# Common Drug Review
## *Patient Group Input Submissions*

**selexipag (Uptravi)** for Pulmonary Arterial Hypertension (WHO class II and III)

| **Patient group input submissions were received from the following patient groups. Those with permission to post are included in this document.** |
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| Pulmonary Hypertension Association of Canada (PHA Canada) & Scleroderma Society of Canada (SSC) — permission granted to post. |

**CADTH received patient group input for this review on or before April 15, 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. This includes patient input received from individual patients and caregivers as part of that pilot project.

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.

# Pulmonary Hypertension Association of Canada & Scleroderma Society of Canada

## Section 1 — General Information

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| **Name of the drug CADTH is reviewing and indication(s) of interest** | UPTRAVI (selexipag) – Pulmonary Arterial Hypertension (WHO Group I) |
| **Name of the patient group** | Pulmonary Hypertension Association of Canada (PHA Canada) & Scleroderma Society of Canada (SSC) |
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| **Permission is granted to post this submission** | Yes |

### 1.1 Submitting Organization

The Pulmonary Hypertension Association of Canada (PHA Canada) is a federally registered charity established by patients, caregivers, and health care professionals collectively referred to as the Canadian pulmonary hypertension community. PHA Canada exists to empower the Canadian PH community through awareness, advocacy, education, research, and patient support.

The Scleroderma Society of Canada (SSC) is the national organization representing all scleroderma organizations and groups in Canada. The SSC works to improve the quality of life of those with scleroderma through promoting public awareness, supporting those affected by scleroderma, and funding research to find a cure. PAH is a common complication of scleroderma and can be very severe in patients affected by this progressive connective tissue disease.

### 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:*

PHA Canada has a standing Corporate Committee that all companies involved in the research, development, and distribution of treatments for PH are invited to join. Committee members pay yearly dues and participate in semi-annual meetings to discuss areas of common interest, such as diagnosis, patient education, public awareness, and research. By working jointly with all committee members, PHA Canada aims to eliminate potential biases in favour of particular companies or products. 2016 Corporate Committee: Actelion Pharmaceuticals, Bayer Inc., GlaxoSmithKline, McKesson Specialty Pharmacy, Pfizer Canada, Shoppers Drug Mart Specialty Health, and United Therapeutics. Each year Committee members may also provide grants and/or event sponsorships in support of PHA Canada programs and services. 2016 Contributors (confirmed): Actelion, Bayer, and United Therapeutics.

In the last five years, the Scleroderma Society of Canada has received unrestricted funding from Actelion, Pfizer, AstraZeneca, GlaxoSmithKline, Bayer, and Shoppers Drug Mart Specialty Health in support of educational and support services.

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

Board Chair of PHA Canada, Dr. Sanjay Mehta, assisted in the preparations of this submission (i.e. reviewed survey, outreach to physicians). Dr. Mehta has received consulting and speaking fees (Actelion, Bayer, GSK), research grant support (Actelion), and investigator fees for participation in pharmaceutical clinical trials (Actelion, Bayer, Gilead, GSK, Ikaria, Lilly, United Therapeutics). The authors and their respective organizations declare no further conflict of interest.

## Section 2 — Condition and Current Therapy Information

### 2.1 Information Gathering

Information for Section 2 was gathered primarily through telephone interviews with patients having direct experience with Uptravi (through the GRIPHON trial) and an online survey of PAH patients and caregivers residing in Canada. Three patients with direct experience with Uptravi were interviewed between March 31 and April 07, 2016. A total of 118 people completed the online survey, which was available in both English and French from March 21 to April 06, 2016 (94 PAH patients; 21 PAH caregivers; 3 parents of paediatric PAH patients). In addition to the three interviewed patients, one survey respondent also answered questions in regards to their personal experience with Uptravi.

Further information is drawn from the findings of PHA Canada's *2013 Burden of Illness Survey* (see Appendix 1 for Summary Report), HrQoL data from the Canadian Scleroderma Research Group's patient registry, previous CADTH submissions by both organizations, and personal stories and information gathered through our collective work supporting patients and their families.

### 2.2 Impact of Condition on Patients

Pulmonary arterial hypertension (PAH) indicates PH that is caused by a narrowing of the pulmonary arteries of the lungs. Like all forms of PH, PAH has a significant impact on the lives of patients. For scleroderma patients, who already experience significantly low quality of life scores prior to getting PAH, a PAH diagnosis may represent the "ending" they have feared since initially acquiring scleroderma.

Amidst the shock, and often despair, of receiving a diagnosis of this rare, life threatening disease, patients are also coping with a wide range of symptoms associated with PH, such as:

- Difficulty breathing upon little or no exertion
- Fatigue
- Dizziness upon chest constriction (i.e. bending forward) or sudden exertion (i.e. standing up)
- Swelling of feet and ankles
- Syncope (loss of consciousness)
- Chest pain

With pulmonary hypertension, day-to-day life is made difficult, exhausting, and challenging.

Indeed, of the patients surveyed, 90% of respondents reported difficulty breathing or shortness of breath upon exertion and 87% reported experiencing fatigue. Over 1/3 of patients also experienced other common symptoms, including swelling of the feet/ankles/belly, chest pains, fainting/light headedness, heart palpitations, and coughing. The affects of these symptoms include difficulty with climbing stairs (as reported by 86% of patients), doing household chores (79% of patients), walking a short distance (55% of patients), and being intimate with a partner (39% of patients). When JN from BC was diagnosed with PAH in 2009, she experienced such severe shortness of breath that she "struggled to get through the day". She was unable to work at her part-time retail job, which required standing and walking. JN says her breathlessness meant she "couldn't walk from the bed to the closet" without having to stop and catch her breath. She was unable to do basic household chores or participate in leisure activities, such as going for a walk. Similarly, SL from Quebec remarked:

> *"I have always been an active person; it was hard for me to sit down. Now I have to space out my activities. If I do too much on one day, I pay for it the next. I am still able to take care of myself, to do laundry, go grocery shopping, and take care of the cooking, but I am not able to clean my house anymore. I have to have help with that. I am less and less capable of doing activities with my husband. We have a cottage and it's getting hard for me to go on the weekends… It's hard to stay positive. It's difficult because you don't know how much longer you have to live."*

The majority of survey respondents reported similar experiences, including limitations to recreation (88%), household chores (76%), and travel (74%). Over half of patients also reported decreased income as a result of having PAH, with 43% no longer able to work. 50% of patients reported experiencing social isolation. Parents reported that children with PAH are unable to participate in many family activities and have frequent medical appointments. Other impacts reported by patients include limitations to caregiving responsibilities, difficulties exercising, and the inability to start a family. While 33% of patients surveyed felt that managing the symptoms or physical impacts of the disease was the most important aspect of PAH to control, the majority of patients (54%) felt it was disease progression. "The progression of the disease R that's what really scares me," stated SL. This was especially true for parent respondents, 100% of whom identified disease progression as the most important aspect of their child's PAH to control.

These findings are consistent with the results of PHA Canada's *2013 Burden of Illness Survey*, where the large majority of patients surveyed (85%) reported mild to severe symptoms or limitations with everyday activities. Symptoms of PH and related heart failure fluctuate, leaving patients uncertain of how they will feel from day-to-day and making planning ahead impossible. Sometimes even getting out of bed is a struggle and patients must learn to cope with their necessary daily activities at a significantly slower pace. Some will lose the ability to care for themselves and fulfill their roles as caregivers for others. Many patients give up careers in the prime of their lives; women may have to

give up dreams of becoming pregnant, as pregnancy in women with PH is often fatal and thus strictly contraindicated.

Patients and healthcare providers are increasingly recognizing the psychological issues related to PH. Patients commonly experience depressed mood, anxiety, feelings of helplessness, and hopelessness as they face the realities of living with a serious illness with a high risk of death within a few years. Although patients often improve physically in response to available therapies, side effects and the complexities of current therapies contribute to these negative feelings. Finally, patients face additional challenges due to the "invisibility" of their condition. Patients do not look sick when resting or seated, and thus often face social stigma. A lack of understanding of PH and its impacts by others, along with the inability to participate in many social activities, contributes to the isolation felt by many patients and caregivers. According to the *Burden of Illness* survey, 71% of patients and 61% of caregivers feel isolated or excluded from society because PH is not a visible disease.

### 2.3 Patients' Experiences With Current Therapy

There are currently nine Health Canada approved therapies available in Canada to treat PAH, including six oral agents: ambrisentan (Volibris), bosentan (Tracleer), macitentan (Opsumit), sildenafil (Revatio, Viagra), tadalafil (AdCirca, Cialis), and riociguat (Adempas), and three infusion therapies: IV epoprostenol (Flolan), IV and SC treprostinil (Remodulin), and IV thermostable epoprostenol (Caripul). Responses to PH monotherapy (single medication) are often limited, such that many patients require two or more PH medications used concurrently (combination/dual therapy). This is especially true for patients with more advanced, moderate-to-severe PH, which is the stage at which more than half of patients are currently being diagnosed. For patients with pre-existing and ongoing damage to the vascular system and fibrosis – hallmarks of scleroderma – PAH treatment is especially complicated and quality of life is profoundly impacted.

Including those on combination therapies (which is the majority of PAH patients), the most common therapies currently being taken by the survey respondents were bosentan/Tracleer (35%), sildenafil/Revatio/Viagra (35%), tadalafil/AdCirca/Cialis (31%), and macitentan/Opsumit (22%). Approximately 30% of respondents were currently on some form of infusion (IV or subcutaneous) therapy. The primary benefit of PH therapy is a reduction in the severity of PH, as measured by reduced pulmonary artery pressures, resulting in decreased workload on the heart, improved cardiac function and blood flow, and – hopefully – delayed disease progression.

Patient experience with PAH treatment is generally positive, with most patients reporting at least some benefit from their current therapies. However, patients surveyed were more likely to report that their treatment was only "somewhat effective", rather than "highly effective", at controlling various symptoms and aspects of PAH. For instance, more that 60% of survey respondents felt that their current therapy is somewhat effective at making it easier to breathe upon exertion, while only 20% felt it is highly effective. Similarly, 56% of patients reported that their treatment was somewhat effective in controlling fatigue and tiredness, compared to only 8% who reported it was highly effective. The greatest percentage of patients to report that current treatment was highly effective was 31%, in regards to controlling breathlessness upon rest. In terms of disease progression, 35% felt current treatments were somewhat effective, while 25% reported high effectiveness and another 22% reported no effectiveness; the remaining respondents indicated they did not know how effective their treatment was at controlling disease progression.

It is inevitable that the effectiveness of therapy will vary drastically from patient to patient, based on many factors: age, gender, type of PH, severity of PH, and underlying medical conditions. For instance, treatment effectiveness and long term survival for patients with scleroderma PAH continues to be worse than in other subsets of PAH patients. Fortunately, some patients do experience dramatic improvements on particular therapies, lessening their shortness of breath and improving their ability to function and be active. People return to work and caregiving; they are able to participate in their communities. However, patients are not "cured" of their PH and despite the response to current therapies, many patients treated with current therapies remain significantly ill with moderate-to-severe PH and progressive right-ventricular heart failure. The emotional and psychological burden is great, as patients face the prospect of more complex and invasive medications, possible lung transplantation, and the high risk of progressive PH with shortened life expectancy.

When patients were interviewed in 2015 in regards to PHA Canada's CDR patient evidence submission for macitentan, most patients stated they considered the effectiveness of current therapies in controlling their condition as being "fair". Canadian patients continue to understand that while treatment is helping to stabilize their condition – making life easier, slowing down disease progression, keeping them alive longer – it is not a cure. Patients remain symptomatic and often severely limited in their daily function; quality of life is negatively impacted and people continue to die.

Patients are also managing the adverse effects of currently approved medications, which commonly include nausea, gastrointestinal distress, fatigue, sleeping difficulties, headaches, and flushing. The side effects most frequently cited by the PAH patients surveyed included: headaches (52%), digestive problems (45%), sleeping difficulties (44%), nausea/stomach pain (42%), and stuffy/runny nose (42%). One third of respondents experienced flushing of the skin; another 1/3, dizziness or fainting. 14% of patients reported pain or infections at their IV site.

Barriers to accessing treatments also exist. At least 1/4 of patients reported facing each of the following difficulties in accessing their current PAH therapies: lack of access to a PH specialist close to home; paying out of pocket for supplies necessary to administer treatment; and relying solely on a manufacturer's compassionate access program. One of the main hardships people experience in accessing therapy is receiving initial approval for combination/dual therapies, primarily due to the costs associated with the treatments. The struggle to get such approvals adds additional stress on patients and their families. This most recent survey revealed at least two more PAH patients who report enrolling in drug trials in order to gain even *potential* access to treatment. Furthermore, the various supplements and medications required to deal with the side effects of PH medications (i.e. anti-nauseants and analgesics) are often extremely expensive and not covered by government funding programs. Many patients rely on private insurance to help cover the costs associated with having PH. Meanwhile, others are grateful for the public coverage they do have; as SL commented:

> *"It's a good thing I switched to public health insurance when I did, otherwise I would never have been able to afford my PAH medications. 20% of $5,000/month* [on private insurance] *would have been unaffordable."*

In light of the reported moderate effectiveness of current therapies and the treatment challenges patients continue to face – both physically and practically – patients identified several needs not being met by current therapies. Half of all survey respondents stated that current therapies are not

addressing their needs in regards to both breathing difficulties (upon even minor exertion) and fatigue. The most significant symptoms faced by PAH patients are not being sufficiently alleviated by currently available treatments. One third of respondents identified both progression of disease and the physical impacts of the disease as further areas not being addressed by current treatments. And almost 60% of patients said that current therapies do not address social and psychological needs such as reducing isolation and depression.

### 2.4 Impact on Caregivers

Of course it seems obvious that 100% of caregiver survey respondents reported an increase in caregiving responsibilities. Similarly, it is unsurprising that they also report the following challenges as PAH caregivers: limitations to travel (88%), increased household responsibilities (75%), and decreased recreation opportunities (75%). A third of caregivers (and 100% of parent respondents) experience social isolation as a result of their role; another third experience a decrease in income, with 17% no longer able to work.

Caregivers are often the main support for patients, taking on the brunt of the work around the home (including caring for any children), often while being sole financial providers. They attend medical appointments, help to administer medication and manage side effects, and give so much of their personal time that they also are living with the disease. In fact, caregivers spend nearly 50% of their time on activities related to caring for their relative with PH. Furthermore, the fear and concern experienced by the children of patients creates additional emotional stress for both patients and caregivers.

Relationships (particularly marriages) are strained, self-care is scarce, and the prospect of losing a loved one creates a heavy emotional burden on everyone. Burnout of caregivers is very real, negatively impacting their own health while also making patients – and entire families – more vulnerable.

Current treatments are further negatively impacting caregivers. The vast majority of caregiver respondents – over three-quarters – reported that current treatments negatively affected many areas of their lives, including caregiving responsibilities, travel opportunities, and personal/social time. Very few respondents indicated any positive impact on their role from current treatments, with only two people stating any positive effect.

## Section 3 — Information about the Drug Being Reviewed

### 3.1 Information Gathering

Information for Section 2 was gathered primarily through telephone interviews with patients having direct experience with Uptravi (through the GRIPHON trial) and an online survey of PAH patients and caregivers residing in Canada. Three patients with direct experience with Uptravi were interviewed between March 31 and April 07, 2016. A total of 118 people completed the online survey, which was available in both English and French from March 21 to April 06, 2016 (94 PAH patients; 21 PAH caregivers; 3 parents of paediatric PAH patients). In addition to the three interviewed patients, one survey respondent also answered questions in regards to their personal experience with Uptravi.

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

*a) Based on no experience using the drug:*

The vast majority of patients surveyed reported moderate or high expectations for this new drug. In fact, only two survey respondents indicated low expectations, in specific regards to improved quality of life for caregivers and addressing unmet needs, respectively. Half of the respondents instead had high expectations that Uptravi would address unmet needs; furthermore 40% of respondents had high expectations for the following: improved health outcomes of patients, improved quality of life of patients, and lessening of adverse effects from treatment.

> *"I am on sub-q Remodulin. If I could go on selexipag, I could stop the sub-q Remodulin, have no pain, and no more changing of the site and reservoir." – Patient Survey Respondent*

The most modest expectations were of the impact on caregivers, with only a third of respondents having high expectations of improvements to their quality of life. Caregivers themselves also held more conservative expectations – approximately half of respondents held only moderate expectations – of the potential positive impact of Uptravi on both their own lives, as well as on the overall well being of patients.

However, much like patients, caregivers are willing to tolerate serious adverse effects from Uptravi, especially if it slows disease progression (79% of patient respondents) or improves the quality of life of patients (100% of caregiver respondents). Two-thirds of patients would tolerate serious adverse effects if they experienced improved quality of life or improved management of disease symptoms. Caregivers consistently reported similar feelings towards such benefits, while the majority also identified reduced hospitalizations as worth tolerating side effects. Caregivers also expressed the hope that Uptravi would reduce the need for more invasive treatment options; for instance:

> *"My daughter is not currently on a prostanoid so we cannot rate the effects or tolerance to side effects from either an invasive treatment or Uptravi. But we do think that if we had a choice between a pill form of medicine or an IV-based medicine, we would like to be able to be given the medication in pill form. My daughter also has two congenital heart defects, which could potentially mean that she would not be eligible for the current IV-based prostanoid therapies because of the risk of blot clots. Uptravi might be her only option when she needs to add a prostanoid." – Caregiver Survey Respondent*

While it is generally expected that any new drugs coming to market should extend life and/or improve quality of life for sufferers, many treatments are less effective in the scleroderma PAH population as they are in the general PAH population. This patient population has a higher tolerance for adverse effects due to the few options available to them to maintain functionality and extend their limited life expectancy. Although, given the diminished quality of life they already experience, any treatment that was effective and had milder side effects would be welcomed.

*b) Based on patients' experiences with the new drug as part of a clinical trial or through a manufacturer's compassionate supply:*

Four PAH patients who participated in the GRIPHON study (Canadian drug trials) for Uptravi responded to questions concerning their personal experiences with the drug over the past one to five years. All four patients, one of whom has since had a double lung transplant, described very positive experiences. They were unanimous in their assertion that taking Uptravi was worthwhile and beneficial to their health.

Three of the four patients experienced positive effects in the form of improved symptoms – in particular reduced shortness of breath and improved stamina/reduced fatigue, the two most important unmet needs identified by surveyed patients. For SL, in Quebec, taking Uptravi diminished her need for oxygen, from 16-18 hours per day to 30 minutes twice a day plus at night. When 72-year-old JN, in BC, was diagnosed with PAH in 2009, she was given three months to live. Her initial treatment regime (sildenafil and Tracleer) resulted in moderate improvements to her symptoms with no treatment-related side effects. JN claimed that adding Uptravi to her combination therapy in 2011 has been "very effective" at controlling her PAH symptoms, in particular breathlessness upon exertion, fatigue, and coughing.

Describing her "immediate" and "enormous improvement" on Uptravi, JN said:

> *"I couldn't fully get through my days before and had to prioritize my activities. For instance I couldn't work two days in a row or make the bed and do the vacuuming on the same day. Now I can do what I want to do, when I want to do it. I couldn't do that without this drug."*

In addition to controlling her symptoms and allowing her to participate again in her regular activities, such as working part-time and traveling within BC, JN has also experienced improvements to her disease progression. Since adding Uptravi to her treatment regime, her PAH has gone from being stage 3/4 to stage 2/3. JN did not experience this kind of improvement from her previous treatments alone. She also continues to experience improvements to her 6-minute walk test.

In contrast to JN, is the patient who recently received a double lung transplant – a mother of three school-aged children in Ontario – who found that her "symptoms stopped increasing for about a year but did not get better". AL stated that this did enable her to help care for her small children and participate in some household responsibilities. After about a year, she required greater amounts of rest/sleep and was not able to walk very far. AL then switched from Uptravi to Remodulin, delivered through continuous subcutaneous IV. Her symptoms continued to get much worse and after six months she began assessment for a double-lung transplant, which took place in late 2015. AL said that taking Uptravi was a "very worthwhile experience", as she found the option of an oral treatment "very appealing". She found Uptravi very easy to take and that the side effects were much more manageable compared to Remodulin, making her very glad that an oral option was available.

All four patients experienced significant side effects from taking Uptravi, in particular headaches/jaw pain/flushing of the face. Some also experienced digestive issues and nausea/stomach pain. When JN joined the Uptravi trial she says she knew immediately that she was not receiving the placebo, because of the side effects she experienced. For all the patients, their side effects were successfully managed by altering the dose. For example, as a result of severe headaches and jaw pain, JN titrated from five pills twice a day down to two pills a day. Eventually however, JN chose to increase her dose again and titrated back up to the maximum dose of eight pills twice a day. JN continues to take the maximum dose and no longer regularly experiences adverse affects. Any flushing/headaches and jaw pain now only occur occasionally and go away within a few hours. JN said that dealing with these side affects is "absolutely worth it" for the benefits she receives from taking Uptravi.

Compared to other therapies, all four patients reported that Uptravi was more effective at managing PAH symptoms, reducing limitations to household/caregiving responsibilities, and improving their ability to be more active. SL was diagnosed with hereditary PAH at age 54; she has lost two brothers to PAH and had this to say about her experience with Uptravi:

> *"I am happy to have persevered through the serious side effects I experienced at first because it really has been beneficial for me. I think that the benefits of selexipag outweigh its negative side effects. When I was diagnosed, I was sure that I was going to die. And now, I have been living with PAH for 7-8 years thanks to the treatments I have been on. I have told my doctors to put me on every trial. I will take everything."*

As for JN, she believes that without treatment – in particular the inclusion of Uptravi in 2011 – she would not be here today. Her final comment: "Pharamacare needs to step up… because without the support of my family and the manufacturer, I would not be able to afford these treatments".