

Patient Input Template for CADTH CDR and pCODR Programs

Name of the Drug and Indication	insulin degludec+liraglutide (Xultophy), Diabetes mellitus, type 2
Name of the Patient Group	Diabetes Canada
Author of the Submission	Ann Besner
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1. About Your Patient Group

If you have not yet registered with CADTH, describe the purpose of your organization. Include a link to your website.

Diabetes Canada is a national health charity representing close to 11 million Canadians living with diabetes or prediabetes. The priorities of our mission are diabetes prevention, care and cure. Our focus on research and policy initiatives helps us to deliver impact at a population level, and our partnerships broaden our reach in communities across the country. We drive excellence in disease management by putting practical, evidence-based tools into the hands of health-care providers. We advocate for environments that make the healthy choice the easy choice. We continue our search for a cure, as well as for better prevention and treatment strategies, by funding the work of innovative scientists. In 1921, Canada changed diabetes for the world with the discovery of insulin. By 2021, we will change the world for those affected by diabetes through healthier communities, exceptional care, and high-impact research. For more information, please visit: www.diabetes.ca.

2. Information Gathering

CADTH is interested in hearing from a wide range of patients and caregivers in this patient input submission. Describe how you gathered the perspectives: for example, by interviews, focus groups, or survey; personal experience; or a combination of these. Where possible, include **when** the data were gathered; if data were gathered **in Canada** or elsewhere; demographics of the respondents; and **how many** patients, caregivers, and individuals with experience with the drug in review contributed insights. We will use this background to better understand the context of the perspectives shared.

This submission contains patient input from online surveys conducted in October 2016 and January/February 2019. Each survey was open for two weeks to people across Canada and consisted of a self-administered questionnaire. The surveys were directed at people living with type 2 diabetes and caregivers of people with type 2 diabetes and inquired about respondents' lived experience with diabetes and diabetes medications, and expectations for new drug therapies in Canada. The more recent of the two surveys posed a number of questions specifically about the drug under review, insulin degludec+liraglutide (Xultophy). Awareness about the surveys was generated through Diabetes Canada's social media channels (Twitter and Facebook); the October 2016 survey was also advertised to Diabetes Canada e-mail subscribers through e-blasts.

A total of 847 people responded to the October 2016 survey – 790 identified as living with type 2 diabetes while 57 said they were caregivers to somebody with type 2 diabetes. Of those who responded to questions about age and time since diagnosis (n=379), 70% were over the age of 55, with the largest number of respondents (56%, n=211) in the 55-69 year old category, and 60% having lived with diabetes for over 10 years (17% of this group reported having diabetes for over 20 years).

Fewer people participated in the January/February 2019 survey (n=9) – all respondents said they live with type 2 diabetes. Of the 5 people who provided age and date of diagnosis data, 100% of respondents were over the age of 40 years (n=2 in the 40-54 year old category, n=2 in the 55-69 year old category, n=1 in the 70 years and over category). There were 2 respondents who reported having lived with diabetes for 3-5 years and 3 respondents who reported 11-20 years with the disease.

3. Disease Experience

CADTH involves clinical experts in every review to explain disease progression and treatment goals. Here we are interested in understanding the illness from a patient's perspective. Describe how the disease impacts patients' and caregivers' day-to-day life and quality of life. Are there any aspects of the illness that are more important to control than others?

Diabetes is a chronic, progressive disease of different types, but none with any known cure. Type 2 diabetes (for which the drug under review is indicated) occurs when the pancreas does not produce enough insulin or the body does not effectively use the insulin that is produced. Common symptoms of diabetes include extreme fatigue, unusual thirst, frequent urination and weight change (gain or loss).

Diabetes requires considerable self-management, including eating well, engaging in regular physical activity, maintaining a healthy body weight, taking medications (oral and/or injectable) as prescribed, monitoring blood glucose and managing stress. Poor glucose control is serious and problematic. Low blood glucose can precipitate an acute crisis, such as confusion, coma, and/or seizure that, in addition to being dangerous, may also contribute to a motor vehicle, workplace or other type of accident causing harm. High blood glucose over time can irreversibly damage blood vessels and nerves, resulting in blindness, heart disease, kidney problems and lower limb amputations, among other issues. The goal of diabetes management is to keep glucose levels within a target range to minimize symptoms and avoid or delay complications.

Most respondents who participated in the October 2016 survey and the January/February 2019 survey spoke negatively of their experience being chronically ill. They said diabetes is “manageable but a bother”, “a constant battle every day”, “a terrible way of life”, inconvenient, frustrating, and exhausting. One respondent said it just “isn't fun to have to live with”, while another commented it has “impacted my life financially, emotionally, physically and socially”. Several people spoke about its permanence, lamenting that there is no “holiday” from diabetes.

Most people surveyed talked about the adverse effect diabetes has had on their lives. They shared that they are constantly thinking about and planning around their disease. It affects everything from eating and exercising to working and socializing. Overall, diabetes makes it difficult to be flexible and spontaneous. It is always top-of-mind when making decisions and can be very stressful. Daily routines end up very “regimented” and closely “controlled”. Diabetes can be even more difficult to manage when someone is also dealing with comorbidity or disability, or is a caregiver to others. Constant monitoring of blood sugar levels and frequent visits to health care providers were described as burdensome.

Respondents said that meal timing, intake and food choices are restricted, which takes away from the pleasure of eating, and that it is demoralizing to always be getting (often unsolicited) dietary advice from people. They said it is challenging to always be taking medication and to experience variability in blood sugar control. Several respondents spoke about the blame they inflict upon themselves for their disease, the shame and guilt they feel, and the stigma they experience. Some talked about how tough it is to interact with people who know very little about diabetes or who offer unwanted insights about its management.

Many people mentioned dealing with, and being apprehensive about, disease symptoms, medication side effects and diabetes complications. Respondents described being chronically in pain and feeling tired a lot. They cited problems ranging from weight management issues, neuropathy and nephropathy, to amputations, changes to circulation and increased risk of heart attack, vision problems, gum disease and sexual changes. They reported living with depression and anxiety.

Respondents to the October 2016 survey said they experienced the following symptoms and conditions “sometimes” (“moderately”), “often” (“severely”) or “very often” (“very severely”) at the time of survey completion (n=691 for this question):

- hyperglycemia (75%)
- hypoglycemia (38%)
- high blood pressure (51%)
- high cholesterol (48%)
- heart problems (18%)
- mental health problems (30%)
- kidney symptoms or disease (19%)
- foot problems (45%)
- eye problems (42%)
- nerve damage (37%)
- damage to blood vessels, heart or brain (10%)
- liver disease (9%)

Other concerns cited include gastroparesis, gastrointestinal issues (nausea, diarrhea), bladder and bowel incontinence, yeast infections, skin rash and weight gain.

Of those who responded to this question in the January/February 2019 survey (n=5), people experienced the following “sometimes” (“moderately”), “often” (“severely”) or “very often” (“very severely”):

- hyperglycemia (100%)
- hypoglycemia (60%)
- high blood pressure (20%)
- high cholesterol (40%)
- mental health problems (20%)
- kidney symptoms or disease (40%)
- foot problems (60%)
- eye problems (40%)
- nerve damage (20%)

People shared that diabetes has negatively affected relationships. It has made it hard for them to work, travel, and drive a vehicle – several respondents mentioned challenges and extra costs associated with their driver’s license renewal because of diabetes. Diabetes decreases independence. People feel concerned about the long-term effects of the disease on health. They also mentioned the significant and overwhelming financial burden diabetes poses on themselves and their families.

Below are some quotes from the two surveys that further illustrate the degree and extent to which diabetes affects daily living and quality of life of those with the disease:

“Type 2 Diabetes[sic] has damaged the nerves in my feet and legs. It is also causing vision problems.”

“It is exhausting to constantly be thinking about food, planning meals, anticipating absences from home, travel. Managing highs and lows with food and exercise takes a great deal of planning. Planning for and shopping for healthy meal options for myself and my family is expensive. Feeling stressed and unwell due to highs/lows negatively impacts my energy and my attitude and my relationships with others.”

“I’m finding it difficult to remember to test my sugars and take insulin before eating each meal.”

“It takes a lot of time and effort to manage, and I’ve had it for [over 20] years. It made shift work even worse, it leaves me very tired for no reason, and people don’t get it. Its[sic] hard to sit in a restaurant and people at adjoining tables stare at you as you inject insulin. If its[sic] children, I take the opportunity to educate - but I’m tired of educating people all the time.”

“We liked to go to different restaurants and that is now limited as many do not have diabetic freindly[sic] food. Also there is a stigma associated with diabetes that others frown on things like taking your insulin in public.”

“I have been a Type II[sic] Diabetic [for many years]... Taking meds & insulin is hard because you don’t really feel sick but you have to take them anyway. I lost a father...and two sisters...due to diabetes.”

“Diabetes[sic] has resulted in the need for dietary changes for everyone in the house. I have neuropathic pain that sometimes makes it difficult to rest comfortably and to be as active as I normally would. I need to pay extra attention to my feet to make sure I don't have sores or infections, as they could take longer to heal than if I was not diabetic. I also have nephropathy, which I hope never progresses to chronic kidney disease.”

“I am a...mother...and hate the fact that I have developed diabetes and have to take medications for it. This disease gets in the way all the time (more trips to the doctor, more trips to the pharmacy, having to remember to take my medication and ensuring that I don't take too much medication so that I can drive my vehicle). My kids have to know what to do if I pass out, and that isn't the type of responsibility that young children should have.”

“I need to watch my carb intake – my food generally, I need to make time to exercise 30 minutes or more most days, I can't skip meals and need to carry food with me, I test my blood sugar – with finger prick as needed, lab work – blood drawn every 3 months, dr.[sic] visit every 3 months.”

“I've had to change my entire way of life, the things I eat, the things I do. Some days I feel sick all day, others I'm just plain tired and can't get motivated.”

4. Experiences With Currently Available Treatments

CADTH examines the clinical benefit and cost-effectiveness of new drugs compared with currently available treatments. We can use this information to evaluate how well the drug under review might address gaps if current therapies fall short for patients and caregivers.

Describe how well patients and caregivers are managing their illnesses with currently available treatments (please specify treatments). Consider benefits seen, and side effects experienced and their management. Also consider any difficulties accessing treatment (cost, travel to clinic, time off work) and receiving treatment (swallowing pills, infusion lines).

There were 667 respondents who reported experience with antihyperglycemic agents in October 2016. The medications being taken at the time of survey completion included metformin (371), GLP-1 receptor agonists (312), SGLT2 inhibitors (165), combination of SGLT2 inhibitors and metformin (45), DPP-4 inhibitors (72), combination of DPP-4 inhibitors and metformin (147), sulfonylureas (140), TZDs (10), combination of TZDs and metformin (17), combination of TZDs and glimepiride (4), meglitinides (9) and acarbose (9). Many people reported taking insulin (309). A number of respondents indicated that they had experience with certain medications in the past as part of a clinical trial. Some reported stopping certain medications due to reasons other than the end of a clinical trial. The most commonly cited medications in this group were TZDs (97), sulfonylureas (94), GLP-1 receptor agonists (94) and DPP-4 inhibitors (92).

Over 60% of respondents to the October 2016 questionnaire noted improvements in meeting target blood glucose levels (fasting, post-prandial, upon waking) and hemoglobin A1c levels after initiation on their current medication regimen, compared to when they were not on treatment. About 46% said they were “better” or “much better” able to avoid hypoglycemia, and 39% said their current regimen helped them maintain or lose weight more effectively than in the past. Gastrointestinal side effects were “neither better nor worse” than previously in 39% of respondents. Close to two-thirds of people indicated they were either “satisfied” or “very satisfied” with the medication or combination of medications they are currently taking for their diabetes management.

Respondents who answered this question (n=382) in the October 2016 survey reported the following benefits and side effects as “quite important” or “very important” when choosing pharmacotherapy for diabetes management:

- keeping blood glucose at satisfactory level during the day or after meals (98%)
- keeping blood glucose at satisfactory level upon waking or after fasting (97%)
- avoiding low blood sugar during the day (90%)
- avoiding low blood sugar overnight (90%)

- avoiding weight gain/facilitating weight loss (91%)
- reducing high blood pressure (79%)
- reducing risk of heart problems (90%)
- avoiding gastrointestinal issues (nausea, vomiting, diarrhea, pain) (87%)
- avoiding urinary tract and/or yeast infections (84%)
- avoiding fluid retention (85%)

In the more recent study conducted in January/February 2019, the following medications were reported as being currently in use by respondents (n=5): metformin (4), GLP-1 receptor agonists (1), combination of DPP-4 inhibitors and metformin (1), sulfonylureas (1), meglitinides (1) and orlistat (1). A few respondents cited use of certain medications in the past. These included sulfonylureas (1) and metformin (1). Reasons for discontinued use of these medications were not provided.

Of those who responded to the question (n=5), 40% said they were “better” or “much better” able to meet fasting blood glucose targets on current antihyperglycemic therapy. With respect to their blood glucose upon waking, 40% said their current therapy was “better” or “much better” at helping them reach their target, but another 40% said it was “worse”. Current therapy was “worse” at helping 60% of respondents reach their post-prandial blood glucose target and 40% of respondents achieve their target hemoglobin A1c level. Over half of respondents said they were “neither satisfied nor unsatisfied” with their current diabetes medication(s).

When asked what factors were “quite important” or “very important” in choosing diabetes medications, 80% or more of respondents (n=5) said the following: keeping blood glucose at satisfactory levels during the day or after meals and upon waking or after fasting, avoiding low blood sugar during the day and overnight and avoiding weight gain/facilitating weight loss. Reducing high blood pressure and the risk of heart problems and avoiding gastrointestinal issues, yeast infections and urinary tract infections were cited as “quite important” or “very important” to 60% of respondents.

Below are some direct quotes from respondents to the October 2016 and January/February 2019 surveys that describe what they like and dislike about current therapy:

“The insulin my husband takes helps control his blood sugar levels. He tests his blood sugar level 3 times a day and adjusts his food intake accordingly.”

- caregiver to a person with type 2 diabetes taking metformin and insulin (age and time since diagnosis not specified)

“Needles to administer insulin twice daily is[sic] painful but necessary. Current medications do not cause adverse side effects.”

- 55-69 year old person with type 2 diabetes, diagnosed 6-10 years ago, taking combination of SGLT2 inhibitor and metformin, and insulin

“[A GLP-1 receptor agonist] has been excellent, has decreased very substantially my need for both basal and bolus insulin as well as other medications, reduced hypoglycemia and achieved weight loss.”

- person over 70 years old with type 2 diabetes, diagnosed more than 20 years ago, taking a GLP-1 receptor agonist, SGLT2 inhibitor, metformin and insulin

“It keeps my sugar level at an ok[sic] range. Makes me gassy and have to use the washroom more.”

- 40-54 year old person with type 2 diabetes, diagnosed 3-5 years ago, taking metformin

“[A GLP-1 receptor agonist] has so far been the best choice for me. The only dislike I have is that it causes the odd nausea and gut discomfort.”

- person with type 2 diabetes taking a GLP-1 receptor agonist, metformin and insulin (age and time since diagnosis not specified)

“[It is] easy to take 1 pill with each meal. I dislike that studies have linked [the medication] with dementia.”

- 55-69 year old person with type 2 diabetes, diagnosed 3-5 years ago, taking metformin

"I have had poor control of my blood sugars over the years. I have tried products that either did nothing or caused more problems. [A GLP-1 receptor agonist] is assisting with better control. However, if my husband's health plan from work didn't cover it, I wouldn't be able to take it as the cost is about [a few hundred dollars] per. I take a lot of meds and wish I didn't have to."

- 40-54 year old person with type 2 diabetes, diagnosed more than 20 years ago, taking a GLP-1 receptor agonist, metformin and insulin

"I can not afford the [GLP-1 receptor agonist previously taken as part of a study] and have been begging to find a way to reduce the cost as I truly believe it was very good [treatment for several years] ..."

- person over 70 years old with type 2 diabetes, diagnosed 11-20 years ago, taking a GLP-1 receptor agonist and metformin

"I feel like I take a huge amount of meds for diabetes and [a second health condition]. Its[sic] scary at times. As my benefits are capped, it is expensive - very. I'd like to say I feel great, but those days are rare."

- person diagnosed with type 2 diabetes taking an SGLT2 inhibitor, metformin and insulin (age and time since diagnosis not specified)

"There are so many [medications] and they cause a[sic] extreme dry mouth, nausea and diarrhea."

- 40-54 year old person with type 2 diabetes, diagnosed 11-20 years ago, taking a GLP-1 receptor agonist, metformin and insulin

5. Improved Outcomes

CADTH is interested in patients' views on what outcomes we should consider when evaluating new therapies. What improvements would patients and caregivers like to see in a new treatment that is not achieved in currently available treatments? How might daily life and quality of life for patients, caregivers, and families be different if the new treatment provided those desired improvements? What trade-offs do patients, families, and caregivers consider when choosing therapy?

When asked about their expectations for new diabetes therapies, respondents to the October 2016 and January/February 2019 surveys expressed a strong desire for medications that can normalize/stabilize blood glucose levels and improve hemoglobin A1c without causing weight gain or hypoglycemia. They wish for new treatments that have been proven to be safe, enhance weight loss and improve health outcomes. They want affordable drug options; ideally, they'd like medications and diabetes devices to be covered by public and private plans. They want treatments that are easily administered, with few to no associated side effects, that cause the least amount of disruption to lifestyle and allow for flexibility with food intake and choices. They also want medications that minimize the risk of diabetes-related complications, help avoid polypharmacy and eliminate the need for injections altogether (or for multiple daily injections). Several respondents hope future treatments will reverse or cure diabetes.

Below, respondents provided input on what they desire in new treatments, the improvements they'd like to see to therapies, and the impact these would have on daily life and overall quality of life:

"Hopefully easier attainment of targets, reduction of complication risks and less of a burden of disease."

"Improve diabetes control and health outcomes. I hope that these medications will be covered and available for all patients living with diabetes."

"Better control with only one daily injection."

"I wish it was more affordable for the masses and covered by FNIHB [First Nations and Inuit Health Branch, Health Canada] for First Nation patients."

"Manage diabetes effectively without needing such a large variety of medications."

“Cure [diabetes].”

“It would be nice to not have to take shots anymore. Would be nice to be able to just take pills again.”

“I am hoping that the newer drugs are approved quicker by my insurance company.”

“Overall better control - not just lower A1C but less hyper[glycemia] & hypo[glycemia] events. Weight neutral or decrease weight. Minimal side effects. Easy to take to improve compliance. Ability to be taken in combination with other med classes.”

“Expectations are that eventually there will be a medication that can be taken once a day that will help my pancreas produce the right amount of insulin to keep up with me (or possibly even cure the disease). I would hope that medications are made available to anyone living with diabetes and covered under by our government benefits.”

6. Experience With Drug Under Review

CADTH will carefully review the relevant scientific literature and clinical studies. We would like to hear from patients about their individual experiences with the new drug. This can help reviewers better understand how the drug under review meets the needs and preferences of patients, caregivers, and families.

How did patients have access to the drug under review (for example, clinical trials, private insurance)? Compared to any previous therapies patients have used, what were the benefits experienced? What were the disadvantages? How did the benefits and disadvantages impact the lives of patients, caregivers, and families? Consider side effects and if they were tolerated or how they were managed. Was the drug easier to use than previous therapies? If so, how? Are there subgroups of patients within this disease state for whom this drug is particularly helpful? In what ways?

Of those who participated in the January/February 2019 survey and answered the questions specific to insulin degludec+liraglutide (Xultophy) (n=5), no one reported taking the medication, either at the time of survey completion or in the past. However, 60% of respondents felt it is “somewhat beneficial” or “very beneficial” to have combination medications available for diabetes treatment (while 40% said they “don’t know”).

7. Companion Diagnostic Test

If the drug in review has a companion diagnostic, please comment. Companion diagnostics are laboratory tests that provide information essential for the safe and effective use of particular therapeutic drugs. They work by detecting specific biomarkers that predict more favourable responses to certain drugs. In practice, companion diagnostics can identify patients who are likely to benefit or experience harms from particular therapies, or monitor clinical responses to optimally guide treatment adjustments.

What are patient and caregiver experiences with the biomarker testing (companion diagnostic) associated with regarding the drug under review?

Insulin degludec+liraglutide (Xultophy) does not have a companion diagnostic, therefore this question is not applicable to our submission.

8. Anything Else?

Is there anything else specifically related to this drug review that CADTH reviewers or the expert committee should know?

Diabetes is a disease that requires intensive self-management. Diabetes Canada’s 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada highlight the importance of personalized care when it comes to the pharmacologic management of the condition. Specifically, after

initiating healthy behaviour measures, the guidelines recommend selecting diabetes treatment modalities based on a patient's degree of glycemic control and various other considerations. To achieve optimal blood glucose levels, individualization of therapy is essential. This includes careful consideration of medication selection, route of administration (oral, injection, infusion), frequency with which someone monitors blood glucose and adjusts dosage, benefits and risks that the patient experiences and/or tolerates, and lifestyle changes the patient is willing or able to make. Our survey responses reinforce the message that different people with diabetes require different medications/treatment modalities to help effectively manage their disease. Their unique clinical profile, preferences and tolerance of therapy should direct prescribers to the most appropriate choice and combination of treatments for disease management. Health-care providers must be supported in prescribing evidence-based therapies and, through public and private drug plans, patients should have access to a range of treatments that will allow them to optimize their health outcomes. For those paying out-of-pocket, costs should not be so high as to prohibit medication procurement.

Many people with diabetes hope for less dependence on medications. While current therapies have generally led to improvement for many people with diabetes in blood glucose and hemoglobin A1c control, respondents hope for even better, more affordable antihyperglycemic agents that they can access equitably, in a timely manner, and with good result to help them lead a normal life. Insulin degludec+liraglutide (Xultophy) may help people to achieve better glycemic control, which could potentially improve lives and save millions in direct health-care costs. For this reason, insulin degludec+liraglutide (Xultophy) should be an option for people living with diabetes.

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH CDR and pCODR programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

There was no assistance from outside Diabetes Canada to complete this submission.

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

There was no assistance from outside Diabetes Canada to collect or analyze data used in this submission.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	\$0 to 5,000	\$5,001 to 10,000	\$10,001 to 50,000	In Excess of \$50,000

Please find attached a list of organizations who have recently supported Diabetes Canada financially, along with the amounts provided.

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Ann Besner, MScA, RD, CDE
 Position: Manager, Research and Policy Analysis
 Patient Group: Diabetes Canada
 Date: February 21, 2019

Financial Contributions to Diabetes Canada (updated 2017)

Constituent/Name	Funder range (\$)
<i>AstraZeneca Canada Inc</i>	350,000+
<i>LifeScan Canada Ltd.</i>	350,000+
<i>Novo Nordisk Canada Inc</i>	350,000+
<i>Sanofi Canada</i>	350,000+
<i>Sun Life Financial</i>	350,000+
<i>Eli Lilly Canada Inc</i>	250,000-349,999
<i>Ascensia Diabetes Care</i>	175,000-249,999
<i>Janssen Inc</i>	175,000-249,999
<i>Medtronic Of Canada Ltd</i>	175,000-249,999
<i>Dairy Farmers Of Canada</i>	100,000-174,999
<i>Merck Canada Inc</i>	100,000-174,999
WEIGHT WATCHERS	100,000-174,999
<i>Abbott Diabetes Care</i>	50,000-99,999
<i>Canola Council Of Canada</i>	50,000-99,999
<i>Insulet Canada Corporation</i>	50,000-99,999
<i>Knight Therapeutics Inc.</i>	50,000-99,999
<i>Manulife Financial</i>	50,000-99,999
<i>Nestle Health Science</i>	50,000-99,999
<i>RBC Foundation</i>	50,000-99,999
<i>The Bank of Nova Scotia</i>	50,000-99,999
<i>Abbott Nutrition</i>	25,000-49,999
<i>BD Medical Diabetes Care</i>	25,000-49,999
<i>Beer Canada</i>	25,000-49,999
<i>Dexcom Canada</i>	25,000-49,999
<i>Dynacare</i>	25,000-49,999
<i>Heartland Food Products Group</i>	25,000-49,999
<i>McNeil Consumer Healthcare</i>	25,000-49,999
<i>Rexall Foundation</i>	25,000-49,999
<i>Roche Diabetes Care</i>	25,000-49,999
<i>SaskCanola</i>	25,000-49,999
<i>Auto Control Medical Inc</i>	5,000-24,999
<i>Bayer Pharmaceuticals</i>	5,000-24,999
<i>Boehringer Ingelheim (Canada) Ltd</i>	5,000-24,999
<i>Canadian Association of Optometrists</i>	5,000-24,999
<i>Canadian Produce Marketing Association</i>	5,000-24,999
CHICKEN FARMERS OF CANADA	5,000-24,999
<i>Edelman Canada</i>	5,000-24,999
<i>EOCI Pharmacomm Ltd.</i>	5,000-24,999
<i>Euro Harvest Bakery Wholesalers</i>	5,000-24,999
<i>Farleyco Marketing Inc</i>	5,000-24,999
<i>ForaCare Technology Canada Inc.</i>	5,000-24,999
<i>Holista Foods</i>	5,000-24,999
<i>InBody Canada</i>	5,000-24,999
<i>Innovative Medicines Canada</i>	5,000-24,999
<i>Ipsen</i>	5,000-24,999
<i>Jays Care Foundation</i>	5,000-24,999
<i>mdBriefCase Group Inc.</i>	5,000-24,999

<i>Montmed</i>	5,000-24,999
<i>Myelin & Associates</i>	5,000-24,999
<i>Novartis Pharmaceuticals Canada Inc</i>	5,000-24,999
<i>Ontario Pork Council</i>	5,000-24,999
<i>Original Energy Sales</i>	5,000-24,999
<i>Paladin Labs Inc</i>	5,000-24,999
<i>Pharmasave Drugs (National) Ltd</i>	5,000-24,999
<i>Prime Strategies Inc.</i>	5,000-24,999
<i>PULSE CANADA</i>	5,000-24,999
<i>Royal College Of Physicians And Surgeons Of Canada</i>	5,000-24,999
<i>Tykes Pharmaceuticals</i>	5,000-24,999
<i>Urban Poling Inc</i>	5,000-24,999
<i>Valeant Canada LP</i>	5,000-24,999
<i>VitalAire Canada Inc</i>	5,000-24,999