|---|---|---|---|
| **Drug** (brand name) | **Bill C-64** | **NIHB** | **Diabetes Canada CPG** |
| canagliflozin **(Invokana)** | | Limited use benefit (prior approval required) | ✓ |
| dapagliflozin **(Forxiga)** | ✓ | ✓ | ✓ |
| dapagliflozin and metformin **(Xigduo)** | | ✓ | ✓ |
| empagliflozin **(Jardiance)** | | ✓ | ✓ |
| empagliflozin and metformin **(Synjardy)** | ✓ | ✓ | ✓ |
| ertugliflozin **(Steglatro)** | | | ✓ |
| **DPP4 Inhibitors** | | | |
| **Drug** (brand name) | **Bill C-64** | **NIHB** | **Diabetes Canada CPG** |
| alogliptin **(Nesina)** | | | ✓ |
| linagliptin **(Trajenta)** | | ✓ | ✓ |
| linagliptin and metformin **(Jentadueto)** | ✓ | ✓ | ✓ |
| saxagliptin **(Onglyza)** | | ✓ | ✓ |
| saxagliptin and metformin **(Komboglyze)** | ✓ | ✓ | ✓ |

| DPP4 Inhibitors (continued) | | | |
|---|---|---|---|
| **Drug** (brand name) | **Bill C-64** | **NIHB** | **Diabetes Canada CPG** |
| sitagliptin **(Januvia)** | | Limited use benefit (prior approval required) | ✓ |
| sitagliptin and metformin **(Janumet)** | | Limited use benefit (prior approval required) | ✓ |
| **GLP1-RAs** | | | |
| **Drug** (brand name) | **Bill C-64** | **NIHB** | **Diabetes Canada CPG** |
| dulaglutide **(Trulicity)** | | | ✓ |
| exenatide **(Bydureon)** | | | ✓ |
| exenatide XR **(Byetta)** | | | ✓ |
| liraglutide **(Victoza)** | | | ✓ |
| lixisenatide **(Adlyxine)** | | ✓ | ✓ |
| semaglutide **(Ozempic; Rybelsus)** | | ✓ | ✓ |
| **Insulins** | | | |
| **Drug** (brand name) | **Bill C-64** | **NIHB** | **Diabetes Canada CPG** |
| aspart **(NovoRapid)** | | ✓ | ✓ |
| aspart (biosimilar) **(Trurapi; Kirsty)** | ✓ | ✓ | ✓ |
| biphasic insulin aspart **(NovoMix 30)** | ✓ | | ✓ |
| concentrated Humulin R **(Entuzity)** | ✓ | ✓ | |
| degludec U100; U200 **(Tresiba)** | | ✓ | ✓ |

| Insulins (continued) | | | |
|---|---|---|---|
| **Drug** (brand name) | **Bill C-64** | **NIHB** | **Diabetes Canada CPG** |
| detemir **(Levemir)** | ✓ | ✓ | ✓ |
| Glargine U100; U300 **(Lantus; Toujeo)** | | ✓ | ✓ |
| glargine (biosimilar) **(Basaglar; Semglee)** | ✓ | ✓ | ✓ |
| glargine and lixisenatide **(Soliqua)** | | ✓ | ✓ |
| glulisine **(Apidra)** | ✓ | ✓ | ✓ |
| isophane, pork pure **(Hypurin NPH)** | ✓ | | Due to lack of published evidence regarding animal-sourced insulins, the guidelines do not offer recommendations for their use. However, it is also specifically stated that the choice of agent should be individualized as per the unique circumstances of the individual living with diabetes. |
| Lispro U100; U200 **(Humalog)** | | ✓ | ✓ |
| lispro (biosimilar) **(Admelog)** | ✓ | ✓ | ✓ |
| lispro/lispro protamine suspension **(Humalog Mix)** | | ✓ | ✓ |

| Insulins (continued) | | | |
|---|---|---|---|
| **Drug** (brand name) | **Bill C-64** | **NIHB** | **Diabetes Canada CPG** |
| pork regular **(Hypurin R)** | ✓ | | Due to lack of published evidence regarding animal-sourced insulins, the guidelines do not offer recommendations for their use. However, it is also specifically stated that the choice of agent should be individualized as per the unique circumstances of the individual living with diabetes. |
| premixed regular NPH **(Humulin 30/70; Novolin 30/70)** | ✓ | ✓ | ✓ |
| regular, human **(Humulin R; Novolin ge Toronto)** | ✓ | ✓ | ✓ |
| **Biguanides** | | | |
| **Drug** (brand name) | **Bill C-64** | **NIHB** | **Diabetes Canada CPG** |
| metformin **(Glucophage; Glumetza)** | ✓ | ✓ | ✓ |
| metformin XR **(Glucophage; Glumetza)** | ✓ | ✓ | ✓ |
| **Insulin Secretagogues (Sulfonylureas)** | | | |
| **Drug** (brand name) | **Bill C-64** | **NIHB** | **Diabetes Canada CPG** |
| gliclazide **(Diamicron; Diamicron MR)** | ✓ | ✓ | ✓ |
| glimepiride **(Amaryl)** | | | ✓ |
| glyburide **(Diabeta; Euglucon)** | ✓ | ✓ | ✓ |

| Insulin Secretagogues (Meglitinides) | | | |
|---|---|---|---|
| **Drug** (brand name) | **Bill C-64** | **NIHB** | **Diabetes Canada CPG** |
| repaglinide **(GlucoNorm)** | | ✓ | ✓ |

| Alpha-glucosidase Inhibitors | | | |
|---|---|---|---|
| **Drug** (brand name) | **Bill C-64** | **NIHB** | **Diabetes Canada CPG** |
| acarbose **(Glucobay)** | | ✓ | ✓ |

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