Common Drug Review
Patient Group Input Submissions

riociguat (Adempas) for Pulmonary arterial hypertension (WHO group 1)

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.

CADTH received patient group input for this review on or before July 17, 2015

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Pulmonary Hypertension Association of Canada

Section 1 — General Information

Name of the drug CADTH is reviewing and indication(s) of interest		Riociguat (Adempas) for Pulmonary arterial hypertension (WHO group 1)
Name of the patient group		Pulmonary Hypertension Association of Canada
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Permission is granted to post this submission		☒ Yes ☐ No

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 which 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 Network 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, Dr. Sanjay Mehta. 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).

Section 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 the 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 Burden of Illness Survey).*

2.2 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 combined with 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 puts 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.

2.3 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 several 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 consideration of 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 available therapies.

Aside from taking PH-specific treatments, many 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
- Weight gain
- Headaches
- Skin flushing, redness and spots on the skin (IV epoprostenol)

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-emetics and analgesics) are 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.

2.4 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

Section 3 — Information about the Drug Being Reviewed

3.1 Information Gathering

Information used to complete this section was gathered by working with the PH treating centres who distributed an anonymous information gathering survey to those patients within their centres who are currently taking riociguat for pulmonary arterial hypertension as part of a study and/or those who are taking it as a result of a post-trial bridging program. 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. Since both riociguat and PDE-5 inhibitors works on the nitric oxide pathway, patients in whom PDE-5 inhibitors are contra-indicated were hopeful that they would still be eligible for treatment with Riociguat and that it would offer significant benefits.

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.

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 who responded to our questionnaire and who had experience with riociguat for pulmonary arterial hypertension as part of a clinical trial, or through compassionate supply, one of the primary effects noticed almost immediately after beginning the drug was decreased shortness of breath.

Beyond this respondents noticed:

- Improved exercise tolerance: under controlled exercise conditions they could walk a given distance at a constant speed on a treadmill while maintaining a lower heart rate than before.
- One respondent mentioned feeling that there was likely some improvement in oxygen transfer but did not feel medically qualified to determine that as definitive.
- Being able to climb stairs without shortness of breath
- End to fainting spells
- Ease in breathing outside in the cold winter air (previously unable to go out in the cold)
- Ability to move around with greater ease

- General improvement in quality of life
- A regain in normalcy in patient lives
- Being able to see/spend time with friends and family which they were doing less and less pre-riociguat
- Ability to resume normal activities: full time work, house work, caring for children

One respondent began riociguat as an add-on therapy to Remodulin and immediately experienced decrease in breathlessness (all respondents mentioned this effect) and fatigue. This respondent's right heart catheterization post-riociguat showed a significant decrease in pulmonary artery pressures.
The initial side effect noticed by some respondents was some dizziness, particularly upon standing after taking a dose, this effect seems to have subsided over time. Others did not experience any negative side effects and were pleased that the main effect they noticed was being able to function much more normally than before taking riociguat. Those who were taking riociguat as an add-on therapy mentioned that there were no additional side effects beyond those experienced on other PAH therapy.

Another respondent was switched from sitaxentan (Thelin) when it was recalled from the market. This patient has not been using any other medication other than Adempas and has seen great improvement: she is able to work full time, do house work and take care of her children. Additionally she is now able to do things like climb stairs without feeling out of breath. She considers herself to be able to live an almost "normal" life (with the exception of not being able to run).

All the patients who responded to our questionnaire found riociguat to be easy to take, even having to take a few times per day. Those who were also on IV or sub-cutaneous therapy found the medication in pill form to be much easier to administer.

In the long term, patients were hopeful that the drug would continue to help their hemodynamics improve, alleviate shortness of breath and decrease fatigue and improve their quality of life. One respondent stated that based on the tremendous improvement she experienced it should be available to anyone who could benefit from it. Another mentioned that taking riociguat has given her back hope that her quality of life will continue to improve and felt that life is significantly easier since beginning riociguat therapy.