



## Common Drug Review *Patient Group Input Submissions*

### **dapagliflozin/metformin hydrochloride (XigDuo) for Diabetes Mellitus, Type 2**

**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.

**CADTH received patient group input for this review on or before January 27, 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	dapagliflozin/metformin hydrochloride (XigDuo) 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)	[REDACTED]
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. A list of organizations and foundations that made donations to the CDA in 2014 can be found in the appendix. 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) solicited patient input through surveys distributed through social media and email blasts. Content of this submission is derived from two surveys. One survey conducted in October 2015 for 10 days gathered information from 212 Canadians with type 2 diabetes and 61 caregivers for people with diabetes about the impacts of diabetes. The other survey, conducted

in April 2015 during 3 weeks, provided information from 349 Canadians with type 2 diabetes and 75 caregivers about current drug therapies and experience with dapagliflozin (Forxiga), and aspects of diabetes they would like medications to address.

## 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.

Respondents were asked to describe the daily impact of diabetes. For the majority of respondents, diabetes has negatively impacted all aspects of their lives and limited daily activities. Some indicated that they were “held captive by diabetes” and that diabetes was “overwhelmingly debilitating.” Diabetes management is a “constant struggle” involving meal planning, testing blood glucose, taking medication and ensuing stress. Many are frustrated that they cannot lead a “normal life” due to diabetes. Other impacts include fatigue and lack of energy. It is also challenging when a person needs to manage diabetes as well as other co-existing conditions/diabetes-related complications. Many respondents reported complications as a result of their diabetes, including neuropathy, foot complications, heart problems, strokes, eye problems/loss of vision, kidney problems (leading to kidney transplant and dialysis), pancreatitis, skin ulcers, erectile dysfunction, amputation and depression.

There was a frequent emphasis on the psychological and emotional impact of diabetes on the lives of respondents and their family members, due to the need to adjust to changes in diet and lifestyle, stress and anxiety about hypoglycemia, daily medication and treatment management, strain on relationships with family, and financial burden. For individuals who have to manage diabetes and care for other members of the family, it is also very difficult.

Direct quotes below further describe the general impact of diabetes on respondents:

*“I need to be careful with what I eat and how much I eat, especially carbohydrates. Also need to balance out a snack, insulin needs and exercise to ensure I don't have a hypoglycemic episode while exercising. I also need to monitor my insulin needs while doing errands, again to avoid a hypoglycemic episode.”*  
– person living with type 2 diabetes

*“[Diabetes has] affected my family also due to my being not able to work while I was waiting for a kidney transplant, which was given to me by ... my son. Because of being on dialysis [sic] I had to spend most of my life's savings. Being sick can be very very expensive.”* – person living with type 2 diabetes

*“It is difficult to lead a normal life when you always need to be taking meds or checking your [blood sugar] levels and reading labels on all your food while your [blood sugar] 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.” – person living with type 2 diabetes*

Respondents to the October 2015 survey reported the following conditions/symptoms. A large proportion of respondents reported hypoglycemia (56%), high blood pressure (55%), high cholesterol (47%), foot problems (43%), eye problems (39%) and nerve damage (38%). The percentages are based on 219–236 people with type 2 diabetes and caregivers who responded to the question about symptoms/conditions they were experiencing (Table 1). In addition, four respondents mentioned experiencing thyroid problems, and one experiencing erectile dysfunction.

Table 1: Conditions experienced by surveyed respondents, by degree of severity

Condition	Moderate/sometimes	Severe/often	Total
Hypoglycemia	50%	6%	56%
High blood pressure	38%	17%	55%
High cholesterol	36%	11%	47%
Mental health problems	17%	5%	22%
Kidney problems	13%	7%	20%
Foot problems	31%	12%	43%
Eye problems	31%	8%	39%
Nerve damage	27%	11%	38%
Damage to blood vessels, heart or brain	13%	7%	20%
Liver disease	8%	3%	11%
Endocrine disorder	17%	6%	23%

### 2.3 Patients’ Experiences With Current Therapy

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. 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.

According to results from the April 2015 survey, a total of 397 Canadians with diabetes and caregivers indicated experience taking diabetes medications. The majority of respondents - 63% (218 people) stated they were “satisfied” or “very satisfied” with their current therapies whereas 18% indicated dissatisfaction. Respondents indicated current therapies resulted in better or much better blood glucose and A1C levels. However, a significant number of respondents reported challenges in avoiding low blood sugar (“the same,” “worse” or “much worse” for 38%), weight gain (“the same,” “worse” or “much worse” for 52%), GI effects (“the same,” “worse” or “much worse” for 57%); 59% and 55% indicating “same,” “worse” or “much worse” for dehydration and urinary tract/yeast infection, respectively.

Overall, respondents were more satisfied than dissatisfied with their medications in terms of the ability to manage their blood sugar levels. However, there were considerable 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.” Over 90% of respondents indicated the following benefits of therapy were “quite” or “very important”:

- blood sugars kept at satisfactory levels in the morning/after fasting (96%),

- blood sugars kept at satisfactory levels during the day/after meals (95%),
- avoiding low blood sugar during the day/overnight (90%).

The following aspects are also considered important by the vast majority:

- avoiding weight gain (89%),
- avoiding GI effects (84%),
- reducing high blood pressure (83%),
- avoiding fluid retention (82%),
- avoiding urinary tract infection (81%).

The medications taken by respondents at the time of survey included metformin (175), insulin (131), sulfonylureas (73), DPP-4 inhibitors (43), SGLT2 inhibitors (124), GLP-1 agonist (27), combination D-PP4 inhibitors+metformin (64), meglitinides (13), TZDs (8), rosiglitazone+metformin (9), and acarbose (4).

Among the 175 people who were on metformin, a large proportion were taking additional medications to manage their diabetes: 51 of them were taking dapagliflozin at the same time, 49 were also taking a sulfonylurea, 32 were taking a DPP-4 inhibitor, 20 were taking a GLP-1 agonist and 71 were on insulin. These sub-groups are not mutually exclusive as some patients were taking multiple drugs.

## 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 April 2015, the survey gathered information from Canadians with type 2 diabetes (n=349) and their caregivers (n=75) about experience with dapagliflozin, and the most important aspects of diabetes they would like new medications to address. As combination medication dapagliflozin+metformin (XigDuo) is not yet available on the market, very few people with type 2 diabetes have had experience with this medication. Since many surveyed indicated current use of both dapagliflozin and metformin, we believe it is relevant to present patients' experience with dapagliflozin 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?

A total of 92 respondents indicated using dapagliflozin at time of survey, and 6 had had to stop for reasons other than completion of clinical trials. A total of 51 of the 92 respondents with experience were also taking metformin and/or other medications. Patients and caregivers who had experience with dapagliflozin highlighted its effectiveness in **lowering blood sugar and blood pressure** compared to other medications. The improvement in blood sugar levels (fasting and throughout the day) and the accompanying weight loss – described as “significant” and “dramatic” – was observed among many who had struggled with keeping glucose at target. In the words of people with type 2 diabetes and their caregivers: “His blood sugar are below 10, he hasn't been below 10 in years, the other day, it was 6.3 that's amazing;” “readings are best I have ever had;” “bloods sugars the best they have been since diagnosis a year ago.” Many who have only been on the medication for a short period of time noticed instant improvement: “I have only taken it for four days and I already feel the effects, which are positive!!” “I've only been on Forxiga for a month, but seems to be doing the job where the other was not quite working.”

Many respondents noted less dependency on other drugs such as insulin as a result of dapagliflozin -- one person was able to get off “one of 3 blood pressure meds,” while another “reduced insulin intake by 75%.” The reduction of medications is viewed as a substantial improvement to quality of life: “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.”

Below are additional quotes from patients/caregivers who have found the experience with dapagliflozin to be very positive, including its effects on their **energy level** and **mental health**:

*“I have only been taking it for a month but it has helped me feel more in control of my diet thus helping me eat better and exercise more.”*

*“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[sic][positive] impact on my self-confidence and feeling of ‘being in control’ with my diabetes.”*

Respondents generally did not describe serious side effects; some who did experience side effects such as frequent urination, dehydration, increased appetite described them as “manageable.” Others, however, had not experienced the same benefits and had found side effects challenging – two respondents had to discontinue the medication because of “face... swollen and broke out in a rash” and “concerns about bladder cancer”:

*“I've been on it two months now, and it seems as if it takes a long time for results to show. Though I have lost weight and my blood pressure is more stable. My morning sugar levels are still higher than I'd like.”*

*“I started taking it about one month ago. I was prescribed 5 mg once daily. My test results did not show improvement and I did not lose weight. My doctor changed my prescription to 10 mg daily. It's only been a couple of days and I don't feel any differences at this point.”*

*“First week experienced vaginal yeast infection, severe constipation and a small weight loss. Subsequently no side effects, no weight loss and no significant change in blood sugar levels.”*

*“I've used forxiga for 2 months and I am now feeling the effects, mineable constipation and I am adjusting my insulin greatly I now use about half the insulin and I still have lows during the day. My physical activity has increased but unfortunately the weight lose[sic] has not happened yet, still hoping.*

*“Did low blood sugar levels but did not reduce weight. 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.”*

*“Have only been taking Forxiga for 2 months... but seems to be increasing my blood Pressure and I have also developed [an] annoying pang in my chest.”*

*“Vaginal yeast infections that I had one after another and constant chapped lips that burned and split were part of the side effects.”*

### **Combination of dapagliflozin and metformin**

Several surveyed respondents found taking multiple medications challenging and expressed the wish of reducing the number of pills: “I hope one day to be able to take only one or two medications to control my diabetes rather than the 3 injectables and 2 tablet medications I take now;” “Would like to be on fewer drugs;” “Combine to only one pill and make it easier for aging patients;” “I hope that it would be a one tablet or injection instead of multiple medications to treat type 2 diabetes;” “A combination pill would be useful.” The availability of XigDuo, as a fixed dose combination of metformin with dapagliflozin, for people with type 2 diabetes stabilized on metformin, dapagliflozin (with or without a sulfonylurea or insulin) 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 doctors **and** patients working together to achieve optimal treatment with the lowest effective dose.

### **Summary**

Diabetes requires intensive self-management and can be challenging; as one respondent put it: “Managing diabetes is very stressful because you take lots of medication and in spite of your best efforts, maintaining target ranges is difficult.” 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 on the experience of respondents, many of these expectations were met by dapagliflozin 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 options in terms of medications to help effectively manage their disease. Their clinical profile, preference and tolerance of therapy can direct physicians to the most appropriate drug therapy.

Several respondents identified taking several medications as a concern, hoping to have access to combined medicines which would reduce the number of medications taken. The availability of a combined dapagliflozin+metformin (XigDuo) may promote adherence to prescribed treatment by reducing pill burden and can offer some patients a good alternative for effective management of diabetes.



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-annual-report.pdf.aspx>

593123 Alberta Ltd.	Community Foundation of Ottawa	Jackson Family Fund	Orville & Alvera Woolcott Foundation	Subway	The Toronto Star Fresh Air Fund
A. E. (Ted) & Deanna M. Turton Charitable Foundation	Community Initiatives Fund	Janssen Inc.	Panasonic Canada Inc.	Sudbury Rocks Running Club	The Walker Lynch Foundation
Abbott Diabetes Care	Connect Marketing Group	Jays Care Foundation	Pfizer Canada Inc.	Sunrise Soya Foods	The WB Family Foundation
Abbott Laboratories Ltd.	Co-operators/CUMIS	Jewish Community Foundation	Pharmasave Central	Sure Flow Equipment Inc.	The Windsor Foundation
Adi Development Group	Crabtree Foundation	Johnson & Johnson	Point Edward Ex-Servicemen's Association	TD Securities	The Winnipeg Foundation
Agway Metals Inc.	Deloitte LLP	Kal Tire	PriceWaterhouse-Coopers LLP	Teck Resources	The Worrall Family Fund
Aqueduct Foundation	Dr. Charles & Margaret Brown Foundation	Kinsmen Club of Kingston	Private Giving Foundation	TELUS Cares	United Way of Lower Mainland
AstraZeneca Canada Inc.	ECCOL Electric	Kinsmen Club of Saskatoon	Raymond James Canada Foundation	The Airlie Foundation	Vale
Aubrey & Marsha Baillie Family Fund	Egg Farmers of Canada	Kiwanis Club of Vancouver	RBC Foundation	The Alice & Murray Maitland Foundation	Vancouver Foundation
Bayer HealthCare – Diabetes Care	Eli Lilly Canada Inc.	Knights Templar Charitable Foundation of Canada	Regina Queen City Kinsmen	The Arthur J. E. Child Foundation	Victoria Foundation
Bayer Inc.	Eli Lilly Canada Inc./Boehringer Ingelheim Alliance	KPMG	Relic Riders	The Barrett Family Foundation	Wellington Laboratories Inc.
BD Medical – Diabetes Care	Enterprise Holdings Inc.	Lagniappe Foundation	Rexall Foundation	The Birks Family Foundation	Zechariah Perlman & Doris Perlman Fund
BHP Billiton	Ernest I. Silverberg, Morris Silverberg, David Silverberg, Maier Silverberg & Antzi Silverberg Fund	Lawson Foundation	Roche Diagnostics Canada	The Brian & Susan Thomas Foundation	
Blistex Corporation	File Hills Qu'Appelle Tribal Council	Leland Industries Inc.	Rotary Club of Bolton	The Charles Norcliffe Baker & Thelma Scott Baker Foundation	
Brandt Group of Companies	Fleming Foundation	Leon's Furniture Ltd.	Royal Bank of Canada	The Co-operators	
Brandt Tractor	G. Murray & Edna Forbes Foundation	Leslie & Irene Dube Foundation	Rubicon	The Edwards Charitable Foundation	
Britton Smith Foundation	Gamma-Dynacare Medical Laboratories	LifeScan Canada Ltd.	Sanofi	The Gill Family Charitable Trust	
Brokerteam Holdings	General Mills Canada Corporation	Lions Clubs of Canada	Saskatchewan Association of Optometrists	The Guelph Community Foundation	
Build-A-Bear Workshop Bear Hugs Foundation	Gerald C. Baines Foundation	Loblaw Companies Ltd.	Saskatchewan Community Initiatives Fund	The J. P. Bickell Foundation	
Burrows Colden Family Foundation	Gerrie Electric Wholesale Ltd.	Longo's Family Charitable Foundation	Saskatchewan Indian Gaming Authority	The Jewish Foundation of Manitoba	
Cameco	GlaxoSmithKline Inc.	Manitoba Association of Healthcare Professionals	Saskatoon Community Foundation	The Kitchener & Waterloo Community Foundation	
Canadian National Railway Company	Glenn's Helping Hand Foundation Inc.	May Court of Oakville Foundation	Scotiabank	The Lawrason Foundation	
Canola Council of Canada	Government of British Columbia	McNeil Consumer Healthcare	Sherry & Sean Bourne Family Charitable Foundation	The Leflar Foundation	
Capital Cosmo	Groupe SEB	Medavie Blue Cross	Shiff Family Charitable Foundation	The Lorne & Evelyn Johnson Foundation	
Carmen's Group	Halifax Protestant Infants' Foundation	MEDEC	SIGA	The M & N Foundation	
Carolyn Sifton Foundation	Halifax Youth Foundation	Medtronic of Canada Ltd.	South Saskatchewan Community Foundation Inc.	The Manchee Foundation	
CCR Building & Remodeling	Husky Energy Inc.	Merck Canada Inc.	Sticklings Bakery	The Mariano Elia Foundation	
Cenovus Employee Foundation	Icecaps Care Foundation	Nestlé Health Science	Strategic Charitable Giving Foundation	The May Court Club of Oakville	
Chartwell Retirement Residences	Inga & Anna Storgaard Fund	Newman's Own Foundation		The Murray & Audrey Neufeld Charitable Foundation Inc.	
		Northland Properties Corp.			
		Novartis Pharmaceuticals Canada Inc.			
		Novo Nordisk Canada Inc.			
		NWM Private Giving Foundation			