



Common Drug Review *Patient Group Input Submissions*

propiverine hydrochloride (Mictoryl) for overactive bladder

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

The Canadian Continence Foundation — permission granted to post.

CADTH received patient group input for this review on or before October 31, 2016.

CADTH posts all patient input submissions to the Common Drug Review received on or after February 1, 2014 for which permission has been given by the submitter.

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.

The Canadian Continence Foundation

Section 1 — General Information

Name of the drug CADTH is reviewing and indication(s) of interest	Propiverine hydrocholride
Name of the patient group	The Canadian Continence Foundation
Name of the primary contact for this submission:	██████████
Position or title with patient group	██████████
Email	████████████████████
Telephone number(s)	██████████
Name of author (if different)	
Patient group's contact information: Email	████████████████████
Telephone	(705) 750-4600
Address	P.O. Box 417 Peterborough, Ontario K9J 6Z3
Website	www.canadiancontinence.ca

1.1 Submitting Organization

Founded in 1986, The Canadian Continence Foundation (formerly The Simon Foundation for Continence Canada) is the only national non-profit organization serving the interests of people experiencing incontinence. The organization is lead by people with incontinence and by professionals from all health disciplines. The Canadian Continence Foundation (TCCF) is supported by donations from the public, healthcare professionals and private industry.

The mission of TCCF is to enhance the quality of life for people experiencing incontinence by helping them and/or their caregivers to confidently seek and access cures and treatment options. To this end, TCCF will implement and encourage important public and professional education, support, advocacy and research to advance incontinence treatment and/or management.

The Canadian Continence Foundation offers a wealth of information on incontinence. Books, factsheets and newsletters are available. We operate a toll free number at 1-800- 265- 9575. Each year the Canadian Continence Foundation responds to thousands of requests for information and education from people experiencing incontinence, healthcare professionals, and industry.

TCCF interacts with the media to increase public awareness and knowledge of incontinence and to encourage people to seek help. It also provides individuals with lists of specialists in their local area. TCCF initiated and now coordinates *Incontinence Awareness Month* in November of each year, promoting public and professional awareness-building and educational activities about incontinence around the country.

The Canadian Continence Foundation encourages and supports research to advance incontinence management/treatment.

1.2 Conflict of Interest Declarations

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

The Canadian Continence Foundation has multiple sources of funding for programs and operations, and is supported by individual and corporate donations. Funding sources include: donations from individuals, healthcare professionals, and industry. TCCF does not receive any government funding.

Our relationship and interactions with pharmaceutical companies remains as transparent as possible and policy positions of the TCCF are developed with input from a large number of stakeholders. Corporate relationships are ongoing with the intention of achieving TCCF goals as they relate to patient support and education.

TCCF has currently received both restricted and unrestricted educational grants from the following health care companies: Astellas, Pfizer, 3M, Tena - a Personal Care brand by SCA, Laborie, and My Liberty Life. These corporate sponsors are disclosed on The Canadian Continence Foundation's website.

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

No conflicts.

Section 2 — Condition and Current Therapy Information

2.1 Information Gathering

The information contained herein was obtained through an online survey of approximately 120 quantitative questions. The survey was active on The Canadian Continence Foundation website and social media platforms between June 2016 and August 2016 and was completed by 21 respondents. The online survey was an update of two surveys conducted and revised between March 2013 and May 2014, which was completed by 169 respondents. The national survey was available in French and English.

Additional information was gathered through one-on-one 45-minute telephone interviews with three patients between September 2016 and October 2016, as well as additional, informal discussions with six patients between June 2016 and August 2016.

2.2 Impact of Condition on Patients

As described in TCCF's previous patient input submissions in April 2013 and June 2014, incontinence is described as involuntary loss of urine. Overactive bladder (OAB), one of the causes of incontinence and troublesome lower urinary tract symptoms, affects approximately 15 per cent of the Canadian adult population. Symptoms include urgency (*an urgent sensation to empty the bladder which is difficult to defer*), usually with frequency (*8 or more voids per 24 hours*) and nocturia (*one or more void during the night*), with or without urgency incontinence (*leakage of urine usually associated with urinary urgency*)

Unfortunately, OAB /urgency incontinence is associated with significant social isolation, stigma, and a marked impairment in quality of life, often causing patients to be very private about their condition and symptoms. For those of working age OAB /urgency incontinence is associated with reduced workplace

productivity and increased absence from work. Very few people will talk to their doctor about their experiences and almost all of them will hide the condition from their family and friends. According to the Canadian Urinary Bladder Survey, 16 per cent of men and 33 per cent of women over the age of 40 have symptoms of urinary incontinence (UI), but only 26 per cent have discussed it with their doctor and this is a conservative estimate. A recent epidemiological survey that TCCF conducted in 2013 found that 36 per cent of community dwelling women suffer from UI. This is further supported by a 2008 OHTAC report, where incontinence was noted as one in four major predictors for Long Term Care (LTC) admissions: falls and fall-related injuries, urinary incontinence, dementia, and social isolation. Incontinence also plays a significant role in the remaining three conditions.

As it pertains to overactive bladder, the aspects of this condition that are most important to control are urinary urgency and involuntary leakage of urine.

All patients surveyed and interviewed experienced symptoms and problems related to overactive bladder, all of which affected their day-to-day living. In almost all cases, these symptoms and problems required limiting or modifying daily activities, such as not leaving the house as often as they would like (leading to isolation and depression), modifying diet and limiting drinking water and other beverages, planning trips to the bathroom, getting up in the night (also leading to sleep deprivation), and wearing incontinence pads to prevent leaking.

Some of the pertinent survey responses from patients living with overactive bladder include the following:

- 71.4% of respondents felt that incontinence / overactive bladder has either a very strong or strong impact on their quality of life. Through the individual patient interviews and discussions, the effect on quality of life and well being includes isolation, embarrassment of living with incontinence / OAB, secrecy or having to hide their symptoms as well as the stains / wetting on their clothes, impact at work (having to explain why they are using the bathroom so often and nocturnal voiding leading to tiredness and disorientation. All patients interviewed said they experienced urinary urgency and urgency incontinence. This was by far the most significant issue that affected their quality of life.
- In the Canadian Continence Foundation Patient Experience Survey, 33.3% of respondents told us that the embarrassment /stigma of living with incontinence and/or OAB had the most severe impact on their quality of life. An additional 33% responded that having to wear incontinence underwear had the most severe impact on their quality of life.
- Managing overactive bladder also has financial consequences, with 35% of patients saying that buying incontinence supplies, such as pads or incontinence underwear, is quite costly. During the individual interviews, one patient described how she had to quit her job because of the impact incontinence was having on relationships with her colleagues at work. Her co-workers felt she was “lazy” and “not efficient or productive in her job” because she was constantly going to the bathroom.
- During the patient interviews and discussions, a common theme that occurred was family relationships. All patients interviewed mentioned their incontinence / OAB had an impact on family vacations, outings and/or daily family interactions. Because of the constant concern of having to be near a bathroom, long trips requiring many hours of driving were out of the question. Similarly, flying was a concern, because of the potential lack of access to a bathroom; with only two bathrooms to serve a full plane, this could lead to line-ups and an increased likelihood of incontinence. With nowhere to go following an accident, a potential incident could lead to hours on a plane with wetness and/or odour, which is a situation many respondents prefer to avoid. From a

family perspective, the most significant impact was seen through spousal interaction and sexual activity. All patients interviewed stated a noticeable decline in sexual activity and a reduction in physical interaction with their spouses. The reason for this decline was the impact on self-esteem and perception; a feeling that their incontinence made them less sexually appealing and “gross to touch”.

2.3 Patients’ Experiences With Current Therapy

All surveyed patients, both through the quantitative survey and the qualitative interviews, were using some form of pharmacotherapy to treat their overactive bladder / incontinence (Myrbetriq, Detrol, Vesicare and oxybutynin were most frequently mentioned), as well as some form of behavioural modification and/or physiotherapy. One patient had undergone surgery only to find symptoms returning over time. In most cases, patients said the treatments were not effective at controlling their symptoms and often, side effects such as constipation and dry mouth, led to concerns over tolerability and affected willingness to continue with the prescribed medications. The most frequently mentioned side effects of current treatments by respondents in the patient survey were dry mouth (38.1 per cent) and dizziness (14.3 per cent)

- Approximately two-thirds of respondents reported trying at least one medication in the past year. Of those that tried medical therapy, 35.7% had tried two medications and 35.7% tried three. This is indicative of the “cycling” of medications patients go through to find a treatment that works and is tolerable for them.
- Of those patients who have tried more than three medications in the past year, 28.6% reported that cycling through treatments was extremely disruptive as they hated having to change treatments; an additional 21.4% reported the impact of cycling treatments as somewhat significant as they don’t like changing treatments but they do so anyway.
- Although most of the treatments used are in the same class of medications (anti-muscarinics), 38.1% of respondents felt there was some difference between medications. The individual interviews qualified this further. Three patients stated that medical therapy for incontinence / OAB “is not a one-size-fits all proposition” and “what may work for one patient, won’t necessarily work for another patient”
- From an unmet need perspective, the following is a list provided by the respondents of the most significant unmet needs for OAB / incontinence:
 - Medications that work (52.4%)
 - Medications with no side effects (42.9%)
 - Education materials and resources (38.1%)
 - Public awareness (to decrease the stigma around the disease) (38.1%)
 - Access to publicly reimbursed medications, access to holistic treatment options and peer support, each (33%)

It is important to note that, while propiverine has been readily available and used quite extensively in Europe for over 30 years, it has never been available nor used in Canada.

2.4 Impact on Caregivers

The impact of overactive bladder can be just as significant on caregivers as on the patient. Below are some of the key findings from the quantitative research conducted between October 2014 and October 2016.

- Half of caregivers are getting up often or always during the night when their family member goes to the bathroom.

- Over half of caregivers often or always have to help eliminate odours or clean up after “accidents”, including doing laundry frequently or often needing to change their bed linens.
- Half of caregivers often or always have to help get their family member to the bathroom on time, and this can be a challenge, particularly when their spouse has other chronic conditions that limit mobility such as a stroke.
- One patient who lives with her daughter and family described that the family have to adjust to her frequent stops to urinate, and that her grandchildren tell her she uses the bathroom more often than they do. The patient finds this embarrassing and feels bad that her need to use the bathroom so often affects everyone in the family.
- Another patient said her husband is now used to taking much longer trips as a result of frequent stops to the bathroom.
- Most patients said their spouses, families, or caregivers are all very understanding and accommodating, but they still feel bad about having everyone adjust to the issues of managing overactive bladder. A few patients interviewed indicated that their family members feel that they may be exaggerating their symptoms and made comments like they “should be able to hold it”.

Section 3 — Information about the Drug Being Reviewed

3.1 Information Gathering

A literature search on PubMed for clinical trials involving the propiverine extended release formulation, including a comparative network meta-analysis on adverse events was performed. One of the authors has previous experience of use of the drug in Europe; this added to the experience presented in Section 3.2a).

The manufacturer’s SmPC for propiverine was also reviewed.

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

Propiverine is a relatively old compound, but the extended release formulation proposed for introduction to Canada here is a more recent development. The once daily formulation will have benefits for patients in terms of their ability to adhere to medication {Scand J Urol. 2014 Feb;48(1):79-83) and, in terms of tolerability. The extended release formulation’s absorption is also not affected by food intake – making dosing easier.

Propiverine has been subject to efficacy and safety / tolerability trials in adults with OAB / UUI, adults with spinal cord injury, men with a combination of storage and voiding lower urinary tract symptoms and children with OAB / UUI. Propiverine has been found effective in controlling all disease related symptoms of OAB (urinary frequency / urgency and urgency incontinence) in studies up to 12 weeks in length (the standard trial length in this area), with a similar frequency of all adverse events to tolterodine. Propiverine in one recent study was associated with fewer adverse events than tolterodine, thus avoiding the need for patients taking propiverine to stop therapy because of tolerability.

The efficacy of propiverine extended release has been assessed in combination with alpha blockers in men in trials lasting up to 1 year in length. Propiverine has, under these circumstances, been shown to be effective in OAB symptom improvement over this time.

In a recent meta-analysis, published in 2015, examining the results of 9 randomised, controlled trials, propiverine treatment resulted in a decrease in the number of micturitions/24 (mean decrease 1.80 to 2.57) statistically significantly more effective than placebo. Propiverine also decreased the number of urgency, urgency incontinence, and nocturia episodes and increased urine volume per void.

The occurrence of difficulty in voiding was higher with propiverine therapy compared with the placebo (mean percentage 0.34 to 4.93 %).

Drawing from NICE in the UK, propiverine extended release has also been shown to be cost effective in the UK healthcare system, allowing it to be one of the recommended treatment options for the NICE guidelines for treatment of OAB /UUI in women (2013).

In comparative studies propiverine results in less dry mouth than oxybutynin, an adverse effect that often leads to discontinuation. In children and adolescents with OAB/ UUI and those with neurological problems, propiverine was generally more effective and better tolerated than oxybutynin. Propiverine may also be an effective agent onto which to swap a patient if the first chosen agent has failed to result in the desired impact on symptoms or has proven intolerable (Adv Urol. 2011; 2011: 714978).

From a clinical perspective, propiverine is a useful drug of similar efficacy to those already available in Canada but with a different side effect profile. This makes it a useful addition to the armamentarium of medications available for this condition where adherence is a challenge. There are data for its use as both a primary treatment and after failure of a first line agent. Previous use has largely been gained in a UK population where, in clinical practice, it was efficacious and chosen as the most suitable drug for some patients. As the patients note, one drug does not fit all. There are still large unmet needs in this disease area. Propiverine helps to fill that gap.