

# Canadian Diabetes Association Patient Input Submission to CADTH New Drugs for Type 2 Diabetes: A Therapeutic Review Update

<b>Name of patient group</b>	Canadian Diabetes Association
<b>Patient group's website</b>	<a href="http://www.diabetes.ca">www.diabetes.ca</a>
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## Section 1 — General Information

### 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.

Our membership consists of people with diabetes and their caregivers, and health-care professionals such as physicians, nurses, educators, pharmacists and other health professionals that care for people with diabetes.

### 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. A list of organizations and foundations that made donations to the CDA in 2015 can be found in the appendix.

The submission was prepared solely by CDA staff. CDA did not have any conflicts of interest in the preparation of this submission.

## Section 2 — Treatment Outcomes

### 1. What would patients, their families, and caregivers like therapies for type 2 diabetes to achieve?

Over the last 3 years, the Association has conducted several patient input surveys on diabetes medications undergoing review by the Common Drug Review. Across these surveys, we asked patients how diabetes impacted their life, and their expectations regarding new diabetes medications. Across surveys, approximately three-quarters of patients with type 2 diabetes reported insulin use.

#### Diabetes: Impact on patient lives

Most survey respondents stated that diabetes had negatively impacted all aspects of their lives and limited daily activities, as well as travel, work and social life. For example, one patient described an inability to work due to kidney problems requiring a kidney transplant; another patient had a limited ability to walk due to neuropathy; yet another patient had to give up driving due to diabetic macular edema; others reported feeling fatigue and low energy and not being able to enjoy life anymore. Direct quotes from patients underscore the impact of this fatigue due to diabetes on overall quality of life: *“I tire too soon, need breaks to complete simple chores. I am unable to work night shifts. I am unable to eat and rest like normal healthy people.” “Having diabetes makes me useless. I have no energy or strength to enjoy life anymore. I can't do partial jobs around house. I can't enjoy sports anymore. Diabetes has instill[sic] a fear in me.”*

Some people felt they were “held captive by diabetes,” that diabetes was “overwhelmingly debilitating,” and were frustrated that they cannot lead a normal life. Many indicated that diabetes management was a “constant struggle” involving meal planning, testing blood glucose, daily medication and treatment management, stress and anxiety about hypoglycemia and complications, strain on relationships with family, and financial burden. One respondent described having diabetes as *“having a huge truck going down a hill and you are trying to stand in front of it and slow it down.”* Compounding the challenges is mental stress over how diabetes is perceived in society: *“stigma of being lazy;” “diabetes is the emotional roll coaster you experience, feeling guilt that you brought diabetes onto yourself, since most people and doctors treat you that way.”* For individuals who have to manage their diabetes and care for other members of the family at the same time, it is particularly difficult. Across our surveys, a high proportion of respondents with diabetes appeared to have advanced disease; they reported complications and/or comorbidities, including neuropathy, foot complications, cardiovascular disease, eye problems or loss of vision, kidney complications, pancreatitis, skin ulcers, erectile dysfunction, amputation and depression. These complications can significantly reduce quality of life through physical and mental illness, and add burden to their families/caregivers.

The patient statements below illustrate the overwhelming burden of diabetes management and limitations on daily lives and finance, due to the need to manage medications including insulin and/or end-stage organ damage:

*“It is impossible to manage because of the effects of insulin resistance. It is difficult to lead a normal life when you always need to be taking meds or checking your BS levels and reading labels on all your food while your BS levels change with or without food intake. The impact of diabetes on all your other organs is another huge problem and when you treat one you harm another. Most difficult disease to manage.”*

*“Because of diabetes my kidneys have failed and also my eyesight has been affected very badly. This has affected my family also due to my being not able to work while I was waiting for a kidney transplant...”*

*Because of being on dialysis[sic] I had to spend most of my life's savings. Being sick can be very very expensive. Medications, insulin, travel (doctors appointments) etc can be so expensive."*

*"My husband has been living with Diabetes[sic] for 15 years ... in the last few years with having to be more rigorous with sugar checking and balancing two types of insulin, diabetes has really taken over our lives. It has negatively affected my husband's health to the point that at 64, he has been forced to give up all work (owner/operator of lumber/shingle/truss mill and wood operations) and be virtually inactive. We still have a year before he can collect old age pension, so income is pretty tight right now. His med list has grown substantially and medicare does not cover the insulin. Neuropathy has started to make an appearance, so nausea is pretty much a daily concern. (nerves in the stomach that perform digestion have started to die). His sugars are pretty stable right now, but diabetes has sure ' changed the water on the beans' for what we envisioned our retirement might be."*

Managing diabetes with medications also contributes to the negative impact of the disease. People with type 2 diabetes often struggle with weight control and many medications contribute to weight gain. Weight gain, and requiring add-on therapies creates a sense of failure and feelings of anxiety. Many respondents found various side effects of medications hard to tolerate, and became depressed when the drug therapies did not work:

*"Dealing with high fasting numbers; taking multiple medications throughout the day at different times and in different amounts; side effects have included coughing to the point of vomiting in the morning, dizziness when I stand after long periods of sitting, emotional frustration on managing my medications in the hopes that things will even out. Diabetes has changed how my life works..."*

*"I suffer from depression and have done for many years. Before I was told that I had to start insulin injections, everything I tried to control my BS did not work. That was very stressful and I was distracted trying to control them, exacerbating the depression. I felt like a failure."*

*"Diabetes controls practically every aspect of my life, from intake of several medications that are causing a deterioration in the effectiveness of my kidneys and liver, body functions, difficult choices in food intake to keep sugar levels low, physical activity, relationships, social activities, long distance travel, cost of prescription drugs."*

There is tremendous amount of fear and stress over potential complications due to type 2 diabetes among respondents, in particular those whose family members suffered diabetes complications:

*"I watched my oldest sister take medications then insulin, have heart issues and after a few years of not looking after herself went on dialysis 3 days a week...in January 2012 she went in to hospital for an infection in her heel. Which she ended up having from her knee down amputated, she never recovered from that. She passed January 15, 2012...I was diagnosed in May 2013...I am so so scared of seeing my life replay like my sisters."*

*"It also scares me because two months after being diagnosed with diabetes I had a heart attack. My Dad lost his eyesight and had a leg amputated due to diabetes. This scares me."*

Among people who are currently on metformin monotherapy or in combination with other drugs (excluding insulin), the impact of diabetes was reflected mostly in the need for lifestyles changes, including restriction in diet, avoiding weight gain, for blood glucose tests and increased exercise. These adjustments can be stressful and can impact social activities and vacations: *"It made me very afraid of*

*eating the wrong foods, the portions, how it would affect my blood sugar, and losing/maintaining a good weight.” “cuts down on being spontaneous;” “having to eat healthy meals at set times.”*

### Expectations for new therapy

Patients have a great deal of fear of the complications of diabetes, and wish for treatment to prevent/delay the progression of disease with minimal side effects, primarily weight gain, hypoglycemia, UTI and GI effects. These side effects were repeatedly raised as problematic. For patients with type 2 diabetes not using insulin, weight gain is a big concern. Many patients feel that therapy should facilitate weight loss as a mechanism to control blood sugar. Being advised to lose weight and then taking a medication that causes weight gain was the cause of distress and anxiety. The fear of hypoglycemic events was also described across surveys, particularly for patient taking insulin. Patients consistently indicated that they would like diabetes medications to be more effective in helping them gain better control of their blood glucose levels especially through the night. Patients often described a sense of failure and inevitability in the progression of their disease with the presence of these effects (unstable blood glucose, weight gain). Improvement of these outcomes is important for patients. They also hoped for a reduction in the symptoms of diabetes (e.g. fatigue).

Many hoped the newer medications would also allow them to reduce the pill burden/stop insulin injections. Insulin administration was generally undesirable. The hopes for new treatment varied by individual. It is critical to understand the goals of treatment and priorities of the individual with type 2 diabetes regarding effects of their medications in the context of how diabetes has impacted their lives.

## 2. Consider the treatment outcomes you have describe above. Which ones are most important?

### Why?

Over 90% of respondents across surveys consistently stressed the following three to be the most important outcomes of diabetes medications:

- Avoiding weight gain
- Blood glucose levels kept at satisfactory levels (fasting, after fasting, during the day, after meals)
- Reduced hypoglycemia (during the day/overnight)

For respondents with type 2 diabetes who are not using insulin, the top two most important treatment outcomes are better blood glucose control and avoiding weight gain.

Overweight and obesity are associated with adverse health outcomes for all age groups, and higher BMI in people with diabetes increases mortality. Given that over 80% of people with type 2 diabetes are overweight or obese, **weight gain** associated with intensive insulin therapy and some antihyperglycemic medications is particularly challenging. A high proportion of respondents across surveys stressed the importance that new diabetes medications do not result in weight gain or help with weight reduction. Some were experienced frustration with trying to lose weight while on medication: *“The most distressing side effect of all of the diabetes drugs is they make you gain weight or prevent weight loss. It is annoying to be told to lose weight then handed a drug that prevents weight loss.”* *“problems are mostly trying to lose weight.....Took 5 Metformin pills (1 a day for 5 days ) and put on 2 pounds a day. Took over a month to loose that 10 pounds.”* Some viewed weight loss as the most important outcome from diabetes medications: *“To control morning highs, all day sugar levels, & most important, weight loss.”* The benefit of weight loss was reported by people with diabetes who often deal with other comorbidities: *“ I am unable to do the walking required as I am on a list for a knee replacement within 6-8 months so the weight loss through Invokana is very welcome.”*

Optimal **glycemic control** is fundamental to diabetes management. Patients are acutely aware that poorly controlled glycemic levels can increase the risk of diabetes complications, and reduction in A1C is associated with reduced risk of complications. The fear of complications like amputations and vision loss are ever-present in the minds of people living with diabetes. The majority of respondents to our surveys emphasized the importance of getting the blood glucose levels in the target range and expressed their fear of complications down the road. Many who have developed complications described their serious impacts on overall quality of life as well as diabetes management:

From a patient with diabetic macular edema: *“Slowly losing or having distorted vision is very difficult as it makes it difficult to read, drive, work or to live life in general. It is hard to measure up insulin and fill cartirdges[sic]. Night driving is especially difficult if not impossible. It greatly impacts on the ability to earn money and provide for myself and my family.”*

From a patient who had amputation: *“It has made it impossible to enjoy life. I had to have third of my foot amputated because of a diabetic sore. Now I stumble around the house with a big heavy brace and a walker. I can not go anywhere because my leg tires too much.”*

From a senior that had foot ulcers: *“I am 72 year old male who was diagnosed with type 2 diabetes 12 years ago... my feet have been affected with a series of ulcers on both feet, which have taken quite a long time to heal. On my left foot under my little callus which has me wearing an Air-cast for over a year this time, and walking with the help of a walker makes getting around rather difficult in winter, especially with snow or ice around.”*

**The risk of hypoglycemia** varies across diabetes drug classes. Hypoglycemia can cause confusion, coma or seizure. Frequency and severity of hypoglycemia negatively impact on quality of life [\(1\)](#) and promote fear of future hypoglycemia. Whether occurring at home, at work or under other circumstances such as driving, operating machinery, hypoglycemia can be very dangerous. There are also long-term complications of severe hypoglycemia. In type 2 diabetes patients at high risk for cardiovascular disease, hypoglycemia is associated with increased mortality. There are also social and emotional impacts. This fear of hypoglycemia is associated with reduced self-care and poor glucose control.

Hypoglycemia is a major concern for people with type 2 diabetes on insulin therapy, as well as a concern for people who are using only oral medications. As such, it is important to prevent, recognize and treat hypoglycemic episodes as well as tailoring treatment to the individual’s clinical needs. The following quotes from patients with type 2 diabetes on insulin therapy in combination with oral agents illustrate their fear of hypoglycemia and efforts made to prevent it from occurring:

*“It requires a lot of time to manage this disease by taking blood sugars several times a day and taking insulin with each meal and bedtime plus managing meals and snacks. My sister lives with me and has helped me out when I have low blood sugars especially at night. It would be scary to live alone!”*

*“Constant monitoring of my blood sugar levels. As I am A Fire Fighter, I have to be aware of my blood sugar levels as when you have aimed at having a proper level overnight, if called to a fire. and activity level rises, the chance of bottoming out or having a blood sugar too low happens regularly. Being prepared and aware is key to insuring I can perform my job properly. “*

**3. If treatment were able to achieve these outcomes, what would it mean for patients', their families', and caregivers' daily activities and quality of life?**

If the therapies were able to achieve optimal glycemic control, with minimal hypoglycemic events and promote weight loss, the long-term complications may be delayed or prevented, leading to better quality of life. Some newer diabetes drugs have helped patients with type 2 diabetes reduce their weight, decrease the pill burden or even insulin needed. To many people with diabetes, better glycemic control and reduced dependency on medications means substantial improvement to quality of life and therefore are both considered desired outcomes:

*"Not having to give myself two needles a day has improved my life drastically."*

When medications were effective in controlling glycemic levels, not causing weight gain with few side effects, respondents reported increased confidence, optimism and positive attitude related to diabetes management, as well as an overall sense of gaining control of diabetes. Below are selected quotes from patients that described the impact of improved control of their diabetes on their life in general:

*"I have lost a surprising amount of weight in a short time. This helps me remain optimistic about my health improving significantly in the long run."*

*"Absolute game changer!!! My numbers were up in the high teens...now numbers are normal, I'm not constantly thirsty[sic] or urinating, my weight has dropped and I feel great! This weight loss has helped put me in a very positive frame of mind and has helped me get off my Anti Depression drugs also."*

*"For me it is the best thing ever with my combination of meds. it is working for me first time my body has been happy i can not tell you how good my body feels."*

*"Huge benefit in reducing fasting glucose and HbA1c. Significant weight reduction ... evident in first 3 months. Very +ve[sic][positive] impact on my self-confidence and feeling of 'being in control' with my diabetes."*

**4. Describe any difficulties patients currently have in achieving desired outcomes. What is the impact of this on patients, their families, and caregivers?** Difficulties could include access to care, coordinating care, or challenges specific to medication.

**Cost of medications** was cited by some respondents as a barrier and cause of anxiety. Respondents reported experiencing, or experienced in the past, difficulty in accessing the treatment due to cost. This may be due to lack of insurance (such as employer insurance, following retirement or job loss, for example) or that the medication is not covered by public or private insurance. Those who have experienced difficulty in the past attributed the eventual ease of financial burden to their work benefits to cover the cost of the treatment. Some people were on clinical trials and worried about not being able to afford the medications after the trials ended. Quotes below demonstrate the financial strain as a result of the need for diabetes medications, insulin and supplies:

*"I certainly [had challenges] when I was employed at a place that did not have benefits. Fortunately, I have a plan now. Without a plan, my A1C would be awful – I would be skimping on insulin and strips."*

*"I am a single mother of twins, insulin dependant[sic] diabetic with no health insurance.....I often have to give up medication for food....I reuse my syringes because the cost of my supplies is tremendous and no health plan will take me on."*

*"I do not have insurance coverage and the cost of two insulins, the test strips, needles and canagliflozin have caused me to have to decide-rent, food, or meds. It is not pleasant to have to be in this position every month."*

*"I have had diabetes for 20 years and just turned 65 years in October 2015... The cost of keeping the diet that I should have is wrecking[sic] havoc in my life. I am now on Old Age Pension and am a little better off with finances but not much. How am I supposed to eat properly and still budget?"*

*"I am encouraged from my early results of taking Invokana and worry about being able to afford it when I no longer receive medical benefits from my employer. I am 61 and hope to retire in the next 4-6 years."*

Also, while some people tolerate **side effects** well, others don't. As explained by one woman with diabetes, side effects [such as yeast infections] may *"deter most women. I now have to purchase additional medications to treat the side affects. However, if you are not prone to yeast infections normally, then this drug may not have the same affect ... and patients may be able to tolerate it well..really depends on the person."* Others had to stop taking certain medications because of persisting side effects: *"metformin made me throw up continuously. I lost 38 lbs. in 1 1/2 weeks. I was past being tired, my vision was blurred & I had intense abdominal cramps. I had to stop taking this medication."*

#### **5. Please briefly identify how the information used to complete Section 2 was obtained.**

Was it obtained, for example, through a survey, focus groups, or one-to-one conversations? Since 2013, our Association have conducted various surveys among our members to gain insight into the impact of type 2 diabetes on quality of life and individuals' experience with diabetes medications including unmet needs and barriers to access medications. The surveys were distributed to our members through e-blasts and social media. Between 360 and 1,000 people with type 2 diabetes and caregivers answered each survey. Information included in Section 2 was based on results from these surveys.

### **Section 3 — Patients' Experiences With Drug Therapies**

CADTH is interested in hearing about patients' and their families' lived experiences with:

- DPP-4 inhibitors (Nesina, Trajenta, Onglyza, Januvia, Kazano, Jentaducto, Komboglyze, Janumet)
- GLP-1 analogues (Trulicity, Byetta, Victoza)
- SGLT-2 inhibitors (Invokana, Forxiga, Jardiance, Xigduo, Synjardy)
- Sulfonylureas (chlorpropamide, gliclazide, glimepiride, glyburide, tolbutamide)
- Insulin and insulin analogues

#### **1. How well does the therapy address outcomes considered important by those with type 2 diabetes?**

Many people with type 2 diabetes have difficulty achieving optimal glycemic control and are therefore at risk for both acute and chronic diabetes complications. The initial therapy they receive is most often metformin, but over time, most people will require the addition of a second or third agent to reach glycemic targets. Weight control is a major physical health and mental health challenge for these patients. Many of the currently available second-line therapies cause significant weight gain. Since 2013, the Canadian Diabetes Association has conducted surveys to our members regarding their experience with newer medications. Below is a summary of how the therapies addressed the needs of people with type 2 diabetes, by drug class:

**DPP-4 inhibitors:** In a survey conducted about drugs in this class, 57 people indicated they were using either DPP-4 inhibitors or combination medications of DPP-4 inhibitors with metformin at the time of survey. The majority reported they were satisfied with their blood sugar and A1C levels kept at target. Reduced hypoglycemia episodes was also noted. People with DPP-4 inhibitor experience were asked to compare this class of drugs with other diabetes drugs they had taken. Patients felt that DPP-4 inhibitors offered better blood glucose control, and about the same in terms of weight gain and GI effects. A respondent reported reduced need for insulin as a result. Below are selected quotes from patients on the effects of this drug class, in combination with other drugs:

*“Metformin 500 mg 2 po bid Januvia 100 Mg 1 OD Metformin alone was taken initially for a couple of years. Januvia was added later and the combination controls my A1C levels well.”*

*“I’m certainly a fan of Januvia: been on it since I was diagnosed (1.5 years). It seems very effective, and so far I haven’t experienced any side effects.”*

*“I started taking the Januvia a few months ago and I have decreased my night time shot of Lantus from 100 units to 60 units. I’m hoping that eventually I will be able to come off the needles for good!”*

*“metformin and Trajenta keep my A1C in check”*

*“Pretty satisfied on Januvia (once a day) and metformin (twice a day). Not an especially hard regimen to follow, no side effects so far, and effective in helping to keep my blood sugar in the normal range.”*

**GLP-1 analogues:** A survey for the CDR review on dulaglutide (Trulicity) was conducted and patient experiences about GLP-1 agonists in general was obtained. This class of injectable drugs known as glucagon-like peptide 1 (GLP-1) receptor agonists lower blood glucose by mimicking the functions of natural incretin hormones, which are (hormones that stimulate the release of insulin after eating, inhibit the release of glucagon, and slow glucose absorption into the blood stream.

Among respondents, 71 reported experience with liraglutide (Victoza), 5 had taken exenatide (Byetta) and 4 had taken dulaglutide (Trulicity). Among these respondents, many were also using other medications --- 65% were also on metformin, 51% on insulin, 28% on a SGLT2 inhibitor, 24% on a sulfonylurea, and 10% using a DPP-4 inhibitor. These sub-groups are not mutually exclusive as some patients were taking multiple drugs. Overall, over 60% of respondents indicated satisfaction with the current combination of therapy, especially with better glycemic control (fasting, upon waking, postprandial) and A1C control. About half reported better weight control, and close to half said their hypoglycemia had improved. Between 16-23% reported improvement in other side effects such as GI, UTI/yeast infection, and dehydration. Below are selected quotes from respondents on the effectiveness of this class of drugs:

*“My quality of life and day-to-day feelings of wellness have dramatically improved since being on this Drug [Victoza]...since I started .... I have felt much, much better. I don’t have severe feelings of hunger every four hours and I have feelings of fullness during eating so it is easier to prevent over eating.”*

*“my experience with Victoza has been very good. It has helped to drastically reduce my blood glucose test results and brought my A1C down significantly from 10.0 to 7.9 in just a few months.”*

*“The GLP-1 drug that I have been taking [Victoza] was very life changing: better numbers, better A1C, lost weight, feel better generally except for occasional nausea and acid reflux.”*

*“Using Victoza has greatly improved my quality of life as a type 2 diabetic (after initial nausea and vomiting) as it is unnecessary for me to carry .... pens with me in my daily life and I avoid low blood sugars when giving a too-high a dose of insulin....better control”*

*From a caregiver for person with type 2 diabetes: “My mother suffered horrible diarrhea with metformin and was miserable. Victoza was a lifesaver! She managed to lose over 50 lbs and was off ALL meds. When she lost drug coverage she had to stop (province doesn't cover), has put on the wait[sic] and is back on a host of medications.”*

*“Victoza works better than Januvia did to control all blood sugars, at all times of the day. Lantus helps when needing to be off Victoza or metformin with surgery or stomach flu.”*

**SGLT2 inhibitors:** We conducted surveys on dapagliflozin (Forxiga), empagliflozin (Jardiance) and canagliflozin (Invokana). These medications belong 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 results in a reduction in blood pressure and weight loss.

A total of 110 people indicated experience with dapagliflozin, 12 with empagliflozin, and 36 with canagliflozin. Among them, 25% were also taking a DPP-4 inhibitor, 35% on a combination DPP-4 and metformin, 67% on metformin, 36% on a sulfonylurea, 21% on a GLP-1 agonist and 50% on insulin. These sub-groups are not mutually exclusive as some patients were taking multiple drugs. Patients and caregivers who had used this class of drugs highlighted their effectiveness in lowering blood sugar, blood pressure and decreasing side effects. While many people using canagliflozin reported yeast infections and frequent urination, most found these effects tolerable and were pleased with this drug. Many who had struggled with keeping glucose at target noted improved in fasting blood glucose levels and during the day; many experienced the benefit of weight loss. Those included people who had been on the drug for a short period of time.

As a result of SGLT2 inhibitor use, some were able to reduce dependency on other drugs or insulin, which was seen as a substantial improvement on quality of life. One person was able to get off “one of 3 blood pressure meds” while another “reduced insulin intake by 75%.” The positive experience of this drug has also resulted in increased energy level and improved mental health. In the words of people with type 2 diabetes using a SGLT2 inhibitor in combination with other medications regarding the effects:

*“Forxiga has replaced two of my insulin needles (breakfast and lunch). Not having to give myself two less needles a day has improved my life drastically.”*

*“Invokana has made a significant change in lowering my A1c and morning fasting sugars. No longer require water pill for blood pressure. I have reduced Lantus by 18 units in the evening and prepared to lower another 5.”*

*“I have lost a surprising amount of weight in a short time. This helps me remain optimistic about my health improving significantly in the long run.”*

*“Absolute game changer!!! My numbers were up in the high teens...now numbers are normal, I'm not constantly thirsty[sic] or urinating, my weight has dropped and I feel great! This weight loss has helped put me in a very positive frame of mind and has helped me get off my Anti Depression drugs also.”*

*“for me it is the best thing ever with my combination of meds. it is working for me first time my body has been happy i can not tell you how good my body feels”*

*“Huge benefit in reducing fasting glucose and HbA1c. Significant weight reduction (loss of > 4 Kg) evident in first 3 months. Very +ve impact on my self-confidence and feeling of ‘being in control’ with my diabetes.”*

*“Invokana has been extremely helpful and worked almost immediately. It has caused me to have a more positive attitude that I can get control of this disease which I have been dealing with for nearly 20 years. The change was dramatic and immediate. I think that doctors should have all available therapies at their disposal. It is far more effective to get positive results quickly. I was feeling that nothing was going to work, and I dreaded have to use an injectable medicine or insulin.”*

From a caregiver to a person with type 2 diabetes using metformin, sulfonylurea, and dapagliflozin: *“It has helped with weight loss, and his blood sugars are below 10, he hasn't been below 10 in years the other day, it was 6.3 that's amazing and his blood pressure has come down also, if he improves the Doctor may decrease some of his other diabetic meds.”*

*“I've only been on Forxiga for a month, but seems to be doing the job where the other was not quite working. side effects seem to be nil”*

Below are additional quotes from respondents who compared BG control, side effects and general sense of well-being before and after canagliflozin was added to their therapy. These quotes show that many people encounter challenges to find an appropriate combination of medications that work for them. Different medications/combination of medications work for different people, and it is important to make various options available:

*“Have been taking Invokana for approximately 2 months, starting with 100 mg per day and now taking 300 mg per day. My rapid and long acting doses are slowly decreasing while maintaining good control and A1C levels. With no serious side effects so far. Previous regimen, without Invokana, my levels were coming down but not as rapidly, and causing more weight gain, than loss.”*

*“I take Metformin, Glyburide and Invokana was added on August 1, 2014. I have managed to lose 21 lbs since August 1 as a result of Invokana being added to my regimen. I am unable to do the walking required as I am on a list for a knee replacement within 6-8 months so the weight loss through Invokana is very welcome. Also, my sugar readings have gone from 20-24 down to 9-14 - I am thrilled. ... I am grateful for the addition of Invokana to my medications.”*

*“Invokana has significantly reduced my glucose levels indicated by my daily testing. Also after 3 months my A1C level has dropped significantly. I have also dropped 10-12 lbs in weight. ... I was previously on Metformin which was not adequately controlling my sugars.”*

**Insulin:** For some people with type 2 diabetes, a combination of oral medications and insulin may be required and suitable to control glucose levels. As type 2 diabetes progresses, insulin requirements will

likely increase, requiring additional doses of basal and/or bolus insulin. From a survey we conducted on long-acting basal insulin analogues (insulin glargine and insulin detemir), respondents noted their effectiveness in maintaining blood glucose control. Some indicated weight loss as a result: *“Diet & exercise worked at first, then needed metformin, then needed insulin plus metformin. Insulin (Lantus) improved my A1c results. Have found weight loss to be beneficial with the Lantus and metformin.”* Studies have also shown that long-acting basal insulin analogues reduce the risk of nocturnal hypoglycemia compared to treatment with NPH insulin.

Some indicated they preferred adding insulin to the combination rather than simply taking oral medications, because of better BG control: *“I am currently satisfied with my medication regime at present for it suits my needs and keeps my blood sugar levels in check. I currently take Metformin with Breakfast and Dinner, I take Apidra before each meal calculating my dosage based on my Carbohydrate intake, and I take Lantus before bed. I really like being on Insulin as opposed to just oral medication because I can better keep my sugar levels in check and with insulin it is easier to quickly adjust my sugar levels if they are higher than my target. This regime of medication really forces me to keep on top of my glucose testing and allows for easy adjustment in insulin dosages to manage my diabetes in a proactive way.”*

## 2. What side effects are experienced and how are they managed?

All drug therapies have benefits and side effects. Sulfonylureas, thiazolidinediones and insulin may cause significant weight gain and hypoglycemia. Other classes such as DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors and acarbose) rarely cause hypoglycemia and are neutral to weight gain/may cause weight loss, but expose patients to higher risk of GI side effects and UTI/yeast infection.

We found that while the newer classes of medications helped achieve better control in blood glucose and weight gain, some people had to stop use for reasons other than termination of clinical trials, or experienced side effects.

**DPP-4 inhibitors:** While most people with type 2 diabetes who answered our survey about DPP-4 inhibitors generally did not report personal experience with side effects, some reported side effects such as stomach pain and nausea with Januvia. People also had concerns about weight gain and GI effects. One issue highlighted by many respondents was the challenge of managing multiple medications, and many expressed the wish to reduce medications as it would be “easier to remember and to get dosing right.” Many people were using metformin and a DPP-4 inhibitor would like to try combination drugs.

**GLP-1 analogues:** Studies have shown that GLP-1 receptor agonists are particularly effective in helping achieve glycemic control and weight reduction. Respondents to the survey on this class of drugs generally did not report side effects.

**SGLT2 inhibitors:** Respondents generally did not report serious side effects. Some reported such side effects as frequent urination, dehydration, increased appetite described them as “manageable,” while others found them challenging: *“Caused repetitive yeast infections and urinary tract infections as well as unpredictable bouts of bowel incontinence. I have never felt so ill in my life.”*

Two respondents had to discontinue drug use because of “face swollen and broken out in a rash” and “concerns about bladder cancer.”

**Insulin:** Insulin use is associated with significant risk of hypoglycemia, especially with regular and NPH insulin, but this risk is lower in people with type 2 diabetes than in those with type 1 diabetes. Episodes of hypoglycemia were not reported by respondents of type 2 diabetes with experience of long-acting insulin analogues. One person had to switch from insulin detemir to insulin glargine due to reactions. Fast-acting insulin has been associated with weight gain. People who are on multiple insulins find the multiple needles daily a significant challenge: *"I am needle-phobic and am looking at combined short-long acting as I take up to 3 shots of insulin per day."* *"I get pain in injection site..."* Some people using insulin reported side effects: *"I dislike the weight gain & fluid retention caused by Lantus and NovoRapid."*

### **3. Are the drugs easy or difficult to use? What is the impact of this on patients and their families or caregivers?**

**Reduced number of injections:** Many people who are using insulins would like to see improvement in the administration of insulins so that they can reduce the number of injections needed to maintain blood glucose control. A number of respondents viewed the less frequent injections as an advantage: *"If you can inject once to manage blood glucose for 1 week then it makes it easier to control."* An individual currently on metformin and insulin noted: *"Save me from taking 4 injections daily [which] complicates life."*

**Pill burden:** Several respondents found taking multiple medications challenging and expressed they wish to reduced pill burden: *"I hope one day to be able to take only one or two medications to control my diabetes, rather than the 3 injectibles and 2 tablet medications I take now;"* *"Combine to only one pill to make it easier for aging patients."* *"I take 3 pills in the morning and 5 at night so sometimes it is difficult to remember if I have taken them."* The availability of combination medications (with metformin), for people with type 2 diabetes stabilized on metformin, and a DPP-4/SGLT2/GLP-1 (with or without a sulfonylurea or insulin) would offer effective therapy while reducing pill burden and promote adherence to prescribed therapy.

### **4. Please briefly identify how the information used to complete Section 3 was obtained.**

Since 2013, our Association have conducted various surveys among our members to gain insight into the impact of type 2 diabetes on the lives of people living with diabetes and individuals' experience with diabetes medications including unmet needs and barriers to access medications. The surveys were distributed to our members via e-blasts and social media. Between 360 and 1,000 people with type 2 diabetes and caregivers answered each surveys. Information included in Section 3 was based on results from these surveys.

## Section 4 — Additional Information

Please provide any additional information related to this Therapeutic Review that would be helpful to CADTH, CDEC, and the participating drug plans.

As type 2 diabetes is a progressive disease in which glucose levels worsen over time, treatment must be dynamic with progression of the disease. As “people with type 2 diabetes” is a heterogeneous group, treatment regimens should be individualized. Responses from our surveys reinforce the understanding that different people with type 2 diabetes require different drug options to help effectively manage their disease. Their clinical profile, goals for treatment, preference and tolerance of therapy can direct their health care providers to the most appropriate drug therapy.

Across surveys, many with type 2 diabetes struggled with keeping their blood glucose at target and/or side effects and were still looking for treatments that would help them manage diabetes better. Based on their experience with drugs included in this therapeutic review, some drugs were able to improve glycemic control and reduce side effects compared to previous treatments. Having the option to choose the most appropriate medication is also of important consideration. In patients’ views, access to new classes of drugs would allow physicians and patients to *“have the flexibility to find the most effective and safe ‘mix’ of drugs to maintain control of diabetes as diabetes changes over time. People may need different medications at different times of their life with diabetes.”* Ultimately, many people with type 2 diabetes simply wish for a treatment that would allow them to lead a normal life again, as one patient pleaded: *“please help us get back to living.”*

## Appendix 1: Organizations and foundations that made donations to the Canadian Diabetes Association in 2015

Source: CDA 2015 Annual Report, available at <http://www.diabetes.ca/getmedia/0204ddb9-8942-4033-9dca-21547d2d8007/2015-cda-annual-report.pdf.aspx>

### Corporate Supporters

\$5,000 – \$24,999

Abkhan & Associates Inc.  
ADI Development Group  
Agway Metals Inc.  
Alberta Blue Cross  
AM Roofing  
Simcoe-Bluewater Ltd.  
Army Navy & Airforce BC  
Ascensia Diabetes Care  
Associated Auto Auction Ltd.  
Association  
Portugaise d'Aylmer  
ATB Financial  
ATCO Electric  
ATCO Gas  
B&T Estevan Gun Show Corp.  
Bank of Nova Scotia  
Basant Motors  
Bazil Developments Inc.  
Benevity Inc.  
Bermuda Tan  
Beverly Charity  
Classic Golf – Hamilton  
Boulangerie St-Méthode  
Briarlane Direct Property  
Management Inc.

Calgary Roadrunners Club  
Cameco Corporation  
Canada's Building  
Trades Unions  
Capital Cosmopolitan Club  
Cenovus Energy Inc.  
Chadi & Company  
Chartwell Seniors  
Housing Reit  
CMG Computer Modelling  
Group Ltd.  
Connect Hearing  
Construction Labour  
Relations Association NL  
Cooperators – Cumis  
Cornerstone Properties Ltd.  
Dairy Farmers  
Dakota Dunes Community  
Development Corporation  
Dauphin Clinic Pharmacy  
Egli's Sheep Farm Ltd.  
Engineering Society B,  
Faculty of Engineering  
Excelleris Technologies Inc.  
Ford Drive 4JR Community &  
School Program  
Forest City Road Races  
Fraternal Order of Eagles –  
BC Provincial Auxiliary  
Gamma Dynacare Medical  
Laboratories  
General Mills Canada Ntl.  
General Presidents'  
Maintenance Committee  
Gerrie Electric Wholesale Ltd.  
Gibbons Ride & Drive –  
Brantford  
Giffen-Mack Funeral Home  
HCI Holdings  
Holy Spirit Charitable Society  
Husky Energy Lloyd  
Charitable Campaign  
Impact Security  
International Credit Experts  
Irish Society of Westman  
Iupat Canadian  
Regional Conference  
Janzen's Pharmacy  
Jarrod Oils Ltd.

John Zubick Ltd.  
Kal Tire  
Kinsmen BC  
Kinsmen Club of Saskatoon  
Kinsmen Club of Thunder Bay  
(Hill City Kinsmen)  
Kiwanis Club of Vancouver  
Kiwanis Clubs of BC  
Knights Therapeutics  
Leon's Furniture Ltd.  
Leslie Street (FGH) Inc.  
Manitoba Association of  
Health Care Professionals  
Manitoba Health  
Manitoba Housing and  
Community Development  
Marshes Golf Club  
Matec Consultants Limited  
Medtronic of Canada Ltd.  
Mihealth Global Systems Inc.  
Nashwaaksis Lions Club Inc.  
Northern (#468)  
Northland Properties  
Corporation  
Ontario Automotive  
Recyclers Association  
Ontario Pork  
PD Management &  
Services Inc.  
PricewaterhouseCoopers LLP  
RBC Dominion Securities  
Regina Capital  
Cosmopolitan Club  
Regina Queen City Kinsmen  
Resources Development  
Trades Council  
Richmond Hill Italian  
Social Club  
Roche  
Rosmar Drywall Ltd.  
Royal Canadian Legion BC  
Royal Regina Golf Club  
(Ladies Section)  
Royal Scenic Holidays Ltd.  
Saskatchewan Indian  
Gaming Authority  
Saskatoon Downtown  
Lions Club  
SaskCanola

Shaw Communications Inc.  
Sherwood Co-Op Association  
Signex Manufacturing Inc.  
Skyway Canada Ltd.  
Sudbury Rocks Running Club  
Sunrise Soya Foods  
Sun-Rype Products Ltd.  
Tangerine  
TD Waterhouse Canada Inc.  
Teck Resources  
Telus  
Thunder Bay  
Real Estate Board  
UBC Alpha Gamma Delta  
Universal Collision Centre  
Vale Newfoundland &  
Labrador Ltd.  
Vancouver Courier  
Wellington Laboratories Inc.  
World Health Edmonton  
Zone 6 Lions Clubs

### Corporate Supporters

\$25,000 – \$49,999

Alberta Building Trades  
Blistex  
Brandt Tractor Inc.  
Connect Marketing Group  
Egg Farmers  
GlaxoSmithKline Inc.  
Group SEB – T-Fal  
Lions Clubs of BC  
Lions Clubs of Saskatchewan  
MEDEC (Diabetes Committee)  
Rogers Communications  
Rogers Radio Vancouver  
Rubicon Pharmacies  
Canada Inc.  
Taste of Kingston  
Ventas Inc.

### Corporate Supporters

\$50,000 – \$99,999

Abbott Nutrition  
Canola  
First Nations Health Authority  
J&J Consumer  
Lions Clubs of Canada

### Corporate Supporters

\$100,000 – \$174,999

Eli Lilly Canada Inc.  
Janssen Inc.  
Loblaws  
MEDT  
Nestle Canada  
Provincial Health  
Services Authority  
Royal Bank of Canada  
Sanofi – Aventis Canada Ltd.  
The North West Company LP

### Diabetes Champion

\$175,000 – \$249,999

Bayer Inc.  
Merck Canada Inc.

### Diabetes Catalyst

\$250,000 – \$349,999

LifeScan Canada Ltd.  
Shaw Media  
Sun Life Financial

### Diabetes Visionary

\$400,000+

AstraZeneca  
Novo Nordisk Canada Inc.

### Foundations

Airlie Foundation  
Alice & Murray  
Maitland Foundation  
Alpha Gamma Delta  
Foundation  
Aqueduct Foundation  
AWB Charitable Foundation  
Brantford Community  
Foundation –  
City of Brantford  
Brian & Susan Thomas  
Foundation  
Burrows Colden Family  
Foundation  
Butler Family Foundation  
Cal Wenzel Family  
Foundation  
Calgary Shaw Charity  
Classic Foundation  
Cambridge & North Dumfries  
Community Foundation  
Canadian MedicAlert  
Foundation  
Genovus Employee  
Foundation  
Chickadee Trust  
Chimp Foundation  
Colin & Lois Pritchard  
Foundation  
Community Foundation  
for Kingston & Area  
Community Foundation  
of Ottawa-Carleton  
Crabtree Foundation  
Deloitte Foundation Canada  
Edmonton Community  
Foundation  
Edwards Charitable  
Foundation  
EnCana Cares Foundation  
Ernst Hansch Foundation/  
Terracon Development  
Eva T. Villanueva Charitable  
Fund at the Strategic  
Charitable Giving  
Foundation  
Flaman Foundation  
Fleming Foundation  
Frederick Community  
Foundation Inc.  
G Grant & Dorothy F  
Armstrong Foundation  
Gift Funds Canada

Gill Family Charitable Trust  
Glenn's Helping Hand  
Foundation Inc.  
Greygates Foundation  
Halifax Protestant Infants'  
Foundation  
Halifax Youth Foundation  
Hamber Foundation  
Harry P. Ward Foundation  
Infinity Community Fund  
Jewish Community  
Foundation  
Jewish Foundation  
of Manitoba  
John M. & Bernice Parrott  
Foundation Inc.  
KPMG Foundation  
Lagniappe Foundation  
Leslie & Irene Dube  
Foundation  
Manitoba Hydro  
Charitable Fund  
Medavie Health Foundation  
Mister Blake Foundation  
Napane District Community  
Foundation  
Newfound Foundation  
NL Retired Teachers  
Foundation  
Northern Ontario Heritage  
Fund Corporation  
NWM Private Giving  
Foundation  
Oakville Community  
Foundation  
Orville & Alvera Woolcott  
Foundation  
PepsiCo Foundation  
Prince Albert & Area  
Community Foundation  
Private Giving Foundation  
Raymond James Canada  
Foundation  
RBC Foundation  
Rexall Foundation  
Salesforce Foundation  
Saskatchewan Community  
Initiatives Fund  
Saskatoon Community  
Foundation  
Sayal Charitable Foundation  
Scotiabank Community  
Program

Sherry & Sean Bourne Family  
Charitable Foundation  
South Saskatchewan  
Community Foundation Inc.  
Strategic Charitable  
Giving Foundation  
The Barrett Family  
Foundation  
The Brockville Community  
Foundation  
The Calgary Foundation  
The Charles Norcliffe Baker &  
Thelma Scott Baker  
Foundation  
The Chatham-Kent  
Community Foundation  
The Dr. Charles & Margaret  
Brown Foundation  
The Edith Lando Charitable  
Foundation  
The Guelph Community  
Foundation  
The Gyro Club of Vancouver  
Charitable Foundation  
The Home Depot Foundation  
The Horn Family Fund  
The John and Judy Bragg  
Family Foundation  
The Kitchener & Waterloo  
Community Foundation  
The Lawrason Foundation  
The Mariano Elia Foundation  
The Poker for Diabetes  
Foundation  
The Ryley Family Foundation  
The Tenaquip Foundation  
The Virmani Family  
Charitable Foundation  
The Walker Lynch Foundation  
The WB Family Foundation  
The Winnipeg Foundation  
Toronto Star Fresh Air Fund  
Valero Energy Foundation  
of Canada  
Vancouver Foundation –  
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William James Henderson  
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