

## Patient Input Template for CADTH CDR and pCODR Programs

<b>Name of the Drug and Indication</b>	<b>Onabotulinum Type A (Botox)</b>
<b>Name of the Patient Group</b>	<b>Migraine Canada Migraine Québec</b>
<b>Author of the Submission</b>	<b>Elizabeth Leroux Beth Kidd</b>
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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.

Migraine Canada is a national patient organization (federal not-for-profit 1100214-7) with a mission to provide support and education as well as raise awareness about the impact of migraines. We advocate for optimal care for those living with migraines and support research to find a cure. Our work is carried out by our volunteer Board of Directors, consisting of patients and healthcare professionals.

We educate patients, caregivers and healthcare professionals by researching, developing and sharing electronic and print materials containing the most current migraine information. We drive awareness and education through our website, social media, workshops and forums. We provide patient support through participation in regional support groups, with more than 1,200 members of our Facebook page and by playing a role with various other online groups. We leverage traditional and social media to empower patients to share stories and experiences in order to advocate for the supports needed to live full and active lives while coping with migraines.

Website (English): [www.migrainecanada.org](http://www.migrainecanada.org)

Facebook (English): <https://www.facebook.com/migrainecanada/>

We partnered with this group for survey diffusion:

Website(French): [www.migrainequebec.com](http://www.migrainequebec.com)

Partage Migraine Québec (French, private)

<https://www.facebook.com/groups/312758085805229/>

## 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.

Data for this review has been obtained through two different surveys. Survey A was designed and analyzed by the volunteer Board members of Migraine Canada for the preparation of the CADTH patient report for Erenumab. Jonathan Guay from 3aLogic was contracted to put it online and extract the data.

As it was our first survey, we gathered a lot of epidemiological data. It was promoted on our Facebook community, shared on Migraine Canada's Twitter account and through migraine clinics in Canada. The survey was open online from June 4<sup>th</sup> to July 4<sup>th</sup>, 2018. A total of 597 patients participated in the survey. As Botox is indicated only for chronic migraine, we analyzed the subgroup of 251 patients suffering from chronic migraine (CM). In this group, 6% were aged <25 years, 35% were 26-39 years old, 43% 40-54 years old and 16% 55 years or older. 90% were female, which is representative of CM as female gender is a risk factor. 39% reported other significant health conditions than migraine. These patients had a long experience of migraine: 29% < 10 years; 33% 10-25%; and, 38% >25 years. Chronic migraine is defined by the frequency of the attack, but is also chronic in the sense of its persistence over many years.

Survey B was targeting patients with CM and receiving Botox treatments to answer questions regarding experience with this therapy. It was designed and analyzed by the volunteer Board members of Migraine Canada. Jonathan Guay from 3aLogic was contracted to put it online and extract the data. It was online on both Migraine Canada and Migraine Québec websites from September 24<sup>th</sup> to October 19<sup>th</sup>, 2018. It was promoted on both Facebook communities. There were 161 participants.

## 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?

**Migraines are not just headaches but a neurological disease.**

Migraines impact 1 billion people worldwide, or about 1 in 7 people. Migraine is most common between the ages of 25 and 55 but it can impact people of all ages including children but it affects three-times as many women as men. Migraines often present with severe, throbbing, recurring pain, usually on one side of the head (or both sides or no pain at all). Nausea, vomiting, dizziness, extreme sensitivity to sound, light, touch and smell, and tingling or numbness in the extremities or face are also common symptoms. About 25% of migraine sufferers also have a visual disturbance called an aura, which usually lasts less than an hour. Attacks usually last between 4 and 72 hours.

**Migraine is usually categorized according to particular accompanying symptoms (aura, vestibular, hemiplegic) but also according to monthly frequency of attacks.**

Episodic migraine refers to attacks occurring 14 days or less, and is now further separated in low-frequency (1-6 days) and high frequency (7-14 days). Chronic migraine is diagnosed when patients have 15 or more headache days per month. Chronic migraine affects 1-2% of population worldwide and is associated with more disability and co-morbidities. It is also associated with medication overuse headache (MOH), a complication of frequent use of acute treatments that induce even more frequent and intractable headaches. The estimated prevalence of MOH varies according to countries but is usually between 0.5% and 2% of the global population (GBD 2015). Medication overuse feeds the headache cycle and patients are trapped in a vicious cycle, unable to get adequate pain relief.

**There are two main states of life for a migraine patient: the active attack (ictal state) and in-between attacks (interictal state).**

During the attack itself, symptoms may prevent the person's ability to accomplish their tasks, work and interactions with others. The pain is at least moderate and often severe, throbbing and diffuse. The nausea and vomiting are obviously disruptive and may prevent oral medications efficiency. The sensory hypersensitivity forces many patients to isolate themselves in a dark room and stop all activities. Auras are neurological deficits that can accompany migraines (including loss of vision, speech, and sensation, even muscle strength) which can last for hours. Some migraines are also accompanied with dizziness, vertigo and loss of balance. Cognition is not normal during a migraine, with slowed thinking, lack of focus, and difficulty reading and speaking. This would disrupt most activities involving a computer or interacting with other people. A controlled migraine attack can be brief, but uncontrolled attacks may last multiple days in a row.

**Chronic migraine (CM) is a disabling condition, both for the personal and professional life.**

Using a new scale for disability, we obtained the following results:

Score		
0	I have no limitations	<1%
1	I avoid triggers, but otherwise I function well	2%

2	I miss some personal activities, but I don't miss work	9%
3	I miss work (including child care and home-making activities) on 1-2 days per month	13%
4	I miss work (including child care and home-making activities) on 3-4 days per month	9%
5	I miss work (including child care and home-making activities) on 5 or more days per month but I am still working full time	15%
6	I work part-time	6%
7	I am disabled (not working), but can still do some desired activities	19%
8	I am disabled (not working) and dependent on others for many activities of daily living	26%

Migraine patients' quality of life is also lowered during the interictal state. Survey respondents indicated in their comments that they fear the next attack, and have difficulty planning ahead. Migraine sufferers end up dreading potential triggers and limiting their activities (personal and professional) to either avoid an attack or avoid blame for having to cancel an activity.

- "I am always managing migraines, or living in a darkened room. I am currently not working because of migraine. Migraines are ruining my life."
- "My chronic daily migraine affects all of my relationships because I often have to cancel plans, miss holidays and decline participating in activities."
- "It is invisible. It is stigmatised. It isolates and diminishes you. Constant pain symptoms from migraine wear on the body and soul. You are trapped unable to escape or explain. Unable to live your life or enjoy simple moments."

**Chronic migraine (CM) has an impact on the family.**

Only 1% of participants said that CM has no impact on their family life. 29% reported a minor negative impact, 57% a major negative impact and 13% reported that CM was the main reason why they did not have a relationship of children. Quotes from participants include:

- "It puts a strain on my marriage, personal life with friends as well as my children have missed out on the joys from my down time when I suffer from a migraine. It maybe an invisible symptom but the repercussions are fully visible."
- "My husband is sometimes not present at family functions. This is difficult to explain to our children. There is a feeling of helplessness, and lack of control where scheduling life is concerned. We are at the mercy of these attacks."
- "Recently separated due to my inability to perform daily living activities and no predictability of how long I will be unable to participate in activities or to be able to plan ahead to future activities."

**Chronic migraine (CM) is associated with anxiety and depression.**

In our survey, only 7% of participants reported that migraine had no effect on their mood. 42% reported a mild effect and 51% a moderate or severe effect (requiring counselling and/or medications).

- “Chronic migraine has turned my wife's life upside down. She suffers with bouts of depression, anxiety and even suicidal thoughts. I can't even begin to imagine the pain she suffers on an almost daily basis.”
- “Migraine not only causes pain nausea and fatigue but it also causes mood swings and depression. The day after a migraine I am hungover from it. Not energetic or bright.”

**Migraine is an important cause of visits to the Emergency Department.**

15% of migraine patients will visit an emergency department (ED) for an intractable attack every year. In our survey, 41% of respondents had been to the ED four times or more since the beginning of their disease, and only 23% never went to the ED for a migraine. Most of those visits are difficult events, where migraine patients often feel stigmatized and blamed for wasting health care resources and the time of the health care providers.

**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).

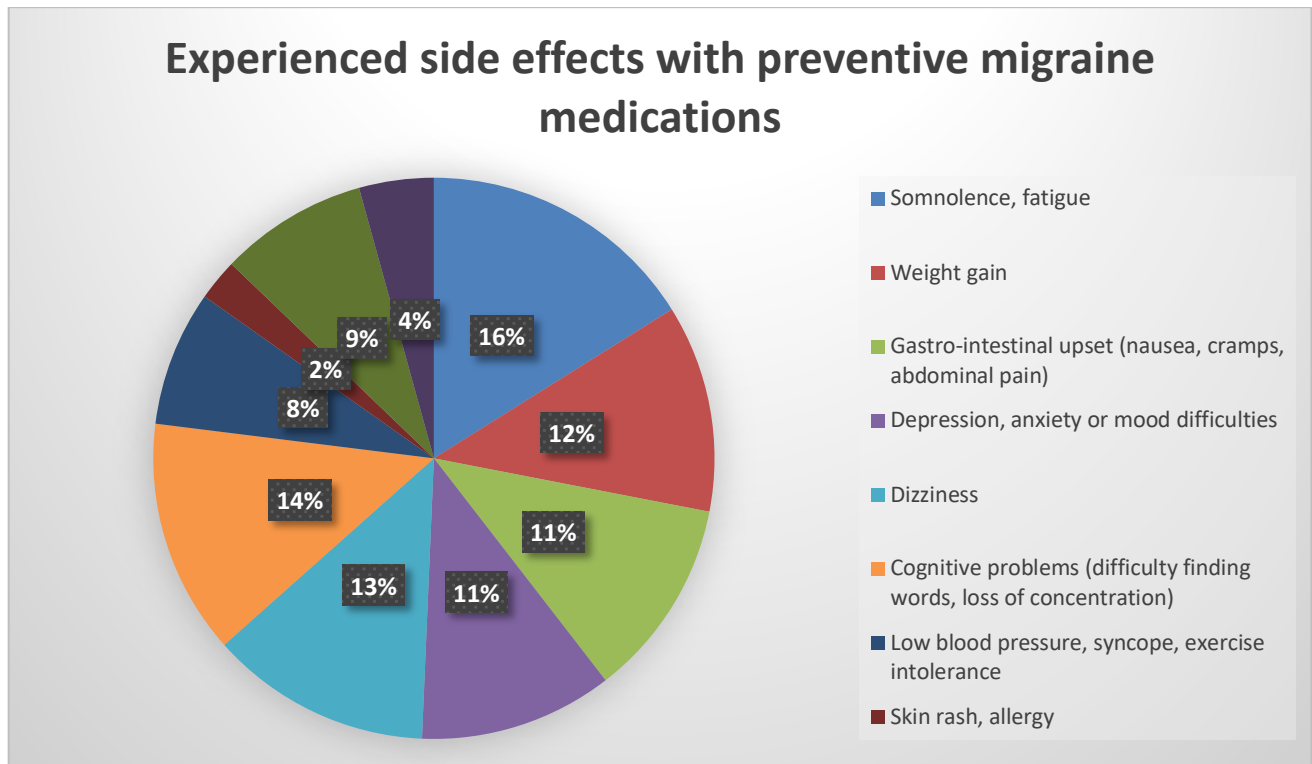
**Current available treatments for CM are insufficient and leave patients in a disabled state for years.**

Satisfaction for the care received by physicians is low: 16% were very dissatisfied; 46% said they were dissatisfied; and, 34% were satisfied. The care received overall at the time of the survey did not lead to major improvements. 38% reported no improvement at all while 51% reported a mild improvement. Only 6% reported a marked improvement and 5% reported a worsening. Patients seek relief with alternative therapies; 62% of participants had consulted five or more health care professionals besides their physician and 34% had consulted three or four. Patients try multiple medications with no success. In survey A, 71% of participants had tried five or more preventive medications. 85% stated that they had not yet found a preventive that was 50% or more effective. This means that only 15% of patients with CM currently found an effective preventive, despite multiple attempts. In Survey B, 65% had tried five preventives or more.

**Current available treatments for CM are poorly tolerated.**

In Survey A, 76% of participants reported that they had experienced side effects severe enough to lead to the discontinuation of the drug they were trying. 21% reported mild side effects and 3% no side effects. The hurdle race of migraine prevention may lead to somnolence, cognitive difficulties, weight gain, tremors, syncope, intolerance to exercise etc. In Survey B, 85% reported stopping at least one medication because of side effects, and 31% reported stopping four drugs or more because of side effects. Once again, we can see the hurdle race these

patients have to run to try to find relief, but positive results are not always present at the finish line.



## 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?

Efficacy is what matters the most (chosen first by 61% of patients) to survey respondents with safety and tolerability as close seconds (chosen as second most important by 39% and 30% respectively). The fact that a therapy is designed specifically for migraine came in last position. As illustrated in the survey feedback listed below, patients do not expect a cure but hope for a better quality of life.

- "Something that brings the frequency of the migraines down to manageable level (would be overjoyed with it coming down to one a week) and helps to stop the full migraine attack including predominantly/aura and postdrome symptoms."
- "Any preventive that could decrease my migraines from almost daily to 2 days per week (8 migraines per month) would be a huge success for me."

- “Anything that would give me relief enough to have somewhat of a normal life. It would be nice to be able to spend time with friends and family, to be able to look after myself and my home, to be able to go for walks and be able to enjoy the outdoors and sunshine.”
- “Something that allows me to live a relatively normal life, thus decreasing my dependence on medication or other life-altering prevention methods (avoiding triggers), and allows me to return to a fully contributing member of the workforce and in my relationships.”
- “I would be very grateful if I could either lower my monthly migraines by 3 or 4, and/or if I could more easily achieve 2 consecutive days in a month without a migraine, and/or if I could lower my use of abortive medications/Triptans by a couple doses a month.”

## 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?

We have utilized Survey B, responses from 151 patients receiving Botox therapy, to provide answers in this section. 27% of respondents used Botox for <1 year (recent trial), 46% used it for 1 to 5 years, and 7% used the treatment for 5-10 years. Surprisingly, 19% of participants did not answer this question. 75% of the injectors were neurologists (one could question if this is the best use of a neurologist as Botox injections could very probably be delegated to trained nurses.).

### **Botox therapy allows patients to endure less frequent headaches.**

Prior the initiation of Botox, patients had very frequent headaches: 15-19 days per month (22%); 20-29 days (41%); and, every day (35%). The severity of headaches in CM can vary from a mild baseline day to a very severe attack. With Botox therapy, patients reported a decrease in headache days: 32% had 1-9 days; 15% had 10-15 days (frequent episodic migraine); 41% had 15-29 days; and, 11% were still experiencing daily headaches.

### **Botox may help patients decrease their medication use -- including opioids.**

Patients reported that Botox allowed them to use less acute medication, which is an important goal in migraine therapy: 20% used 25% less medication; 32% used 50% less; and, 22% used

75% less (major improvement). Before Botox, 21% of participants reported that they were using opioids mostly for migraine and 12% for migraine and co-morbid pains.

Reported opioids use included: every day or almost (38% of users); 10-20 days per month (35%); and, less than 10 days per month (27%, in theory below the threshold for medication overuse). Botox helped an impressive 50% of users to completely stop opioids or use them very rarely. 12% were still using opioids less than 10 days per month while 20% were still using them 10-20 days and 18% were still using them daily (possibly patients who were using them for other pain).

**Botox improves the quality of life and the ability to work. It has a good tolerability profile.**

We asked participants to evaluate the impact of Botox on their overall quality of life. 34% reported a major impact, 35% a moderate impact, 16% a minor impact and 12% no impact. 3% reported a negative impact, presumably because of side effects.

16% of patients reported some side effects, but 84% did not report any side effects, and according to the comments of patients, they were representative of published evidence (minor cosmetic, neck pain, transient increase in headache or neck pain prior to improvement).

15% of participants reported that they were disabled and could go back to part-time or full-time work after using Botox. 37% reported that they were missing less work days after treatment.

**Botox may be sufficient as the only preventive, but is sometimes combined with oral preventives.**

In Survey B, 42% of patients reported that Botox was their only current preventive treatment. 26% of patients were able to stop preventives after the initiation of Botox. 33% did combine Botox with another preventive and 25% were using Botox in combination with two or more preventives. It is important to note that, chronic migraine can be a refractory condition requiring combination therapy.

**Botox makes the remaining attacks easier to treat.**

For patients suffering from CM, it is very important to be able to treat attacks, even if their frequency has decreased. 45% of participants found that their remaining attacks were a little easier to control, and 34% stated they were much easier to control. This is an important factor to reduce the burden of CM.

**Botox seems to be a long term therapy for CM.**

We asked patients if they had ever tried to stop Botox over the course of their treatments. Some patients reported a recurrence of migraine. Patients who answered this question also seemed to be non responders who stopped it for lack of efficacy.

- “I have tried to stop Botox twice, and both times headaches returned to original severity.”
- “Yes. I experienced a return of chronic migraine.”
- “I have tried to lengthen the time between injections from 3 months to 4 or 5 months, but the pain and other symptoms were too difficult to deal with.”



In conclusion, we asked patients to write down what they would tell a migraine patient who is considering Botox therapy. Comments include:

- “Anything is worth trying to stop the constant interruptions to my life and pain. It helped with intensity for me.”
- “Try it. It’s a miracle and will allow you to start enjoying your life again.”
- “It was life changing for me for the better, try it, no side effects and so much relief!”
- “It's worth it. It reduced my headaches by roughly 35-50%. The higher percentage arises if more is put into the forehead for me. This also reduced my dependency on relpax.”
- “I understand it doesn't work for everyone, but given that there are virtually zero side effects that I've experienced, I would encourage ANYONE with chronic migraine to at least give it a try.”

## 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.

There is no companion test for migraine or Botox therapy. At present time, we are lacking a biomarker or imaging marker for chronic migraine.

## 8. Anything Else?

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

We have a significant concern that public access to Botox is limited in part because migraine is stigmatized and unrecognized. As stated in the World Health Organization’s *Atlas of Headache Disorders and Resources*, migraine patients are under-diagnosed and under-treated. Migraine is a severely neglected chronic illness in comparison to other diseases, such as diabetes, epilepsy or multiple sclerosis, and is associated to significant years lost to disability. Despite all this, it is neglected in medical training and there are very few specialized headache clinics in Canada.

## 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.

Migraine Canada received funding from Allergan for a variety of projects. It was primarily used to pay our contractant 3aLogic for the online survey and the production of its results.

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.

Our patient survey was posted online by our webmaster Jonathan Guay from 3aLogic. He also collected and collated our raw survey data however, Migraine Canada assessed the results.

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
Allergan via Canadian Headache Society			X	
Eli Lilly Canada via Canadian Headache Society			X	
Novartis Canada via Canadian Headache Society			X	

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: Beth Kidd

Position: Board of Directors member

Patient Group: Migraine Canada

Date: November 12, 2018