



Common Drug Review *Patient Group Input Submissions*

Canagliflozin and metformin hydrochloride (Invokamet) for Type 2 diabetes

Patient group input submissions were received from the following patient groups. Those with permission to post are included in this document.

Canadian Diabetes Association — permission granted to post

Kidney Foundation of Canada — permission granted to post

CADTH received patient group input for this review on or before March 24, 2016

The views expressed in each submission are those of the submitting organization or individual; not necessarily the views of CADTH or of other organizations.

While CADTH formats the patient input submissions for posting, it does not edit the content of the submissions.

CADTH does use reasonable care to prevent disclosure of personal information in posted material; however, it is ultimately the submitter's responsibility to ensure no personal information is included in the submission. The name of the submitting patient group and all conflict of interest information are included in the posted patient group submission; however, the name of the author, including the name of an individual patient or caregiver submitting the patient input, are not posted.

Canadian Diabetes Association

Section 1 – General Information

Name of the drug CADTH is reviewing and indication(s) of interest	canagliflozin + metformin Type 2 diabetes
Name of patient group	Canadian Diabetes Association
Name of primary contact for this submission:	[REDACTED]
Position or title with patient group	[REDACTED]
Email	[REDACTED]
Telephone number(s)	[REDACTED]
Name of author (if different)	
Patient group's contact information:	Canadian Diabetes Association
Email	advocacy@diabetes.ca
Telephone	613 688 5938
Address	45 Montreal Road Ottawa, ON, K1L 6E8
Website	www.diabetes.ca

1.1 Submitting Organization

The Canadian Diabetes Association (the CDA) leads the fight against diabetes by helping people with diabetes live healthy lives while we work to find a cure. It has a heritage of excellence and leadership, and its co-founder, Dr. Charles Best, along with Dr. Frederick Banting, is credited with the co-discovery of insulin. The CDA is supported in its efforts by a community-based network of volunteers, employees, health care professionals, researchers, and partners. By providing education and services, advocating on behalf of people with diabetes, supporting research, and translating research into practical applications, the CDA is delivering on its mission.

1.2 Conflict of Interest Declarations

The Canadian Diabetes Association (the CDA) solicits and receives unrestricted educational grants from multiple manufacturers/vendors of pharmaceuticals, supplies and devices for diabetes and its complications. These funds help the CDA to support community programs and services for people with diabetes, fund research and advocacy, across Canada. Sponsors were not involved in developing this submission. The CDA did not have any conflicts of interest in the preparation of this submission.

Section 2 — Condition and Current Therapy Information

2.1 Information Gathering

The Canadian Diabetes Association (the CDA) solicits patient input through surveys distributed through social media and email blasts. Content of this submission is derived a survey, conducted during March 2016, to which 1198 Canadians responded. Of these respondents, 988 were living with type 2 diabetes and 61 respondents were caregivers. Not all respondents answered all questions

2.2 Impact of Condition on Patients

Type 2 diabetes is a chronic (progressive) condition that occurs when the pancreas does not produce enough insulin or when the body does not effectively use the insulin that is produced. Insulin is a hormone that controls the amount of glucose in the blood. Common symptoms of diabetes include fatigue, thirst and weight change. High blood glucose levels can cause long-term complications such as blindness, heart disease, kidney problems, nerve damage and erectile dysfunction. The goal of diabetes management is to keep glucose levels within the target range to minimize symptoms and avoid or delay the complications.

Diabetes requires considerable self-management, including healthy eating, regular physical activity, healthy body weight, taking diabetes medications (oral and/or injection) as prescribed, monitoring blood glucose and stress management. Poor glucose control can result in acute crises, and serious long-term complications.

Surveyed patients were asked which aspects of diabetes management were the most important. The majority of patients indicated that constant monitoring of food intake, activity and blood sugar is unrelenting and overwhelming. Fluctuations in blood sugar were the most important aspect of diabetes to control during the day and overnight. The fluctuations impact the ability to work, interactions with friends and family, causes stress and worry as well as ability to participate in normal activities of daily living. Uncontrolled diabetes and the stigma associated with the disease can result in reduced quality of life. Maintaining control of diabetes has potential to reduce anxiety and avoid or delay complications as well as improve overall quality of life.

There was a frequent emphasis on the psychological and emotional impact of diabetes on the lives of respondents (effect on stress, anxiety, adjusting to changes in diet and lifestyle, medication and treatment management as well as relationships with family). Respondents also described fatigue, and lack of energy.

Management of diabetes includes lifestyle changes (diet, exercise and stress management). Inevitably, most patients are prescribed one or more medications to achieve glucose control. This usually starts with metformin (oral agent) and, if target glucose levels are not met, other medications are added. Over time most patients will be treated with multiple diabetes medications in order to achieve glycemic control.

Selected quotes from respondents when asked about challenges related to diabetes:

“Always evaluating diabetes management and it's affect on everything from activity to lifestyle,eating out, etc. It is exhausting and relentless and has managed to introduce anxiety concerns over not developing complications. My family are very supportive but as always concerned over my diabetes management.”

“It affects all aspects of life from work to travel to everyday meal planning. Consequences such as the feelings of numbness in feet and blurry vision, fatty liver...it is depressing to have to monitor every bit of food. Costs for necessary equip/medication is expensive....i often dont test because the money is going elsewhere.”

2.3 Patients' Experiences With Current Therapy

A large proportion of people with type 2 diabetes fail to achieve optimal glycemic control, which places patients at risk for both acute and chronic diabetes complications. Initial therapy is most often with metformin, but over time, most patients will require the addition of a second or third agent to reach glycemic targets. Many of the currently available second-line therapies cause significant weight gain while their ability to achieve optimal glycemic control may be limited by hypoglycemia.

A total of 616 respondents with type 2 diabetes and their caregivers indicated experience taking diabetes medications. Approximately 20% (103 of 515 people) stated they were very unsatisfied or unsatisfied with their current therapies whereas 80% indicated satisfaction. Respondents indicated current therapies resulted in better or much better blood glucose and A1C levels. However, a significant number of respondents have not found it easier to avoid low blood sugar (“the same,” “worse” or “much worse” for 38%), weight gain (“the same,” “worse” or “much worse” for over 40%), GI effects (“the same,” “worse” or “much worse” for approximately 60%).

Overall, respondents were more satisfied than dissatisfied with their medications in terms of the ability to manage their blood sugar levels. However, there were issues with side effects.

Surveyed patients were also asked to rate the importance of benefits/side effects when choosing diabetes medications, using a five-point scale from “not at all important” to “very important.”

The vast majority of respondents indicated the following benefits of therapy were “quite” or “very important”:

- blood sugars kept at satisfactory levels in the morning/after fasting (93%),
- blood sugars kept at satisfactory levels during the day/after meals (94%),
- avoiding weight gain (87%),
- avoiding low blood sugar during the day/overnight (84%).

The following aspects are also considered important:

- avoiding GI effects (84%),
- reducing high blood pressure (82%),
- avoiding fluid retention (82%),
- avoiding urinary tract infection (81%).

Section 3 — Information about the Drug Being Reviewed

3.1 Information Gathering

The Canadian Diabetes Association (the CDA) solicited patient input on the drug being reviewed through a survey distributed through social media and email blasts. Conducted in March 2016, the survey gathered information from Canadians with type 2 diabetes and their caregivers about experience with canagliflozin+metformin and the most important aspects of diabetes they would like new medications to address. As the combination medication canagliflozin+metformin is not yet available on the market, it is likely that the very few people with type 2 diabetes have had experience with this medication. Since many surveyed indicated current use of both canagliflozin+metformin, we believe it is relevant to present these patients’ experience while stressing the potential for the new combination medication to reduce the burden of having to take multiple medications.

3.2 What Are the Expectations for the New Drug or What Experiences Have Patients Had With the New Drug?

The availability of canagliflozin to offer an alternative treatment option for stabilizing blood glucose is important to patients. Canagliflozin belongs to a new class of drugs to lower blood glucose through inhibition of subtype 2 sodium-glucose transport protein (SGLT2), which is responsible for at least 90% of the glucose reabsorption in the kidney. The SGLT2 inhibition also causes a reduction in blood pressure and weight loss.

A total of 574 respondents indicated they (or people with diabetes for whom they care) are taking or have taken canagliflozin (alone or with metformin). Patients and caregivers who have experience with canagliflozin highlighted its effectiveness in **lowering blood sugar** compared to other medications. The improvement in blood sugar levels (“fasting and throughout the day”) and the accompanying weight loss was broadly described as “life is better” and “I feel my diabetes is under control”

Many respondents noted less dependency on other drugs such as insulin as a result of canagliflozin – this is considered to be a desirable outcome: treatment without insulin.

In addition, respondents generally did not describe serious side effects; although some did experience side effects such as frequent urination, dehydration, increased appetite. These were described as “manageable.

Below are other quotes from patients/caregivers who have found the experience with canagliflozin (with or without metformin) very positive, including its effects on their **energy level** and **mental health**:

“I am feeling better, more in control mentally as well” “I feel more energetic and better in control of myself.”

“Envokana (sic) has helped me to lose weight and meet blood sugar targets. I am very happy with it”

Patients also described the challenge of needing to take too many medications.

“Taking too many pills?” Would be great if only 1 pill for diabetes would solve the problem. Having to take so many medications at one time!”

How important is the access to canagliflozin+metformin?

People with diabetes usually require escalating doses, and add-on therapies. Most people taking canagliflozin+metformin indicated that they were satisfied with treatment and found it helped control blood sugar, weight and also improved mental health. Survey respondents emphasized the importance of giving patients options particularly if other medications don’t work.

Several surveyed respondents described that taking multiple medications was challenging and expressed the desire to reduce the number of pills. The availability of canagliflozin+metformin, as a fixed dose combination for people with type 2 diabetes stabilized on metformin and canagliflozin would serve the purpose of offering effective therapy while reducing pill burden and promoting adherence to prescribed therapy. This would offer a significant advantage for physicians and patients working together to achieve optimal treatment with the lowest effective dose.

In summary, diabetes requires intensive self-management and can be challenging and overwhelming. To achieve optimal blood glucose levels, individualization of therapy is essential, including selecting the drug or combination of drugs, route of administration (oral, injection, pen or pump), how frequently the patient monitors blood glucose and adjusts dosage, the benefits and risks that the patient experiences and/or tolerates, and the lifestyle changes the patient is willing or able to make.

There are clear expectations that new drugs should offer better blood glucose control to prevent hyperglycemic and hypoglycemic episodes, as well as longer term control, with minimal side effects and long term damage to organs, at affordable costs, and reduced dependency on other drugs such as

insulin. Based the experience of respondents, many of these expectations were met by canagliflozin+metformin in providing better control of blood glucose levels and of diabetes in general.

Some people did not have a positive experience, which reinforces the understanding that different people living with diabetes require different medication options to help effectively manage their disease. Their clinical profile, preference and tolerance of therapy can direct physicians to the most appropriate drug therapy

Appendix: Organizations and foundations that made donations to the Canadian Diabetes Association in 2014 (up to December 31, 2014). Source: CDA 2014 Annual Report, available at <http://www.diabetes.ca/getmedia/d4beee80-01c5-46a1-b2f6-37cbb49e9c61/2014-cda-annualreport.pdf.aspx>

Kidney Foundation of Canada

Section 1 – General Information

Name of the drug CADTH is reviewing and indication(s) of interest	Canagliflozin and metformin hydrochloride
Name of the patient group	BC & Yukon Branch, Kidney Foundation of Canada
Name of the primary contact for this submission:	[REDACTED]
Position or title with patient group	[REDACTED]
Email	[REDACTED]
Telephone number(s)	[REDACTED]
Name of author (if different)	
Patient group's contact information:	
Email	[REDACTED]
Telephone	604-736-9775
Address	200 – 4940 Canada Way, Burnaby, BC V5G 4K6
Website	www.kidney.bc.ca
Permission is granted to post this submission	Yes

1.1 Submitting Organization

The Kidney Foundation of Canada's vision is kidney health, and improved lives for all people affected by kidney disease. For more than 50 years, we have helped Canadians prevent kidney disease, and if they can't, we help them until there is a cure. Our mission is to:

- Fund and stimulate innovative research
- Provide education and support
- Promote access to high quality healthcare
- Increase public awareness and commitment to advancing kidney health and organ donation.

To accomplish our mission, the BC & Yukon Branch relies on the dedication, skills and passion of more than 7,000 volunteers across British Columbia and the Yukon, many of whom are kidney patients, caregivers and family members. We are also supported by many of the dedicated healthcare professionals who work with kidney patients in health care clinics, hospitals and community renal clinics.

In BC, volunteers from our Chapters located in Victoria, Nanaimo, Eagle Ridge, Surrey (South Asian Community) Fraser Valley, MSA Upper Fraser Valley, Chilliwack, the Interior (Kamloops), Penticton, Prince George, Quesnel, Terrace, Richmond (Chinese community) and Vancouver present the face of the Kidney Foundation in their communities. Our Chapter in Whitehorse represents our Branch across the Yukon. Our volunteers provide on-the-ground impetus for public education and patient support, fundraising and awareness-building activities on behalf of the more than 300,000 kidney patients we serve.

The BC & Yukon Branch also seeks to encourage the prevention and early detection of chronic kidney disease – particularly amongst high risk communities. Since 2005, there has been a 148% increase in the total number of patients diagnosed with chronic kidney disease (CKD) in British Columbia¹.

- a. 70% of kidney patients who require costly dialysis² have:
 - i. Diabetes
 - ii. Autosomal dominant polycystic kidney disease (ADPKD)
 - iii. Glomerulonephritis (GN)

Therefore our Branch encourages diabetes patients, their families and caregivers to manage their chronic disease effectively in order to lower A1c levels as well as lower their blood pressure in order to protect and promote the health of their kidneys in order to avoid or delay the onset of kidney failure.

1.2 Conflict of Interest Declarations

a) We have the following declaration(s) of conflict of interest in respect of corporate members and joint working, sponsorship, or funding arrangements:

The BC & Yukon Branch of the Kidney Foundation of Canada receives unrestricted educational grants from the pharmaceutical industry each year. In 2015, approximately 4% of our gross revenues (\$4m in 2015) resulted from unrestricted educational grants or event sponsorship from the pharmaceutical industry. Approximately 30% of our gross revenues come from our own social enterprise called Kidney Car; another 35% of our funding were donations from individuals, other corporate donors (banks, insurance companies grocery stores, etc.), charitable Foundations (Margaret Rottweiller Foundation, Vancouver Foundation, etc), Social organizations (Lions Club, Legion, Kinsmen, Rotary, etc.), Employee Groups (United Way, hospital employees, government employees, unions, firefighters, etc.) as well as from bequests and in memorium donations made by individuals and groups; and the remainder of our funding comes from events organized by our Branch (Kidney Walks, March Drive door to door campaigns; annual Kidney Gala, community fundraisers, etc.) or from the BC government for the annual community gaming grant or for Living Organ Donor Expense Reimbursement.

Pharmaceutical companies who have supported our Branch with unrestricted educational grants or through sponsoring or purchasing a table at our fundraising events include: Alexion, Amgen, Aspreva, Astellas, Baxter, Boehringer Ingelheim, Eli Lilly, Fresenius, GSK, Janssen, Johnson & Johnson, Otsuka, Pfizer, Sanofi, Takeda, Vifor Pharma

b) We have the following declaration(s) of conflict of interest in respect of those playing a significant role in compiling this submission:

Not applicable.

¹ BC Provincial Renal Agency, Number of Chronic Kidney Patients in BC by Type, July 1, 2005 to July 1, 2015.

² Levin, A., Can-Solve CKD, October 2015, p. 7.

Section 2 — Condition and Current Therapy Information

2.1 Information Gathering

In January 2016, we surveyed our supporter database to identify patients who developed kidney disease or kidney failure as a result of their diabetes or high blood pressure. We identified that 35% of our supporters in our database were living with or had had diabetes related kidney disease. We then invited 20 patients with diabetes and kidney disease to participate in a conversation held on February 6th, 2016 during our annual BC & Yukon Branch Volunteers Training Workshop in Richmond, BC. During this workshop, volunteers (patients, families & caregivers) were asked to share their personal experiences in breakout groups which we recorded as part of our efforts to identify and develop information and tools on preventative steps that might inform people who are at high risk of kidney failure.

Chronic kidney disease represents a major public health burden, affecting nearly 300,000 British Columbians and Yukoners, particularly vulnerable populations, such as Indigenous Peoples, children and the elderly. The risk of chronic kidney disease, which rises with age, is higher than that of diabetes or cardiovascular disease, and survival and quality of life among advanced chronic kidney disease is worse than for people with breast or lung cancer. Chronic kidney disease symptoms, including pain, fatigue, and depression, lead to significant financial and social consequences for patients, their families, and the economy at large.

Chronic kidney disease is common in those with diabetes, high blood pressure, and heart disease. For patients who develop kidney disease through diabetes, living well begins with effective management of their diabetes. Their experience differs from patients who develop kidney from genetic like PKD or acute kidney failure. The adoption of effective therapies to manage their diabetes to prevent or slow their progression towards kidney failure and dialysis is critical, and the pathway and the treatments or therapies are not always the same as for PKD or AKI patients.

2.2 Impact of Condition on Patients

The majority of kidney patients with diabetes who shared their personal story about developing kidney failure as a result of their diabetes said that they wished they knew how important it was to manage their diabetes – particularly their blood glucose and blood pressure levels - effectively to avoid or delay the onset of kidney failure. As part of better management, the strategies they suggested we encourage as part of prevention of kidney failure amongst diabetes patients included:

- Lifestyle and behavioural changes
- Understanding the importance of drugs and their appropriate use to lower blood glucose and blood pressure
- Following their doctors' recommendations more frequently
- More information about the complications that can result from not adhering to their treatments as recommended by their doctor

Like many chronic disease patients, managing multiple activities daily while living with diabetes, is time consuming, frustrating and challenging in a world where type 2 diabetes isn't an obvious disease for most of the public, and where there is a sense of "shame" for having brought on the disease through lifestyle choices. Whether correct or not, some patients with type 2 diabetes feel others judge them negatively, and therefore depression and feelings of unworthiness increase feelings of "not being worth it".

Patients also told us that the number of medications they need to take daily is also challenging sometimes. Taking multiple medications not only reminds them that they have a life threatening disease - diabetes, but there are busy days when keeping track of medications is challenging, and a medication can be missed. Taking multiple medications as recommended is easier if there are fewer drugs overall according to some patients. Please note that kidney patients are also on a “cocktail” of multiple medications, and so the challenges of taking multiple medications increases for diabetes patients who progress to kidney failure.

Patients also recommended informing diabetes patients about the need to take medications that help avoid or delay kidney failure was critical. The majority of patients said that they did not personally connect the dots between managing their diabetes effectively and kidney failure. If they had known that, they would have followed their doctors’ advice more rigorously in particular to keep their blood glucose closer to target, to maintain a healthier weight and to lower their blood pressure. Kidney failure added a new dimension to the challenges faced with their diabetes management and it was recommended that our Foundation should do as much as possible to support diabetes patients to manage their disease more effectively to prevent kidney failure.

2.3 Patients’ Experiences With Current Therapy

Patients were not asked specifics about their current therapy during our February 2016 workshop. Rather they were asked to identify how we might encourage better diabetes management to avoid or delay the onset of kidney failure and subsequently dialysis and/or transplant.

An almost unanimous recommendation was for making it easier or more convenient for diabetes patients to manage more effectively through information and access to medications that their physicians think would improve blood glucose and blood pressure levels.

Making things convenient and less complicated for patients feeling already overwhelmed with their self-management responsibilities is a critical step.

2.4 Impact on Caregivers

We did not ask this question.

Section 3 — Information about the Drug Being Reviewed

3.1 Information Gathering

In January 2016, we surveyed our supporter database to identify patients who developed kidney disease or kidney failure as a result of their diabetes or high blood pressure. We identified that 35% of our supporters in our database had diabetes related kidney disease. We then invited 20 people to participate in a follow up conversation held on February 6th, 2016 during our annual BC & Yukon Branch Volunteers Training Workshop in Richmond, BC. During this workshop, volunteers (patients, families & caregivers) were asked to share their personal experiences in breakout groups which we recorded as part of our efforts to develop information and tools on preventative steps that might inform people at high risk of kidney failure.

We had no patients who currently have used the drug being reviewed. We understand that canagliflozin and metformin hydrochloride is contraindicated for patients with end stage renal disease

or who are on dialysis, and therefore diabetes patients with kidney failure would not have access to this specific medication and therefore cannot comment on experience using this medication.

3.2 What Are the Expectations for the New Drug or What Experiences Have Patients Had With the New Drug?

a) *Based on no experience using the drug:*

- Lives of diabetes patients who do not currently have renal failure will be improved by the convenience of an alternative single dose medication like canagliflozin and metformin hydrochloride that replaces two medications. Patients speak of the benefits of fewer medications in terms of adhering to their prescribed medications, and the improvements to medication compliance is known to result in improvements to blood glucose and blood pressure levels for many. This in turn is known to reduce the likelihood of serious complications like kidney failure for the patient.
- The prevention or delay of kidney failure amongst type 2 diabetes patients has significant benefits for both the patients as well as for the health care system and government finances.
- Diabetes is the leading cause of kidney failure which requires dialysis and ultimately a kidney transplant. The failure of kidneys requires an additional cocktail of medications, hospital visits, and dialysis that costs the health care system an estimated \$70,000 to \$100,000 per year depending on where you live. In BC & the Yukon patients wait on dialysis approximately 5 years before they receive a transplant.
- As important for the patient is the fact that 80% of kidney patients on dialysis are unable to work as a result of their dialysis. Dialysis 3 times a week, for approximately 6 hours a day, is exhausting and it generally takes one whole day to recover – just in time to return to the dialysis clinic. Patients also require transportation both to and from their dialysis clinic which can amount to a two hour return trip for people living outside of an urban community and for people with limited incomes, can be a significant expense.
- Therefore a medication that is more convenient to use and encourages adherence to physician prescribed therapies should enable a type 2 diabetes patient to remain employed and contribute more to families and communities than someone who progresses to kidney failure requiring dialysis.
- A kidney transplant is not a cure for kidney disease, and requires anti-rejection medications that may cost upwards of \$6,000 a year. However a transplant will allow a diabetes patient to return to employment.

b) *Based on patients' experiences with the new drug as part of a clinical trial or through a manufacturer's compassionate supply:*

Not applicable.