



Section 1 — General Information

Name of the therapeutic review	Drugs for Pulmonary Arterial Hypertension
Name of patient group	Scleroderma Society of Canada
Patient group's contact information	info@scleroderma.ca 41 King William St, Ste 206, Hamilton ON L8H1A2 1-866-279-0632 www.scleroderma.ca
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1.1 Submitting Organization

The Scleroderma Society of Canada is the national organization representing all scleroderma organizations and groups in Canada. Our objectives are to:

- Provide information about scleroderma and methods of managing and treating it
- Raise awareness of scleroderma
- Support research and provide information about developments in research
- Foster the growth and development of scleroderma organizations in Canada
- Provide a communication service in Canada for individuals and groups concerned with scleroderma
- Serve as an advocate for the interests of scleroderma in Canada and work collaboratively with other health organizations to serve those interests.

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:

In the last five years, the Scleroderma Society of Canada has received unrestricted funding from Actelion, Pfizer, AstraZeneca, GlaxoSmithKline, Bayer and Shoppers Drug Mart. These unrestricted grants offset the cost of providing 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:

Not Applicable

Section 2 — Condition and Current Therapy Information

2.1 Information Gathering

A call for patient participation in a survey was disseminated through our websites, social media and support groups. The patients who participated in this survey did so either digitally or by telephone interview at their preference. Additionally, the Canadian Scleroderma Research Group was asked to mine the patient registry for data relevant to the HrQOL of scleroderma patients with PAH.

2.2 Impact of Condition on Patients

Scleroderma patients who develop Pulmonary Arterial Hypertension have significantly low quality of life measures. For many, the development of PAH has been feared as an end point since receiving their initial scleroderma diagnosis. They are generally aware that this condition is typically fatal. At the point when PAH is diagnosed, these patients are emotionally and psychologically fragile. It is necessary for context to realize that scleroderma patients have significantly low HrQoL's before developing PAH.

The lists of common symptoms of PAH are easily available to the expert review panel so they are not listed here. However, it is important to note that PAH may exacerbate or be exacerbated by previously existing conditions such as Interstitial Lung Disease (ILD) and Raynaud's Phenomenon. Pre-existing and ongoing damage to the vascular system and fibrosis that are the hallmark of scleroderma makes the treatment of PAH complicated and the quality of life impact profound. The most common symptoms of ILD include: shortness of breath (especially with exertion), fatigue and weakness, loss of appetite, loss of weight, dry cough that does not produce phlegm, discomfort in chest, labored breathing and hemorrhage in lungs. *For those of our patients who have PAH & ILD these symptoms and the impact on quality of life are exacerbated.*

Shortness of breath, fatigue, dizziness and fainting (syncope), and swelling of the arms and legs (edema) are the symptoms consistently reported in the survey as most affecting the patient's ability to be reasonably functional on a day to day basis. They are also the symptoms most important to control.

Patients report that they need to ration their energy and take frequent rests to try to control the fatigue and shortness of breath. Take a shower, rest, get dressed, rest, brush their teeth, rest, etc. This type of task management as a coping skill is commonly reported from everything from basic hygiene to household chores, and is varied only in the degree to which the tasks are broken down. While this balancing of energy and effort is helpful, it is not always adequate. Patients report that they attempt to balance their week by ensuring a free day before and after appointments or social engagements that they know are likely to tax their energy reserves.

Shortness of breath limits everything a patient does in a day. At its most extreme they experience shortness of breath from walking just a few feet, stairs are an impossible obstacle, and day to day functioning is severely limited. Even when the shortness of breath is more controlled, they report fear of being out of breath, and becoming dizzy or fainting as limiting their independence and ability to enjoy some of the simplest things in day to day life. From housework to the ability to walk the dog, play with the children and enjoying sexual relations, their quality of life is severely diminished.

Difficulty lifting without causing shortening of breath (SOB) is also cited as a common and significant problem. The degree to which this problem affects their lives varies based on the extent to which their symptoms are currently being controlled, but also varies based on the family dynamics. In households with older children or no children, household chores can often be delegated so that the laundry, cleaning and grocery shopping are done by other family members. But in a household with young children the dynamics and psychological impact of this limitation are significantly different, as our patients attest.

Pain in the legs due to swelling or edema is also reported to be a problem that limits mobility and impacts quality of life.

Bending over, or standing up suddenly are the type of activities where patients report dizziness and a feeling of tightness in their chests. Patients report that it is a challenge to start the day as they take time to ensure that they slowly get out of bed, and begin to dress. Everything they wear from the waist down; underwear, pants, socks and shoes, requires that they bend over. Throughout the day as they reach into cupboards, as they cook and do laundry, they struggle to find ways to maintain independence without bending, lifting or climbing stairs.

Syncope or fainting spells cause tremendous anxiety and limit many day to day activities. Something as simple as a walk with the family reportedly brought on fainting episodes. These episodes cause many patients to fear being alone, or going out alone in public. Dizziness and fainting have a significant impact on a patient's degree of independence and ability to function in a day to day fashion.

There are unique challenges to living with PAH when there are children in the home. The parent of a young child spends a lot of time bent over whether that is talking to the child, wiping hands and faces, picking up toys, etc. Simple things such as playing with a ball, going for a walk to the park and swimming are compromised due to shortness of breath. The inability to pick them up without worrying about being short of breath, getting dizzy or at its worst fainting has been cited. They have expressed worry that they are worsening their health through the simple act of caring for their families. The limitations on their ability to care for their families, the fear of dying, and of knowing that there is limited time to enjoy their children and mentor them has a profound effect on the psychological well being of patients.

It would be significantly easier to list the athletic and recreational activities available to PAH patients i.e. anything sedentary or extremely low energy; reading, watching movies, playing cards or board games, than it is to list the types of activities and sports that they can no longer participate in.

The impact on the quality of life reported by scleroderma PAH patients is significant and this was quantified by the Canadian Scleroderma Research Group:

According to the Canadian Scleroderma Research Group, the Canadian Scleroderma Patient Registry/Data Base calculates the CF-36v2 for PAH at 31.7 +/- 10.7, for ILD at 35.7 +/-11.2 and for PAH & ILD at 30.3 +/-9.5. The percentage of patients represented by these groups are; 6% PAH, 26%ILD, 5% PAH & ILD, and 63% with no PAH or ILD (see appendix).

In conclusion, the quality of life for these patients is extraordinarily diminished. Menial day to day tasks become a struggle and their own homes are transformed into obstacle courses when significant shortness of breath makes climbing stairs impossible. Their dependence upon other members of the household due to this and the potential for dizziness and fainting results in a significant loss of independence with the resulting burden impacting the rest of the household. When we factor in pain, fatigue, loss of or limited intimacy with their partners and other emotional aspects of living with a terminal illness, it is difficult to define what part of their day to day lives are not significantly affected. The impact on these patients and their families is profound.

2.3 Patients' Experiences With Current Therapy

Our PAH patients are currently taking Sildenafil (Revatio), Tadalafil (Adcirca), Bosentan (Tracleer), Ambrisentan (Volivris), Epoprostenol (Flolan, Caripul) and Trepostinil (Remodulin).

The majority of patients reported that they started on monotherapy, usually Sildenafil or Tadalafil. However, there is some uncertainty as to whether the monotherapy, specifically Sildenafil or Tadalafil, was originally prescribed for severe raynauds or PAH. Many of these patients started combination therapy as symptoms progressed.

The effectiveness of these mono and combination therapies varies according to reports from patients. Most reported that there was improvement at the outset of a new therapy, with decreased incidents of shortness of breath, fatigue, dizziness and fainting. This resulted in improved ability to function. The degree of improvement in functionality reported ranged dramatically. Most have stated that this improvement diminishes over time with increasing incidents of shortness of breath. The use of epoprostenol was common, as was continuous oxygen therapy.

The most common adverse effects that were difficult to tolerate were reportedly nausea, diarrhea, headaches and insomnia. Lifestyle limitations as well as site infections from IV were mentioned frequently. Difficulty sleeping and coughing were also noted.

Access to PAH therapies is challenging at best. The high costs associated with such treatments means that private insurance rarely covers all of the cost, and the process of special approvals from the various provincial plans is stressful. Access to combination therapies are not universal throughout Canada, leaving some patients with few options but to try to enroll in clinical trials. This could be a short term solution to their dilemma if the trials are not blinded. The fact remains that when the only treatments available to them are not controlling their disease, their prognosis for survival and quality of life are grim.

Treatment effectiveness for scleroderma PAH and long term survival continue to be worse than in other subsets of PAH patients. Current therapies do not go far enough in extending life expectancy.

2.4 Impact on Caregivers

What challenges do caregivers face in caring for patients with this condition? How do treatments impact on the caregivers' daily routine or lifestyle? Are there challenges in dealing with adverse effects related to the current therapy?

Overall the impact on caregivers can be summed up as severe. Spouses struggle with increased responsibilities and additional stress in the household. Most household duties from cleaning to shopping and to taxiing children, fall to the caregiver. Working and organizing from the moment they wake up until the moment they fall in to bed is how many have characterized their daily routine. The time pressures in their day have led some to describing themselves as single parents. While they are needed to accompany their spouse on regular errands, it is their need to accompany them to the many medical appointments that create added stress at work. Both the problems with getting the required time off of work and the financial strain that results, exacerbate the issues. Those with extended families and other support networks obviously fair better, however, this has been the exception and not the rule for those who have participated in the survey.

The effects on the children of these patients are also significant. Their parent's limited ability to interact in family activities; playing in the yard, swimming, biking is often resented. In many cases their performance and behaviours in the academic setting have led to the involvement of social workers and grief counsellors. Some of these children have been traumatized when the need for emergency medical

assistance due to a fainting spell has resulted in 911 calls and resulting ambulance delivery to hospital. The children's fears and concerns over their parent's situation and prognosis add tremendous emotional strain to both the patient and the caregiver.

It is a daily battle for the caregiver to juggle the many serious needs and demands of all of the family members. Maintaining a stress free environment for their spouses is next to impossible under all of these strains.

In summary, the emotional, psychological, physical and financial impact of PAH on the caregivers is profound.

Section 3 — Information about New Drugs

3.1 Information Gathering

A call for patient participation in a survey was disseminated through our websites, social media and support groups. The patients who participated in this survey did so either digitally or by phone interview at their preference. Additionally, published studies Patent-1, Patent-2, CHEST-1 and the Seraphin trials results were referenced.

3.2 What Are the Expectations for New Drugs or What Experiences Have Patients Had to Date With New Drugs?

a) Based on no experience using new drug(s):

It is expected that any new drugs coming to market should extend life and/or improve quality of life for sufferers. Existing treatments for PAH are not cures, but rather treatments. Many of those treatments are less effective in the scleroderma PAH population as they are in the general PAH population. Our patients expect that with advances in science, these treatments will one day significantly improve the quality and quantity of their lives, and are hopeful that those treatments are available soon. This patient population has a higher tolerance for adverse effects than average 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.

As detailed above, the burden of disease remains high and increases as the disease state progresses. Drugs to effectively improve survival are critical for our patients.

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

Our ability to answer these questions effectively is hampered by the fact that we were only able to find one patient who had participated in one of these trials. And while that individual reported sustained improvement and functionality, it is impossible to establish if this is representative except to compare to these comments to the published trial literature.

"It is a gift to have been given my life back, I am able to participate in a productive way and I have energy to enjoy both my children and my husband." This patient was convinced that her treatment would extend her life expectancy and that her improved quality her life had resulted in a significantly lesser burden to her family. While this is still not a cure, it appears to be a significant improvement in how the disease is treated.

The new drugs riociguat and macitentan are expected to do both based on the information available from the Seraphin, PATENT and CHEST trials. Patients are generally of an age where they are still raising families, and their desire to be there for them, and more actively participate in their lives is a heavily motivating factor for tolerating serious adverse effects. These studies also indicate fewer adverse effects than standard treatment.

Section 4 — Additional Information

As a Rare Disease Patient Organization, the timelines for a therapeutic review are exceptionally onerous. Operating predominantly with volunteers, our ability to set up a patient survey, communicate it, collate the information and analyze the information in a clear and coherent fashion within the 15 business day time frame is almost impossible. We believe that CADTH and CDR are sincere in seeking patients' perspectives on drugs, and within the therapeutic review process, but am concerned that the average rare disease organization will be unable to provide the type of comprehensive feedback this type of review deserves. We sincerely appreciate that CADTH sent a notice of the Upcoming Call for Feedback on the 29th of August, and extended the deadline for patients groups to the 3rd of October.

Again, within the framework of rare diseases, it is challenging to find sufficient patients who were included in the clinical trials to ensure the validity of the information and context we are attempting to provide to the process. In this instance, this was particularly challenging in that not all Scleroderma patients develop PAH, so to find a subset of patients who participated in the trials within the subset of patients who have PAH, was the equivalent of finding the proverbial needle in a haystack. In this case, the extension to the 3rd worked well for us as our National Conference was held on the weekend of the 28th of September and we were able to locate one of those patients. With additional lead time, we would be far more likely to have found others to ensure that the information we are presenting is appropriately representative.

While the questions within this questionnaire are clear, there was confusion over the process of commenting on the 'Proposed Project Scope' versus completing the 'Template for Submitting Patient Group Input for CADTH Therapeutic Reviews (Pilot Project)'.