

CADTH COMMON DRUG REVIEW

# Patient Group Input Submissions

**APOMORPHINE HYDROCHLORIDE (MOVAPO)**

(Paladin Labs Inc.)

**Indication: Parkinson's disease**

CADTH received patient input for this review from:

Parkinson Canada

Parkinson Society British Columbia

On or before July 27, 2017

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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.

## 1. About Your Patient Group

Parkinson Canada provides support services and education to people living with Parkinson's disease, their families, and the health care professionals who treat them.

Operating since 1965, the organization advocates on issues that concern the Parkinson's community in Canada. The Parkinson Canada Research Program funds innovative research for better treatments and a cure.

A national registered charity, Parkinson Canada fulfils its mission through the generosity of donors and is an accredited organization under the Imagine Canada Standards Program.

[www.parkinson.ca](http://www.parkinson.ca)

## 2. Information Gathering

Parkinson Canada gathered perspectives from the Parkinson's community by conducting an online survey that was distributed across Canada and internationally. 863 responses were gathered between June 28, 2017 to July 17, 2017. The vast majority of responses were gathered from Canada with the following breakdown:

53 per cent from Ontario; 12 per cent from Quebec; 11 per cent from Manitoba; 9 per cent from British Columbia; 5 per cent from Atlantic Canada; 4 per cent from Alberta; 3 per cent from Saskatchewan; Less than 1 per cent from the territories; and less than 3 per cent of the responses were gathered internationally from people in the United States and Europe.

61 percent (526) of respondents are people with Parkinson's disease and 39 per cent (337) are caregivers of people with Parkinson's disease.

In terms of gender, 52 per cent identified as female, 48 percent identified as male, and less than 1 percent identified as a gender other than female or male.

42 per cent of respondents are between the ages of 65-74. This is followed by 23 per cent between the ages of 55-64, 17 per cent between the ages of 75-84, and nearly 10 per cent are 45-54, nearly six per cent were under the age of 53, and three per cent were over the age of 85.

63 per cent of respondents are retired. This is followed by 16 per cent who are working full-time. Eight per cent are working part-time or on disability respectively. The remaining respondents are home full time, volunteers, students or looking for work.

Parkinson Canada has gathered information from five patients who have experience using apomorphine. Four were gathered from our survey responses and one was provided via an email exchange with Parkinson Canada staff directly.

## 3. Disease Experience

From Parkinson Canada's survey results, overwhelmingly people with Parkinson's describe the "loss of confidence" that they have experienced since developing Parkinson's disease and the impact that has on their daily life:

*"It is increasingly more challenging to manage care of myself, dog, & home. Also attending the local Parkinson's exercise group, and other activities is becoming more limited.*

*Because of my Parkinson's tremor, even with medication, I have lost my confidence in any social situations where food is served, and so no longer want to participate in these activities."*

This "loss of confidence" reported is in large part due medication "wearing off". Medication "wearing off" also described as "off times". This is when the effectiveness of medication stops causing a resurgence of motor and non-motor Parkinson's symptoms (e.g. freezing episodes, tremor, mood swings, panic attacks etc.). For some people there is a certain degree of predictability to "off times", but for many these fluctuations are unpredictable.

*“My father’s quality of life has been impacted and that’s what has been most difficult. He has to plan his day and time out of the house based on his [sic] medication schedule because he can’t be out when the meds start to wear off and he gets stiff. This makes it difficult for him to enjoy time with family”.*

Nearly 40 per cent of respondents specifically mentioned that Parkinson’s has negatively impacted their ability to socialize and maintain relationships because they have had to stop engaging in recreational activities (e.g. sport) or family life:

*“I have a hard time with all aspects of daily life (recreational, meal prep, have to cancel planned activities with family and friends) because of the following: very low energy, fall asleep unexpectedly, emotional, difficulty walking for prolong period, hard time moving my body at night in bed.”*

*“Loss of independence in many areas including driving a car, relationships, social interactions, reading and writing.”*

Nearly 10 per cent of respondents discussed having to leave the workforce or reduce hours due to Parkinson’s:

*“I had to go on disability and stop working, which made me sad and also put more stress on my husband as he became the sole supporter of our family.”*

In addition to the ability to maintain relationships, many survey respondents also discussed their loss of independence citing challenges in doing household chores and getting dressed.

People with Parkinson’s who report being able to maintain relationships and engage in daily activities often reported slowness and balance issues as being a challenge to their participation. It is important to understand that Parkinson’s is a progressive disease causing abilities to change and making participation in daily activities increasingly more difficult overtime.

Survey respondents ranked the following symptoms of Parkinson’s as most important to control: slowness and stiffness, impaired balance, cognitive changes and memory, and rigidity of the muscles.

Survey respondents who are caregivers most often reported a lack of time due to the demands of caring for a person with Parkinson’s. This lack of time creates a challenge for maintaining social and/or recreational activities. Caregivers also discussed that the loss of confidence being experienced by the person they care for (due to “off times”) as being a barrier to engaging in social or daily activities with the person they care for:

*“The disease has a direct impact on every aspect of life for the caregiver. As the symptoms develop and increase in severity, everything becomes unpredictable. Managing household chores, planning for the day’s and week’s activities, etc. all become difficult. The stress takes its toll on the caregiver...”*

#### 4. Experiences With Currently Available Treatments

There are a wide number of symptomatic treatments that are available for Parkinson’s disease. These include medications (e.g. levodopa carbidopa), surgical procedures (e.g. Deep Brain Stimulation), and other forms of therapy (e.g. physiotherapy, occupational therapy, speech therapy, exercise) and psychological follow up. All of these treatments can have a significant impact on improving an individual’s quality of life and should be available. However, an individual with Parkinson’s becomes more reliant on their medication to maintain their ability to function as the disease progresses, and dosage has to be increased over time, for as long as possible. A balance between the side effects of the medication and the benefit often becomes more difficult with time. Medication schedules become more complex and the timing of when medications are given becomes crucial.

The benefit to taking medications can be a return to regular daily living activities and functionality:

*“Every morning it takes an hour for my multiple medications to take effect, so that I can perform activities at a comfortable pace such as dressing and meal preparation. The effect of my medications wears off within 2 1/2 hours, causing very painful foot dystonia two to three times a day.”*

However, 67 per cent of survey respondents have experienced side effects when taking medications to manage their Parkinson’s. The most reported side effects, according to survey respondents, are disturbed sleep, nausea, constipation, dyskinesia, fatigue and hallucinations.

14 per cent of survey respondents have experienced difficulty in accessing treatments for Parkinson's disease. The following challenges are reported: wait times to see a physician to have medication prescribed or adjusted; transportation and travel to receive treatment; insurance requirements to receive a branded medication over the generic; cost; and drug shortages.

*"Cost, constantly traveling to drug store to pick up something as the insurance company only releases the coverage dependent of the individual cost. Very frustrating to have to drive back and forth 4 x to get the pills I need for my husband every month."*

The most common reported difficulties in receiving treatment from survey respondents are swallowing, remembering to take medication, and timing their medication with meals.

## Swallowing

Difficulty in swallowing is present in many people with Parkinson's. The reason for this difficulty is a prolongation of the triggering of the swallowing reflex, a reduced rate of swallowing, and slowness of sequential muscle movements.

## Remembering to take medication

The daily medication regimen for individuals with Parkinson's can be complicated. As Parkinson's progresses many individuals have to take more types of medication, adjust dosing and increase the frequency of taking medication. In addition to this, the majority of people with Parkinson's will experience some degree of cognitive changes with 30 per cent having dementia.

## Medication and meals

The medication levodopa (currently the gold standard in treating Parkinson's disease) is a protein building block, so it competes for absorption with other proteins. Eating a meal high in protein reduces the likelihood of effectively absorbing levodopa; therefore meals need to be timed and/or adjusted to ensure medication is properly absorbed.

*"Frequency and timing in conjunction with meals. Nobody with Parkinson's moves quickly and many have difficulty swallowing . A half hour window in which to eat, so that protein does not interfere with the Levodopa is impossible to realize and causes stress for the person with Parkinson's and for the caregiver."*

## 5. Improved Outcomes

Survey respondents indicated many improvements that they would like to see from new treatments that are not currently achieved. Frequently reported is the need for longer lasting medications that limit or eliminate "off times". Apomorphine offers a rescue to the "off times" and would provide increased confidence and security for people, especially when they are leaving their home or participating in social outings. This has the potential to help reduce the isolation and fears that many people with Parkinson's have described regarding "off times".

*"I am tired of the unpredictability of my current meds regime and having several times per day when I am not feeling well".*

There is also an expressed need for medications that provide overall better symptom control with less side effects:

*"Control of hallucinations and elimination of off times. If these symptoms were controlled I would hope to have a much more normal lifestyle".*

The described improvements would restore quality of life by allowing the freedom to make plans without fear of an "off time" resulting in loss of ability to function:

*"To be able to go out and stay out for awhile, that he would last a little longer on an outing. We do not go out on planned outings"*

*"Medication that takes more rapid effect, does not lose it's effectiveness before the next dose is due (effectiveness wears off), and is more effective in treating inertia (freezing) and inability to walk; also medication to permit intelligible and normal speech. These improvements would enable more normal mobility and communication with family and others."*

Overall, 70 per cent of survey respondents have experienced "off" periods with their medication regime.

*“Parkinson disease, even on the best of days, severely limits ones daily activity. Off-periods bring everything to a halt and are disorienting and uncomfortable. Adding extra functionality to a day makes a significant difference when one has only a few hours to begin with.”*

Side effects are definitely a major consideration and concern for people with Parkinson’s and caregivers before starting a new treatment. Survey respondents indicated that the benefits versus potential side effects would need to be carefully weighed before starting any new medication.

## 6. Experience With Drug Under Review

Parkinson Canada has connected with five people with Parkinson’s who are using apomorphine. They have accessed this drug through public coverage in their respective jurisdictions or by participating in clinical trials.

### Patient #1 from Ontario

- Uses the injectable pen and reports it is easy to administer and not more difficult than administering other medications for Parkinson’s
- Has experienced nausea and vomiting as side effect, but reports that it is not difficult to manage the side effects
- Reports that injectable apomorphine helps with end of dose “wearing off” and claims it has improved quality of life

### Patient #2 from Quebec

- Uses apomorphine by injection and reports it is moderately easy to administer, but more difficult to use than other medications to treat Parkinson’s
- Has experienced nausea and vomiting and confusion as side effects, but report that they “wait it out”
- Reports that injection of apomorphine helps with end of dose “wearing off” and claims it has improved quality of life

### Patient #3 from France

- Uses the injectable pen and reports it is easy to administer, but finds that although it is easy to administer it is more difficult to use than other medications to treat Parkinson’s
- Has experienced dyskinesia as a side effect that is difficult to manage
- Reports that the injectable pen helps with unpredictable “off” times and claims it has improved quality of life

### Patient #4 from France

- Uses the injectable pen and reports it is easy to administer, but finds that although it is easy to administer it is more difficult to use than other medications to treat Parkinson’s
- Has experienced drowsiness or falling asleep, dyskinesia and pain in joints as side effects that are very difficult to manage
- Reports that the injectable pen did not improve quality of life and resulted in this patient stopping the drug

### Patient #5 from Sweden

- Used the apomorphine injectable pen and is now using the pump (based on information received from Spain if a patient gets to the maximum allowable daily amount of apomorphine they become a candidate to receive the drug in pump form) . She claims that both have been “life changing” for her.  
*“Life is good, but when I'm stuck, locked in my own body, helpless and sad. When I can't communicate with the outside world - if that's the way it will be, I do not really want to live. But even from the darkest moments, the rebirth is "halleluja moment" when the rigidity disappears and life returns and it's good to live again”.*

Patient evidence was also gathered from a friend of a person in the US who has reported an improved quality of life and better management of symptoms using apomorphine via pump.

## 7. Anything Else?

People with Parkinson’s need access to a variety of options to ensure they can be on a treatment regimen that offers the best possible control of their unique set of symptoms and an improved quality of life. The unpredictability of the disease and loss of confidence and independence that one experiences due to this unpredictability is forcing people with Parkinson’s to withdraw from normal activities too soon (e.g. work, travel, daily chores, maintaining relationships etc.). Many people with Parkinson’s report anxiety

and excessive worry over the inability to appropriately control their symptoms on a continuous or predictable basis. Overall this causes a breakdown in relationships resulting in isolation.

Furthermore, survey respondents reported it would be a significant financial burden if they did not have coverage to help with their drug costs. As discussed earlier, many people with Parkinson's and caregivers report having to leave the workforce early or reduce hours due to the progression of the disease. This limit of incoming resources coupled with increasing expenses for travel to appointments for follow-up/treatment and any incurring drug costs causes a great amount of additional stress and strain on families.

When a disease is as life limiting as Parkinson's it is essential to provide coverage to ensure treatments are affordable and accessible for all who need it.

## Appendix: Patient Group Conflict of Interest Declaration

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

No. We requested help from other Parkinson organizations in order to get input from patients in jurisdictions outside of Canada. There was no exchange of funds for this partnership.

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.

No.

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
N/A				
N/A				
N/A				

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: Jacquie Micallef

Position: Sr. Manager, Public Affairs and Partnerships

Patient Group: Parkinson Canada

Date: July 27, 2017



## 1. About Your Patient Group

Established in 1969, Parkinson Society British Columbia (PSBC) is a non-profit organization governed by a volunteer Board of Directors. The Society receives no government funding and is supported entirely by donations from individuals, members, corporations, foundations and the dedicated efforts of volunteers.

We believe that every person touched by Parkinson's deserves to know that they are not alone in their journey. We are here for the person with Parkinson's, their care partners, family and friends. Our friendly and knowledgeable staff is committed to offering support, sharing reliable information and raising funds for programs and research.

<https://www.parkinson.bc.ca/>

## 2. Information Gathering

Please see the survey results in Parkinson Canada's submission as British Columbians participated in their survey.

PSBC also contacted Parkinson UK and the National Parkinson Society (NPF), USA.

Apokyn (Apomorphine) has been approved for use with Parkinson's patients in the USA since April, 2004. NPF's experience with people using Apokyn was collected from their 1-800 information and referral service as well as online blog, July 2017s. See Appendix A.

PSBC also consulted with Dr. Andrew Lees, UK. Andrew John Lees is Professor of Neurology at the National Hospital for Neurology and Neurosurgery, Queen Square, London and University College London. In 2011 he was named as the world's most highly cited Parkinson's disease researcher.

Dr. Lees was responsible for the introduction of [apomorphine](#) in Britain to treat advanced complications of [Parkinson's disease](#) including [L-dopa](#) induced refractory off periods and [dyskinesias](#).

<http://www.ucl.ac.uk/ukpdc/co-investigators/andrew-lees>

Dr. Lees strongly endorses the availability of apomorphine to patients. Following is an e-mail he wrote to PSBC, July 6, 2017:

*"Apomorphine is what is known in the industry as a mature product which means there is no patent and therefore no protection and no profit. It should cost no more than a few bucks a week to treat a patient with the pump but even in England where it was resurrected as an important therapy for advanced disease in the late 1980s it costs about 5000 pounds a year to treat a patient with the pump.*

*The drug is as powerful as L-DOPA but perhaps because of its unfortunate name ( it is not a narcotic) and the need for injection it has been slow to spread round the world. Nevertheless there are 42 countries where it is licensed and in most of Europe it is reimbursed. If I may say so I think it is almost criminal that such an efficacious drug has taken so long to reach Canada.*

*Can you imagine the same thing happening in AIDS or cancer.*

*You may find some helpful information in the NICE guidelines to help you where it is recommended for all patients with advanced disease and in many centres is offered before deep brain stimulation ( cheaper, safer and can achieve as good results in many patients)*

*Over 25 years I have treated about 1000 patients personally. Younger onset patients and those where oral medication can be markedly reduced or even discontinued entirely do best in the long term and I have some patients who continue to benefit after more than 15 years of sustained treatment.*

*You are probably aware that a randomised controlled trial called TOLEDO has been completed this year and the paper will be published in the autumn- abstracts of the data are available from American Academy and Vancouver where the positive results were published.*

*Britannia Pharmaceuticals may also be able to provide you with helpful information ( they are the company who market apomorphine in the UK and Germany and some other parts of the world)*

*I hope this is helpful – there are many publications in the literature and **no dispute that it is a treatment far more effective than oral or patch dopamine agonists and a treatment which may have a much lower incidence of impulse control disorders and dopamine dysregulation when used as pump therapy.***

### 3. Disease Experience

Parkinson's disease is one of the most common illnesses of the nervous system. It is mainly identified by a loss of the ability to move normally. These changes appear slowly. They gradually become worse over time. Symptoms vary quite a bit from person to person. Often changes start on one side of the body and eventually spread to the other side.

**Tremor while at rest, rigidity, slowness of movement, and postural instability** are the main problems people experience.

Other symptoms can include:

- **Hypomimia** – This means reduced facial expression which makes a person appear uninterested or sad when they are not.
- **Hypophonia** – A person's voice may become very soft. Deterioration in the rhythm and quality of the voice is common.
- **Micrographia** – Handwriting may become small and cramped.
- **Changes in mind, mood and memory** – Depression and anxiety are very common. Forgetfulness and confusion can also occur.
- **Difficulties with sleep** – This can include insomnia, vivid dreams, nightmares and daytime sleepiness.
- **Constipation** – Approximately 50% of people with Parkinson's experience cramps and/or constipation.
- **Pain** – Different kinds of pain are common.
- **Fatigue** – A person may feel tired or exhausted, and the capacity for normal work or activity is reduced.

All can worsen over time.

An unfortunate side effect of levodopa, over time, is dyskinesia or involuntary writhing movements, and people in an advanced state of Parkinson's frequently experience these when they are 'on' to a severe extent. However, without levodopa, they are then reduced to an "off" state, an even more disabling, frightening stage where breathing and swallowing are at risk as described in this eloquent description that follows:

My Issues in Living with Parkinson's Disease and it's Progression – Chris Olsen, April, 2016 (see also <https://www.youtube.com/watch?v=wtyOF9XhQ0A&feature=youtu.be>)

*"I spend approximately 65% of my waking day in the "off" state when my medication is not working. This causes me to have difficulty moving independently, feeding myself, and performing basic tasks. The 35% I manage in the "on" state is with troublesome dyskinesia, very violent movements that again prevent me from doing most activities.*

*Overall my health and safety are concerning for the following reasons:*

*I have lost approximately 100 lbs in the past few years largely due to dyskinesias, these violent movements that are a side effect of my medication.*

*I am at serious risk of aspiration and choking due to my inability to swallow properly when medication is not working.*

*I have frequent dose failures with my medication, possibly due to my stomach not emptying properly. Medications to assist with stomach emptying have had adverse effects and made me even more ill. This makes my off periods fairly unpredictable and makes it difficult to plan my day (and my husband's day).*

*Additionally, I am also at risk for malnutrition due to difficulties with swallowing as well as the increased caloric expenditure due to dyskinesia, and difficulty feeding myself while dyskinetic or in an 'off' state.*

*If the serious symptom of not swallowing properly continues, there is a chance I may need a PEG tube for feeding to eliminate the risk of choking and ensure proper nutrition.*

*I suffer from rigidity, bradykinesia, dystonia, tremor, and more recently freezing while off. I fell and hurt my hip recently due to a freezing episode in the night when I was up to the washroom. Due to my low weight and new freezing, there is a real concern of a*

*serious fall resulting in a fracture which could lead to a further decline in my condition and the need for community support or an increased level of care*

*These are the main safety concerns, although I have many severe symptoms that cause me to need help with my activities of daily living (such as dressing, getting to the toilet, eating)."*

<https://www.parkinson.bc.ca/media/30933/what-is-parkinsons-disease.pdf>

<https://www.parkinson.bc.ca/media/31548/progression-of-parkinsons.pdf>

#### 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).

##### PD's Progression

Although PD can be a frightening diagnosis, life expectancy is about the same as for people without the disease. For some people, symptoms evolve slowly over 20 years. Early treatment can provide years that are virtually symptom-free. About 5 to 10% of cases occur before age 50. Famous examples are: Boxer Muhammad Ali at age 42 and actor Michael J. Fox at age 30.

##### How is PD Diagnosed?

There are no lab tests that can diagnose Parkinson's. A diagnosis of Parkinson's disease is based on medical history and a thorough neurological exam. In some cases, the doctor will have the patient try Levodopa treatment. If Levodopa helps alleviate the PD symptoms, it typically means that the accurate diagnosis has been made.

##### Treatment: Levodopa

Levodopa (L-dopa) is a drug that the brain converts into dopamine. It has been used since the 1970's and is still the most effective PD medication. It reduces bradykinesia and rigidity, helping people to move more easily. Eventually, levodopa may wear off quickly. It should not be taken with a high-protein diet. Common side effects are nausea, vomiting and drowsiness.

**Parkinson's disease (PD) is one of the most treatable of all neurological conditions.** Medical treatment increases longevity and allows most people with PD to remain active and productive for many years.

**However, the medical treatment of PD, is not always simple.** The choice of drug, dose and timing are crucial. Motor and non-motor symptoms must be treated and the need for specialist care increases with the advancing disease. *The difference between optimal versus ineffective therapy may be the difference between a nursing home and independent living.*

Because of the complexity of this disease, general practitioners often find it difficult to diagnose and then to treat. They may refer patients to either a community neurologist who specializes in a variety of neurological conditions or to a neurologist who specializes in Movement Disorders.

Patients in a more advanced stage of the disease are likely on a 'cocktail' of oral medications averaging a cost of \$1000 per month.

**Control Costs** - The Public Health Agency of Canada estimates the costs associated with PD in 2000-2001 were \$446.8 million annually. As roughly 10% of people with PD in Canada are British Columbians, in BC, that cost would have been roughly \$45 million.

In 2012/13, the BC Ministry of Health estimated that \$1.12 billion was spent in BC on direct care related to PD including hospital, MSP, and Pharmacare costs. As the number of people with PD is expected to roughly double by 2031, costs can be projected to double as well to \$2.24 billion in 2031.

Parkinson's disease is the second most common neurological disease after Alzheimer's. BC's Ministry of Health data indicates the number of Parkinson's patients in BC has increased by 39% in the last decade from around 8,600 in 2001-02 to 12,500 in 2012-13. There are also many hidden costs associated with lost wages and informal care.

## More Complex Care

*Deep brain stimulation (DBS)* is a surgical procedure used to treat a variety of disabling neurological symptoms—most commonly the debilitating symptoms of Parkinson’s disease (PD), such as tremor, rigidity, stiffness, slowed movement, and walking problems.

At present, the procedure is used only for patients whose symptoms cannot be adequately controlled with medications. DBS uses a surgically implanted, battery-operated medical device called a neurostimulator—similar to a heart pacemaker and approximately the size of a stopwatch—to deliver electrical stimulation to targeted areas in the brain that control movement, blocking the abnormal nerve signals that cause tremor and PD symptoms.

In British Columbia, there is currently a four to five year waitlist for DBS. As Parkinson’s is a progressive disease, in five years a patient may no longer be eligible for DBS as the disease may have created symptoms that make them no longer a good candidate.

Patients with PD who have undergone DBS have been able to return to work and potentially reduce their dose of medication by approximately 75%, while many others have been able to come off their medication entirely.

As there is only one neurosurgeon in BC, located in Vancouver, patients must travel there from other parts of the province, initially for an assessment from a movement disorder specialist (waitlist up to two years), be referred to the neurosurgeon (waitlist up to another two years) and if they meet the criteria, be placed on another waitlist for up to another two years. They must travel to Vancouver for all of these appointments, have recovery time in Vancouver from the DBS surgery, travel home, recover, come back to Vancouver for day surgery for installation of a ‘pacemaker’ type battery, then stay for several more days to have electronic signals calibrated for their device. Any complications require travel back to Vancouver.

Batteries need to be replaced every 4 to 5 years. Patients must travel to Vancouver for this procedure.

DUODOPA<sup>®</sup> is a levodopa and carbidopa combination in the form of a gel that is delivered directly into the small intestine. This type of treatment is for use in patients with advanced Parkinson’s disease who have severe and disabling motor symptoms that cannot be well controlled with available combinations of medications for Parkinson’s disease.

The gel is delivered continuously throughout the day with a pump via a tube, directly into the small intestine to provide more constant amounts of levodopa and carbidopa in the body throughout the day.

The therapy is expensive, approximately \$60,000 a year, and although recently made available on a case by case basis for people with advanced Parkinson’s disease in BC, still not easily accessible. Patients must travel to Vancouver for gastrointestinal surgery to place a stoma into the small intestine. After recovery of two to four weeks, patients again travel to Vancouver to the Movement Disorder clinic for titration of Duodopa appropriate to their needs. Titration takes 3 to 4 days as an outpatient process.

See also UK NICE Pathways or a Paradigm for Disease Management of Parkinson’s Disease, Appendix B

## 5. Improved Outcomes

Patients would like to see their symptoms controlled and to have an acceptable quality of life. Severe “off” periods are disabling to the point of life threatening as breathing becomes difficult, speech impossible and collapse immediate causing sudden falls with the risk of serious injuries.

Trade-offs with other oral medication are the use of other dopamine agonists which create possible risky behavior with compulsive gambling, sex and shopping.

Apomorphine is used to control “off” episodes in people with Parkinson’s disease. At present, the drug is given by injection under the skin and starts to relieve symptoms within 20-30 minutes. A side effect is nausea but people take anti-nausea medication to relieve this and/or lie down for awhile until the nausea passes.

Dr. Ahlskog, a foremost clinician in treating Parkinson’s disease states: “Although a dopamine agonist, apomorphine is quite different from the other dopamine agonists – praxipexole, ropinirole, and rotigotine. These three agonists have limited potential to activate brain dopamine receptors. Apomorphine has broad affinity for dopamine receptors and produces a similar response to that of full doses of carbidopa/levodopa.” (Ahlskog, J. Eric’ 2015, The New Parkinson’s Disease Treatment Book)

Duodopa therapy and Deep Brain Stimulation both involve surgery and although these may be indicated in the disease progression for symptom management, apomorphine provides an alternate therapy prior to considering surgical interventions.

## 6. Experience With Drug Under Review

Clients (patients) that PSBC serves have not had any experience with Movpro (Apomorphine); however, we reached out to other societies, Parkinson's UK and the National Parkinson Foundation, USA. The patients they serve reported substantial benefits. These people experience difficult "off" periods, when their other Parkinson's medication's effectiveness has worn off and they need a 'grace' period or rescue medication. Otherwise, they exist in a frozen state and are unable to move or otherwise continue to function while they wait for the dopamine replacement medications to begin working again.

These "off" periods are incredibly disabling, terrifying and life threatening, ranging from sudden collapse with resultant fall injuries to difficulty breathing and swallowing. Apokyn, when injected, gives them back this functioning almost immediately.

Please see **Appendix A** for comments from patients on the NPF help line and links to blogs where patients discuss the benefits as well as difficult side effects for some.

**Here is an example from Parkinson UK:** a woman who had been living with Parkinson's disease for around 4 years at 47 years old. Her oral medication wasn't as effective at controlling her symptoms and she started to use the apo-pen – she used it for about 2 years. She was quite candid about the pluses and minuses of the pen. She has recently had DBS (March) and doesn't need the pen, but carries it with her in case she gets a dystonia attack.

### Her General Thoughts Were:

It's definitely worth having

- It's important that if you do use the pen, you have to be prepared when you go out, you've got to have fresh needles for instance
- You also need to find your own way on which part of the body to inject and make sure you're comfortable with this just in case you have to do it in public places.

### How Did Apo Improve Your Quality of Life?

- Positive
  - My oral medications weren't controlling my dystonia so I went onto apo go as a muscle relaxant and its brilliant
  - I usually get a 30 second warning of a dystonia attack so I have some time to get my pen ready – but I have them in every room of the house and every bag to make sure I can respond quickly
  - I always had to make sure that the needles are fresh and pen is full and working
- Negative
  - I did however become reliant on it, I wouldn't go anywhere without it
  - I started to hate the treatment with a vengeance, but it was a lifesaver
  - It did compromise how I dressed as I needed to have my legs accessible to inject
  - You have to work out how to inject – sometimes this led to being shouted at or verbally abused in public situations, even when trying to do it in a discrete manner
  - It could sometimes take 20 minutes to get the injection right of having a dystonia attack
  - Sometimes can't do it myself if too long into attack so showed some people how to do it and they were across the city so if I did have an attack I'd ask whoever found me to go to the specific place and bring the person who can help me to inject

### How Convenient is APO as a Treatment?

- Very convenient – can take it anywhere
- You must have clean needles and ensure the pen is working

- Great that it's a pen, I refused a pump as I wasn't comfortable cutting holes in all my clothes

### **How Does APO Enable You To Manage Your Condition And Maintain Your Independence?**

- At first it was very good, but after a while on the smallest amount I had issues with nausea
- Had to make sure I had domperidone in my system when taking it or I had to lay down for 40 mins or until nausea passed

### **7. Anything Else?**

Parkinson's is a tough disease but more manageable if people and their physicians have access to different medications.

Apomorphine (Movapro) provides a useful tool for those experiencing the sudden 'off' periods which can be not only disabling but life threatening as they involve 'freezing' and sudden loss of balance.

## 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.

Parkinson UK and National Parkinson Foundation provided information from their Helpline and blogs.

Dr. Andrew Lees provided his recommendation for approval and support and links to several documents.

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.

As above.

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

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: Jean Blake

Position: CEO

Patient Group: Parkinson Society BC

Date: July 26, 2017



## Appendix A: National Parkinson Foundation, USA - Patient Services, July 2017

Most of the calls received are from persons who have heard about the medication (Apomorphine) and want to know general information. Although they have not had a lot of calls from actual users, below are some comments and excerpts from case notes from callers to the Helpline who were actually using apomorphine. It is interesting that one of them describing ICD issues. Besides these, staff reported knowing a former Board member, was one of those who reported it that without it they would not be able to get out of bed in the morning.

- Woman with PD, 3 years since dx, feels she isn't responding to medications, her tremors did stop but has a lot of difficulty moving feet and picking them up from the floor. says she can't walk, taking Apokyn, Sinemet, Mirapex.
- Woman who is now on apomorphine to improve on times. She says it is working well.
- Patient who is experiencing shortness of breath which does seem to be related to wearing off times. She takes c/l every 3 hrs. and uses Apokyn 2-3X per day. Dr. mentioned DBS at last visit. She has been checked for other possible causes - doctors think it is anxiety. She has started Zolofit at 25 mg. and also has Xanax which doesn't seem to help.
- Man had deep brain stimulation and it caused him some problems as it was "battery operated and it failed " which caused him serious stress. He is currently using apomorphine which he injects himself , this is how he medicates himself for the day, all of this injecting of himself has caused infections and he has black sores on his belly.
- Caller in tears. Husb. hospitalized w/ psychosis, delusions of infidelity. "He held me hostage at home" by blocking her car with another car when she tried to leave. He was on Apokyn & Neupro patch, both of which have been D/C'ed during his 2-week hospitalization. To be D/C'ed today & delusions continue. Husb. will stay w/ adult son who is out of town @ present but she is the person who's supposed to pick him up & she's afraid.
- Wife is on Rytary for about a month now and has had severe dyskinesia. She is also on Apokyn, Requip, Amantadine, Xanax. She has lost weight and was confused with hallucinations last night. SHE had a similar episode about a week ago and she was taken to the ER. They gave her a bolus of fluids and she began to show cognitive improvement. He is thinking of taking her there again but wanted to know if he should or not. IS recommended emailing and calling the Neuro office and speaking with her MD. Her doctor has visiting rights and can see her at the hospital. He was going to call the MD and inform her of his decision in taking her to the ER. Medication adjustments needed by the Neuro.
- Caller reports he may have taken two morning doses of his meds, just started on Apokyn and wondered how much he could take. Very confused about the use of C/L and Apokyn. Referred him back to his dr.'s instructions . He is falling a great deal - not nOH. He mentioned getting a bike and Information Specialist discouraged this and suggested consult with PT for balance issues.
- Wife and brother of man w/ PD call together. Hospitalized for stroke last week. Meds reduced from C/L 5x/d and ~2 doses of Apokyn/d to C/L qid. Now very stiff and immobile; cries in pain when they try to move him. Meds have been cut almost in half. Stroke and dementia over past year also cloud picture.
- Caller who is a businessman always keeps it handy for whenever he is in a business/public speaking situation
- Patient very insecure about using an injectable and in spite of MD's recommendation they cannot get past this fear.
- Patient says we should be "marketing" it more, that it has literally saved her life and she would not be able to function without it.

Also, from NPF's *Ask the Pharmacist* and *Ask the Doctor* online forums, here are a few examples of the many threads available.

<http://forum.parkinson.org/topic/10308-extreme-cramps/#comment-35161>

<http://forum.parkinson.org/topic/21332-frozen/#comment-115513>

<http://forum.parkinson.org/topic/13347-apokyn-apomorphine-worth-trying/#comment-51207>



## Appendix B

### **UK NICE Pathways or a Paradigm for Disease Management of Parkinson's Disease,**

As the disease progresses, patients go through a diagnostic stage to a maintenance phase, then complex and then palliative. According to this model, a patient requiring Movpro would like be in the complex phase.

**AIMS in treating the complex patient:** It is not possible to identify a universal first choice adjuvant drug therapy for people with later PD. The choice of drug prescribed should take into account:

- Clinical and lifestyle characteristics
- Patient preference

### **Consider Apomorphine in Those with Severe Motor Complications Unresponsive to Oral Medication:**

- Intermittent injections to reduce refractory on-offs
- Continuous subcutaneous infusion to reduce off time and dyskinesia

### **Consider surgery:**

- Bilateral STN stimulation for suitable people refractory to best medical therapy
- Thalamic stimulation for people with severe tremor for whom STN stimulation is unsuitable

*NICE recommendations reproduced with Royal College of Physicians copyright permission. The National Collaborating Centre for Chronic Conditions Parkinson's disease National Clinical guideline for diagnosis and management in primary and secondary care. Royal College of Physicians London 2006.*

- Morbidity relief
- Maintenance of function and self-care despite advancing disease
- Assistance and adaptation of environment to promote daily living activities
- Re-assessment because of increasing disability and complexity
- Symptom control

### **Management**

- Support and explore areas of uncertainty
- Advice on practical problems, management of non- motor symptoms & prevention of complications
- Referral liaison may be required as in stage 1 +
- Psychiatrist/CPN
- Neuro surgery
- Career support

### **Outcomes**

- Optimum symptom control
- Minimalisation of disability
- Treatment concordance
- Reassess goals of therapy/care

### **Non Motor Symptoms**

- Balance
- Sleep disturbance
- Anxiety/worry
- Urinary problems
- Bowel problems
- Dribbling saliva
- Speech difficulties
- Memory failure and confusional episodes