Common Drug Review
Patient Group Input Submissions

Macitentan (Opsumit) for Pulmonary Arterial Hypertension

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

CADTH received patient group input for this review on or before June 19, 2014

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

1. General Information

Name of the drug CADTH is reviewing and indication(s) of interest	Macitentan (Opsumit)for Pulmonary Arterial Hypertension
Name of the patient group	Pulmonary Hypertension Association of Canada
Patient group's contact information:	1311 Howe Street, Suite 208, Vancouver BC V6Z 2P3 604-682-1036 www.phacanada.ca
Permission is granted to post this submission	Yes

1.1 Submitting Organization

The Pulmonary Hypertension Association of Canada (PHA Canada) is a charitable organization established by patients, caregivers, parents and family members collectively referred to as "Canadians living with PH". PHA Canada aims to end isolation, provide education, support PH patients and their caregivers and create a united Canadian PH community. We strive to connect the PH community from coast to coast to bring awareness to this rare disease. Our membership consists of patients, caregivers, family members and health care workers who are directly affected by and/or involved in the care of patients with and the treatment of pulmonary hypertension.

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, where all members of industry involved in research and development and distribution of drugs that treat pulmonary hypertension are invited to participate. Current members are: Actelion Pharmaceuticals, Bayer Inc, GlaxoSmithKline, McKesson Specialty Pharmacy, Pfizer Canada, Shoppers Drug Mart Specialty Health and Unither Biotech. These members pay yearly dues and participate in discussions at regular, typically semi-annual meetings surrounding the areas of common interest within our community. These members also provide sponsorship funds (in the form of unrestricted grants), which support our programs and campaigns. We feel that bringing all members to the table jointly allows us to eliminate bias in favouring any one company and/or medication.

Our stance is that we support access to any and all medications that have received a Notice of Compliance through Health Canada based on clinical trials demonstrating they are safe and effective in the treatment of pulmonary hypertension. PHA Canada does not favour or recommend any specific treatment, as the critical decision of what course of treatment is best for each individual patient should be determined by his or her PH treating specialist in conjunction with the patient.

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

This submission has been reviewed and approved by the Chair of our Board of Directors, who 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).

2. Condition and Current Therapy Information

2.1 Information Gathering

Information used to complete this section was gathered by interviewing patients living with pulmonary hypertension and their caregivers. Information has also been included from a Burden of Illness Survey conducted by PHA Canada in the fall of 2013, which contains data from 179 respondents (118 patients and 61 caregivers). Beyond this, information has been added based on PHA Canada's history of six years of working within the PH community and stories from patients and caregivers, which we have gathered and heard during that time. *(Please see appendix 1 for a report prepared by PHA Canada on the results of the Burden of Illness Survey).*

2.1 Impact of Condition on Patients

Pulmonary hypertension has a significant impact on the lives of patients. Pulmonary hypertension is most often a disease of which the newly diagnosed patient has never heard until the time of diagnosis. It is a shock and life-changing experience to learn that one has a rare, usually progressive and typically terminal illness. Patients and their caregivers go through abrupt life changes as a result.

Symptoms and challenges posed by pulmonary hypertension include, but are not limited to:

- Difficulty breathing with any or little exertion
- Dizziness with chest constriction (i.e. bending forward) and with sudden exertion (i.e. standing up)
- Fatigue
- Swelling of feet and ankles
- Syncope
- Chest pain

The following aspects are those most important to control:

- Breathing ability
- Peripheral edema
- Dizziness and syncope

With pulmonary hypertension, day-to-day life is made difficult, exhausting and challenging. According to the PHA Canada Burden of Illness Survey, the large majority of patients surveyed (85%) experience mild to severe symptoms or limitation with every-day activities. These include: difficulty climbing stairs or walking a short distance, difficulty having a telephone conversation, as well as difficulty performing other activities including carrying heavy and medium weight objects (laundry, grocery bags, small children); household chores (such as cutting grass, vacuuming, shovelling); dancing; and exercise. Indeed, patients can struggle with even basic tasks such as bathing, dressing, and in some instances completing simple household chores such as preparing meals, or making a bed. More than one in five patients reports being unable to be fully intimate with their partner, due to their PH. More than 40% of those surveyed report frequently suffering from fatigue, low energy and breathlessness.

Planning ahead for activities and tasks is nearly impossible. As the symptoms of pulmonary hypertension and related heart failure can fluctuate from day to day, patients may never be certain of how they will feel. Sometimes even getting out of bed is a struggle because of a lack of strength and physical symptoms such as aching legs. Patients learn to cope and look after their necessary daily activities, but at a significantly slower pace. Many patients must travel great distances to see their specialists, which places additional physical, emotional and financial burdens on them.

On a daily basis, patients struggle with the physical symptoms of shortness of breath, fatigue, and a low tolerance for physical exertion of any kind. However, some also experience other general medical symptoms, such as headaches and sleep disturbance. Patients also suffer with a loss of ability to care for themselves and fulfill their roles as caregivers for others. Some struggle with a new limited ability to care for their children. Many patients have to give up careers in the prime of their lives (nearly 60% of patients surveyed say they can no longer work or have partially stopped working due to their PH). Women must often give up dreams of themselves becoming parents, as pregnancy in women diagnosed with pulmonary hypertension is often fatal, and thus strictly contraindicated. There are increasing reports from patients and growing recognition amongst healthcare providers about psychological issues related to PH. Patients commonly experience depressed mood, anxiety, feelings of helplessness and hopelessness as they are faced with a serious illness with a high risk of death within a few years. Although patients often improve physically in response available therapies, side effects and complexities of current therapies contribute to these negative feelings.

An additional major frustration for patients is the fact that pulmonary hypertension most often is an invisible disease. Patients do not look sick when resting or seated, and thus often have to face social stigma. This is exemplified when parking in a handicapped spot and receiving comments of “abusing the system”. As the disease is unknown and misunderstood, many patients struggle with the additional challenge of having to explain their disease due to a lack of understanding from even close family members. This lack of understanding and an inability to participate in many social activities contribute to a sense of isolation felt by many patients and caregivers. The ‘invisibility’ factor places a major burden on patients and their caregivers. 71% of patients and 61% of caregivers reported feeling isolated or excluded from society because PH is not a visible disease.

Facing such pronounced challenges in so many aspects of regular day-to-day living results in a severely compromised quality of life for pulmonary hypertension patients.

2.2 Patients’ Experiences With Current Therapy

Canadian patients with PH are fortunate in that there are currently nine Health Canada approved therapies. Approved therapies include the oral agents: Sildenafil (Revatio); Tadalafil (Adcirca); Ambrisentan (Volibris); Bosentan (Tracleer); Riociguat (Adempas); Macitentan (Opsumit) and the infusion therapies: IV epoprostenol (Flolan); IV and SC Treprostinil (Remodulin); and IV Thermostable epoprostenol (Caripul).

We have received feedback from patients on most of the above-mentioned medications. The vast majority were taking a combination of 2 drugs.

Experience with therapy is generally positive. One of the main benefits is the reduction in the severity of pulmonary hypertension, as measured by reduced pulmonary artery pressures, a resulting decrease in workload on the heart associated with improved cardiac function and blood flow, and some evidence of a delay of disease progression. Patients also saw an increased ability to carry out light physical activity

such as making the bed, which was impossible before treatment. The medications help to keep the PH stable, and play a role in increasing the quality of life of patients.

While 24% of patients surveyed were unable to carry out any physical activity without symptoms and experienced symptoms even at rest, that number decreased to 5% after being placed on therapy. However, it is important to note that 27% of those on therapy continue to experience significant limitations in their ordinary physical activity due to their symptoms, and are generally only comfortable when resting. 53% of those on therapy indicate that they experience mild symptoms and slight limitations during ordinary activity (for example breathlessness while walking, climbing stairs, running errands and so on).

The effectiveness of therapy varies drastically from patient to patient, based on many factors: the patient's age, gender, type of PH, severity of PH, and underlying medical conditions. Some patients experience a dramatic improvement on a particular therapy, with less shortness of breath and other disease-related symptoms, and improved ability to function and exercise. With treatment, some patients are able to return to work, caregiver roles, and other social involvement. However, patients with PH are rarely "cured" of their disease. Despite responding to current PH therapies, many patients with PH treated with current PH therapies remain quite ill with moderate to severe PH and significant ongoing right-ventricular heart failure. In addition, they have to deal with the prospect of more complex medications, possible lung transplantation, and high risk of progressive PH with shortened survival.

Responses to PH monotherapy (single medication) are often limited, such that many patients require the use of two different PH medications concurrently (combination PH 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.

Most patients stated that they would consider the effectiveness of current therapies in controlling their condition as being "fair". While the medication is helping to keep them alive and delaying the progression of the disease, as well as alleviating some of the symptoms and making certain tasks easier, it is not a cure. Patients often remain quite symptomatic and limited, and people continue to die from this disease despite the current therapies.

Aside from taking PH-specific treatments, most patients also take diuretics and blood thinners as well as anti-nausea medication in order to control one of the side effects of PH treatment.

The adverse effects of currently approved medications include:

- Nausea (stated by all patients who provided feedback – most end up having to take anti-emetic medications to control this)
- Gastrointestinal discomfort and pain
- Diarrhea (particularly IV epoprostenol)
- Fatigue
- Insomnia
- Bruising
- Headaches
- Skin flushing, redness and spots on the skin (IV epoprostenol, IV/SC treprostinil)

One of the main hardships people discussed as far as accessing therapy was the initial approval for combination dual therapies, and cost associated with the medicines. Initial approvals were often difficult to obtain and caused hardship and additional stress on patients and their families. One patient enrolled herself in a double-blinded trial in order to have at least a chance of receiving combination therapy for which she could not get coverage. Additionally, the supplements and treatments needed for dealing with the side effects of the PH medications (such as anti-nauseants and analgesics) are typically not covered and can be extremely costly.

The unmet need described most often by patients was a cure for the disease. Additionally, they stated that dizziness and breathing continue to be issues even when on currently available medications. Their daily activities continue to be limited and they are certainly not physically capable of doing many of the things they could prior to their disease. Most patients even when on treatment are unable to work or are limited to very part time work. The difficulties of managing some medications such as IV epoprostenol and the limitations and impact on quality of life that such medications put on the lives of patients, was also seen as a need that is not being met.

2.3 Impact on Caregivers

One patient who provided us with feedback best described the impact on caregivers by stating: “If PH patients are suffering from an invisible disability, then their caregivers are even more invisible victims”.

Caregivers are often the main support for patients. As PH primarily affects women, their husbands and partners are often thrown into very difficult roles: they are financial providers (especially when patients cannot work, which is more often than not); they take on the bulk of the work around the home (household chores are often a great difficulty for patients); and in many instances, they become the main care provider for any children. In addition, caregivers support patients through attending doctors’ appointments, helping with managing side effects, mixing medications and many other duties.

According to our survey, nearly 40% of caregivers have been forced to make changes to their employment to care for someone with PH. Additionally; caregivers spend nearly 50% of their time on activities related to caring for their relative with PH.

Not only do caregivers take the brunt of the work around the home and financial responsibilities, they also become psychological support systems for these patients. They often give up their personal time, and are also living with the disease. In addition, they face the very grave reality that there is no cure and that at some point they will likely lose their loved one to this disease. Caregivers often face burnout and need many reminders to also care for themselves, something that tends to get forgotten. Relationships, particularly marriages, are sometimes victims to the strains of a patient/caregiver dynamic.

Caregivers also experience a significant amount of social isolation. 54% of caregivers responding to our survey stated that social isolation caused by a lack of understanding of the disease among friends and colleagues is a primary concern.

3. Information about the Drug Being Reviewed

3.1 Information Gathering

Information used to complete this section was gathered by conducting telephone interviews with patients who have been taking macitentan as part of a study and/or those who are taking it as a result of a post-trial bridging program. PHA Canada also conducted interviews with those not on macitentan, who are on other therapies, and/or who have been unable to take other Endothelin Receptor Antagonists due to complications with liver function. Additional information has been added based on PHA Canada's history of six years of working within the PH community and stories from patients and caregivers, which we have gathered and heard during that time.

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 hope and expectations of those we interviewed who had no experience with the new drug were that it would offer an additional option when current therapies stopped being effective. Others described the fact they have previously been prescribed endothelin receptor antagonists (ERA) such as Tracleer and were unable to continue taking them due to liver toxicity issues. The fact that macitentan seems to not have as many liver toxicity problems associated with it made those we interviewed hopeful that it could be a good option for them.

Many patients have benefitted from currently available ERAs, with symptomatic and functional improvement; having to discontinue effective ERA therapy because of liver toxicity often lead to clinical worsening. One patient in particular had been unable to continue on the ERAs due to liver toxicity problems, but did have an increase in pulmonary pressures when it was discontinued. This patient hoped that macitentan would be a good alternative choice that would allow taking an ERA without the associated liver toxicity issues.

Beyond this, the expectations were that the new drug would help to alleviate symptoms and allow patients to have more energy to do day-to-day activities. Many patients continue to experience limitations in activity even when on therapy. The hope was that quality of life, as a result of lessened symptoms, would be improved with the new drug.

Most patients are willing to tolerate some measure of side effects, as long as the benefits outweigh the side effects. For most patients, benefits include less shortness of breath, less fatigue and being able to live a more normal (closer to that which they lived prior to developing the disease) life. For these patients, side-effects such as headaches, nausea and nasal pharyngitis are tolerable, as long as their overall condition is stabilized, they see improvement in their ability to perform day to day tasks, and they are able to function with less shortness of breath.

Patients believed that a major benefit of macitentan over other drugs in the ERA class was the lower risk of liver toxicity, which, they hoped, would lead to freedom from the monthly blood work required with currently available ERAs.

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

For those patients we interviewed who had experience with macitentan as part of a clinical trial, or through compassionate supply, lessening of shortness of breath was seen. Additionally, based on test results, the progression of the disease seemed slowed as all PH test numbers (i.e. pressures, six-minute walk distance, etc.), were stable or improved.

One of the patients we interviewed had been on a clinical trial from 2009 to 2012. Originally in the 'low-dose' arm of the trial, as part of the extension study, she was given the full dose. This patient noticed improvement of her symptoms on the lower dose (less shortness of breath, stable test results), and even more of a difference when given the full 10mg dose. This patient noted significantly less shortness of breath and more "spring in the step", with a good amount more energy than she had previously.

The primary effect that was noticed by those taking the new drug versus other therapies was increased energy. One patient remarked that when she forgot to take the new drug in the morning, she noticed extreme shortness of breath by the afternoon.

The most notable side effect reported was nasal congestion, which was a tolerable side effect. No intolerable adverse effects were noted with macitentan.

One of the patients interviewed found the packaging a little difficult to manage, especially for older patients or those suffering from arthritis. Beyond this, however, patients found a once-a-day oral medication quite easy to use.

In the long term, patients were hopeful that the drug would slow the progression of their disease and allow them to live longer with decreased fatigue and shortness of breath. That being said, all patients are aware of the fact that they still face significant limitations to their lives even on this drug and that eventually their disease will continue to progress.

4. Additional Information

Scleroderma Society of Canada

1. General Information

Name of the drug CADTH is reviewing and indication(s) of interest	Macitentan (Opsumit)for Pulmonary Arterial Hypertension
Name of the patient group	Scleroderma Society of Canada
Patient group's contact information:	41 King William St, Ste 206, Hamilton ON L8H1A2 1-866-279-0632 info@scleroderma.ca www.scleroderma.ca
Permission is granted to post this submission	Yes

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 and or sponsorship 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

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 in everything from basic hygiene to household chores, and varies 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), Ambristentan (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 Sildenfil 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 and edema. 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

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 describe 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.

3. Information about the Drug Being Reviewed

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-1and the Seraphin trials results were referenced.

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:

How much improvement in the condition would be considered adequate? What other benefits might this drug have — for example, fewer hospital visits or less time off work?

Long-term survival and quality of life for Scleroderma patients with PAH has historically been very poor and for this reason any improvements that slow the progression of Scleroderma PAH would be considered sufficient to use a new drug.

With Opsumit, patients expect that it will significantly reduce their risk of death and hospitalization due to PAH, as reported in the Seraphin Trial. These improvements to their long-term outlook are not only welcome, but treasured.

In addition to longer, healthier lives, our patients are anticipating that their quality of life will be dramatically improved due to the resultant improvements in pulmonary function. With improved lung function, patient's ability to walk, care for their families, do housework and perform even the most basic tasks is augmented.

This patient population has a higher tolerance for adverse effect than average due to the few options available to them to maintain or improve functionality and extend their limited life expectancy. Given the diminished quality of life they already experience, any treatment that was effective and has milder side effects is highly valued.

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

Patients are expecting Opsumit to improve their quality and quantity of life. It is easy to use, one pill daily with or without food, and has been well tolerated.

Patients report experiencing stuffy noses, the occasional headache (particularly at the start of the drug) and overall mild flu like symptoms with Opsumit. While these side effects are annoying, they are tolerable, particularly in light of the improvements they are experiencing. Although anemia is listed as a side effect, none of the patients we spoke with stated any issues. A couple of patients reported a significant improvement in water retention (edema).

The fact that liver function tests are not required monthly, as it is for other ERAs has eased their worry about serious side effects that could damage their liver.

Patients are describing tremendous improvements in functionality and consequently quality of life. Shortness of breath and fatigue are decidedly improved. This impacts their day to day lives in very significant ways, from increased mobility to decreased dependency. The effect is profound.

> "Opsumit to me is a miracle because no side effects for me, no blood work monthly, and I can be off oxygen sometimes an hour here or there."

"I can walk to the park without having to stop...doesn't sound like much to other people, but it was the equivalent of climbing Kilimanjaro to me. I can now walk my children to the park and watch them play."
"I have been able to do light exercise for the first time in what feels like forever. This makes me feel that I have some control over my life."

4. Additional Information