

Pharmaceutical Benefits Scheme

Post-market Review of

Medicines to treat Pulmonary Arterial Hypertension

ToR 3

Final Report

November 2018

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Abbreviations

Abbreviation	Full Name / Wording
6MWT	Six minute walk test
6MWD	Six minute walk distance
CAMPHOR	Cambridge Pulmonary Hypertension Outcome Review
EQ-5D	EuroQol 5-dimension
ESC	Economics Sub Committee
FC	Functional class
HRQoL	Health related quality of life measures
ICER	Incremental cost effectiveness ratio
MM	mortality/morbidity
mPAP	Mean pulmonary arterial pressure
mRAP	Mean right atrial pressure
PAH	Pulmonary arterial hypertension
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PDE-5	Phosphodiesterase-5 inhibitor
PHAA	Pulmonary Hypertension Association of Australia
PSD	Public Summary Document
QoL	Quality of life
QALY	Quality-adjusted life years
Review	Post-market Review
RHC	Right heart catheterisation
SF36	36-Item short form survey
ToR	Term(s) of Reference
WHO	World Health Organization

Section 3: ToR 3

Patient relevant clinical outcomes

Review the clinical outcomes that are most important or clinically relevant to patients with PAH, and the extent to which these outcomes are included in the evidence previously considered by PBAC.

3.1 Key findings for ToR 3

- Historically, the Pharmaceutical Benefits Advisory Committee (PBAC) has primarily used the Six Minute Walk Test (6MWT) results as the main surrogate outcome when assessing submissions for pulmonary arterial hypertension (PAH) medicines.
- Clinical trials for PAH medicines may also measure a range of other clinical outcomes such as changes in World Health Organization (WHO) Functional Class (FC), clinical worsening, haemodynamic parameters, adverse events and survival.
- Treatment goals for PAH patients have evolved over time to become more patient centred and can include attaining an improved FC status, an improved six minute walk distance (6MWD) and exercise capacity, and haemodynamic parameter improvements.
- Patient relevant outcomes are reflected only in part in the evidence which the PBAC has considered in relation to submissions for PAH medicines. The key clinical outcome of relevance and significance to PAH patients is their quality of life, as reflected in their ability to function and complete everyday activities and live as normal a life as possible.
- Patients do relate improvement in their 6MWD results with their treatment efficacy but note that the results are subjective and not fully reflective of their health status.
- Patients considered that other measures, including quality of life (QoL) assessments, assessments of everyday functional ability, right heart catheterisation (RHC) measurement, echo results, and use of supplemental oxygen could also be considered as clinically relevant outcomes.
- The use of composite outcomes to assess the clinical and cost-effectiveness of PAH medicine is increasing in clinical trials.

3.1.1 Stakeholder views

- The Reference Group has noted the usefulness of health related quality of life measures (HRQoL) and their potential value in capturing benefits associated with medicines for PAH. HRQoL measures could include the EQ-5D, SF36 and the PAH specific Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR).
- The Pulmonary Hypertension Association Australia (PHAA) notes that most studies have assessed clinical outcomes through changes in exercise capacity, however, PHAA

members also consider how patients feel, daily function, prevention of hospitalisation, and survival as patient relevant outcomes.

- Consumer views on patient relevant outcomes are described in detail in section 3.2.

3.2 Patient views on relevant clinical outcomes

3.2.1 Consumer session

Three departmental representatives and the Chair of the Reference Group attended the Pulmonary Hypertension Association of Australia (PHAA) Members & Carers Day on 14 October 2017 and held a consumer session with PAH patients, their families and carers. The aim of the consumer session was to ensure that the views of a wide range of consumers were able to be included in this report.

Prior to the meeting, attendees were provided with a discussion paper that included information on the Review Terms of Reference (ToR), and identified key issues and questions for consumers and their families and carers. The questions from the discussion paper were used as the basis for prompting small group discussions where the common themes were captured on butchers' paper. Consumers and carers were also able to submit their responses to the discussion paper by email. Both small group and individual input were synthesised in a consumer summary which was reviewed by several PHAA members (refer to Appendix 3A - Consumer Outcome Statement).

The following is a summary of issues raised by consumers in relation to patient relevant outcomes and their views on the relevance of the 6MWD.

3.2.2 Impact of PAH medicines

- Consumers noted that medicines made a significant difference to their lives, and noted specific relief of PAH symptoms with ongoing medicine use, including reduced fatigue, breathlessness and heart racing.
- Some consumers reported they had improved from the point of heart failure to FC II, where they were able to come off the transplant list and recommence a semi normal life.

3.2.3 Patient relevant outcomes

- The most commonly reported symptoms of PAH from patients are fatigue, chest pain, difficulty breathing, syncope (fainting) and reduced ability to perform daily physical activities – all of which have an extensive impact on patients' QoL.
- Beyond mortality, the recurring feedback from consumers was that they primarily valued their QoL – that is, their ability to function in everyday life and an increased tolerance to exercise/activity.
- Everyday activities that consumers described as important included the ability to work, get out of bed, attend to household chores, be able to socialise, to climb stairs

and walk further. Some consumers valued the ability to travel and compete in sporting events.

- Consumers commented they may have reduced anxiety when their PAH is stable.

3.2.4 Relevance of 6MWD to patients

- Consumers did relate improvements in their 6MWD to the effectiveness of PAH medicines, and some consumers described their health status by referring to their 6MWD results or FC status.
- Some consumers linked an improvement in their exercise capacity with an improvement in their QoL and functional daily ability.
- However, consumers commented that the 6MWD can be somewhat subjective as a means of assessing their disease, as the results are a 'snapshot' of their overall health only. They noted that results can change daily and can be impacted a number of variables related to the day, time and location of the actual test, for example, travel required on the day of the test, the test area or exercise/stair climbing prior to the test. Consumers acknowledged a tendency to plan for the 6MWT.
- Consumers considered that RHC is invasive but likely more accurate than the 6MWT in assessing disease pathology for some patients.

3.2.5 Other patient relevant outcomes

- The firm view of patients was that their QoL and functional ability day to day were the most relevant outcomes to them.
- Written submissions from consumers also noted the following outcomes were patient relevant and could also be used to inform considerations of the effectiveness of PAH medicines:
 - QoL assessments
 - Everyday functional ability
 - RHC measurements
 - Echocardiogram outcomes
 - Changes in oxygen use from medications
 - Changes in exercise capacity
 - Ability to work and/or travel.

3.2.6 Adverse events

- Many consumers described side effects ranging from minor to severe, including headaches, sinus, jaw and muscle pain, foot pain, dizziness, chest tightness, gastrointestinal complications, palpitations, flushing and unwanted erections in males (associated with the use of PDE-5 inhibitors).
- Consumers also noted side effects associated with use of intravenous epoprostenol, such as infections and allergic reactions to the dressings.

- Despite these side effects, consumers generally considered that the benefits gained from PAH medicines outweighed the side effects.
- Where necessary, consumers commented that they used other medicines to treat the side effects, such as pain killers.

3.3 Outcomes considered by the PBAC in submissions for PAH medicines

A range of outcomes have been considered by the PBAC in submissions for the PBS listing of PAH medicines, as captured in table 3.1. The outcomes reported in submissions and considered by the PBAC are dominated by 6MWD, which is captured for every submission except the most recent selexipag submissions.

Table 3.1 Outcomes considered by the Pharmaceutical Benefits Advisory Committee in submissions for PAH medicines

Name of active ingredient (brand name and strength)	PBAC Meeting Date	Source	Outcomes considered by the Pharmaceutical Benefits Advisory Committee
ERAs			
Bosentan (tablets, 62.5 mg and 125 mg (base), Tracleer®)	December 2002 ¹ [REDACTED]	[REDACTED]	[REDACTED]
Sitaxentan (tablet 100 mg, Thelin®) <i>*No longer PBS listed - delisted 31 March 2011</i>	July 2007 ²	Public Summary Document (PSD) Sitaxentan July 2007	<ul style="list-style-type: none"> • 6MWD • Adverse events
Bosentan (tablets, 62.5 mg and 125 mg (base), Tracleer®)	March 2008 ³	PSD Bosentan monohydrate March 2008	<ul style="list-style-type: none"> • 6MWD • Indexed pulmonary vascular resistance • Oxygen saturation • WHO FC • Haemodynamic parameters • Adverse events
Bosentan (tablets, 62.5 mg and 125 mg (base), Tracleer®)	March 2009 ⁴ [REDACTED]	[REDACTED]	[REDACTED]

Name of active ingredient (brand name and strength)	PBAC Meeting Date	Source	Outcomes considered by the Pharmaceutical Benefits Advisory Committee
Ambrisentan (tablets, 5 mg and 10 mg, Volibris®)	July 2009 ⁵	PSD Ambrisentan July 2009	<ul style="list-style-type: none"> • 6MWD • Borg Dyspnoea Index • WHO FC • Clinical worsening • Adverse events
Macitentan (tablet 10 mg, Opsumit®)	March 2014 ⁶	PSD Macitentan March 2014	<ul style="list-style-type: none"> • 6MWD • Composite endpoint of mortality/morbidity events: <ul style="list-style-type: none"> ➢ prostanoid initiation ➢ death ➢ clinical worsening • Adverse events
PDE-5 inhibitors			
Sildenafil citrate (20 mg tablet, Revatio®)	November 2006 ⁷	PSD Sildenafil Citrate November 2006	<ul style="list-style-type: none"> • 6MWD • Adverse events
Tadalafil (20 mg tablet, Adcirca®)	November 2011 ⁸	PSD Tadalafil November 2011	<ul style="list-style-type: none"> • 6MWD • WHO FC • Clinical worsening • Haemodynamic parameters • Adverse events
Prostacyclins			
Iloprost (nebuliser solution, 10 mcg in 1 mL, 2 mL ampoule, Ventavis®)	November 2004 ⁹		
Epoprostenol Sodium (inj set containing 1 vial powder for I.V. infusion 500 mcg and 1 vial diluent 50 mL, inj set containing 1 vial powder for I.V.	March 2006 ¹⁰	PSD Epoprostenol March 2006	<ul style="list-style-type: none"> • 6MWD

Name of active ingredient (brand name and strength)	PBAC Meeting Date	Source	Outcomes considered by the Pharmaceutical Benefits Advisory Committee
infusion 1.5 mg and 2 vials diluent 50 mL, Flolan®)			
Epoprostenol sodium (500 mcg powder for I.V. infusion, (base) with diluent, 1.5 mg powder for I.V infusion (base) with diluent, Flolan®)	November 2011 ¹¹	PSD Epoprostenol November 2011	<ul style="list-style-type: none"> • 6MWD • Haemodynamic parameters: <ul style="list-style-type: none"> ➢ Mean Pulmonary vascular resistance ➢ Mean Pulmonary Arterial Pressure • Adverse events
Selexipag (tablets, 200, 400, 600, 800, 1000, 1200, 1400 and 1600 mcg, Uptravi®)	March 2016 ¹² (rejected)	PSD Selexipag March 2016	<ul style="list-style-type: none"> • Composite endpoint of time to first mortality/morbidity event: <ul style="list-style-type: none"> ➢ death ➢ hospitalisation for PAH worsening ➢ lung transplantation or balloon atrial septostomy due to worsening PAH ➢ initiation of parenteral prostanoid or chronic oxygen therapy due to worsening PAH ➢ Disease progression confirmed by decrease in 6MWD from baseline of at least 15%, and either worsening of WHO FC or need for additional PAH specific therapy (depending on WHO FC at baseline) • Adverse events
Selexipag (tablets, 200, 400, 600, 800, 1000, 1200, 1400 and 1600 mcg, Uptravi®)	March 2017 ¹³ (rejected)	PSD Selexipag March 2017	<ul style="list-style-type: none"> • Composite endpoint of time to first mortality/morbidity event: <ul style="list-style-type: none"> ➢ death ➢ hospitalisations for PAH worsening ➢ increase in WHO FC ➢ signs/symptoms of right-sided heart failure ➢ ≥ 15% decrease in 6MWD from baseline • Overall survival • Adverse events

Name of active ingredient (brand name and strength)	PBAC Meeting Date	Source	Outcomes considered by the Pharmaceutical Benefits Advisory Committee
sGC stimulators			
Riociguat (tablets, 500 mcg, 1 mg, 1.5 mg, 2 mg, 2.5 mg, Adempas®)	March 2014 ¹⁴	PSD Riociguat March 2014	<ul style="list-style-type: none"> • 6MWD • Adverse events

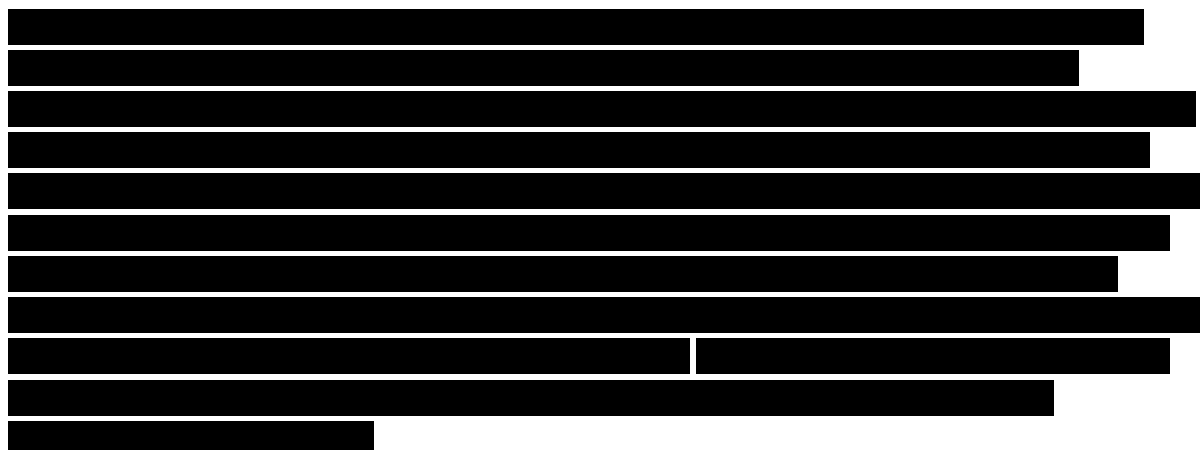
Abbreviations: 6MWD=six minute walk distance, PSD=Public Summary Document, WHO FC=World Health Organization Functional Class

3.4 Discussion

Historically, as evidenced in table 3.1, the outcomes reported in clinical trials and those presented in submissions to the PBAC are dominated by the 6MWD, which is reported in all of the submissions except the recent selexipag submissions, and has remained the common outcome relied on in each of the PBAC's decisions related to PAH medicines.

The 6MWD is a simple, inexpensive, reproducible tool that is a validated measure of exercise capacity and has been widely accepted by other international regulatory authorities for the registration of PAH drugs, as well as the PBAC. By measuring the distance a patient can walk, the 6MWD test can indirectly quantify shortness of breath and fatigue, two of the most common and debilitating symptoms of PAH. Therefore, the change in 6MWD from baseline following an intervention indicates symptomatic improvement over a time period. It can be assumed that this change manifests in improvements in a patient's ability to perform daily activities, and is therefore correlated with improvements in their QoL.

However, PAH is a chronic, progressive, functionally debilitating disease, and the prognostic relevance of 6MWD to long-term outcomes has been questioned more recently. While 6MWD was a useful primary end-point when the study and assessment of drugs for PAH was relatively new, in today's more advanced setting, disadvantages are emerging. For example, a 'ceiling effect' in 6MWD may mask efficacy in patients with less severe symptomatic disease who have high baseline walk distances but, nevertheless, may have substantial pathology. The specificity of 6MWD as a measure of exercise capacity can also be confounded, especially at low walk distances or for reasons not related to PAH. For example, in a patient with scleroderma, walk distance might be compromised as a result of frailty and other mobility problems. Deconditioning, or loss of muscle tone and endurance, can also occur in chronically ill patients and affect the distance a patient is able to walk. Further, 6MWD results cannot be fully reliable if patients are already on a background therapy that may have improved their exercise capacity to the point at which additional treatment may not provide further gains¹⁵.



The PBAC has reinforced that view since, commenting that haemodynamic parameters may provide some basis for predicting survival in patients with PAH, although noting this has not been conclusively demonstrated by appropriate clinical trials¹⁶. The PBAC has considered that haemodynamic parameters correlate with clinical state, functional class, exercise capacity, and prognosis in patients with PAH¹⁷.


Further, the PBAC has also noted that while the 6MWD is an established outcome measure, it should not be considered in isolation. In March 2014 the PBAC considered that the time to first mortality/morbidity event were the more patient relevant outcomes¹⁸.

Following this advice, the 2016 and 2017 submissions to the PBAC for an oral prostacyclin, selexipag, did not present 6MWD results as the primary outcome measure, but rather presented a trial-based cost-effectiveness analysis, in which the incremental effectiveness was measured in terms of the reduction in the number of first mortality/morbidity (MM) events per person-year over the duration of the trial. Although the submissions were rejected, the PBAC noted that the translation of first MM events prevented to life-years gained or quality-adjusted life years (QALYs) gained would be informative for the PBAC in comparing the incremental cost effectiveness ratios (ICERs) across drugs for the same disease, and agreed with the Economics Sub Committee (ESC) of the PBAC that the use of a composite outcome where death has the same clinical relevance as hospitalisation made the results difficult to interpret. The PBAC noted that the results for selexipag appeared to be largely driven by the hospitalisation and escalation of treatment, and that the relationship between these outcomes and disease progression remains unclear¹⁹.

3.5 Summary

There is some disparity between the clinical outcomes which are most relevant to patients with PAH and the extent to which these have been measured in clinical trials and included in the evidence considered by the PBAC. Patients have a strong view that the most relevant outcomes to them are reflected in their everyday functional ability and associated QoL, while the evidence considered by the PBAC has been dominated by assessment of change in exercise capacity using the 6MWD, which is the established primary end-point for PAH clinical trials. The disparity is exacerbated by the difficulty collecting strong evidence for PAH medicines given the small patient numbers, short term studies and natural history of the disease. However, the PBAC has acknowledged that the 6MWD alone is not fully reflective of clinically relevant outcomes and that composite outcomes may be considered when assessing the clinical and cost effectiveness of PAH medicines.

References



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³ PBAC, March 2008, <http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2008-03/pbac-psd-bosentan-mar08.pdf> [accessed 23 March 2018]


⁵ PBAC, July 2009, <http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2009-07/pbac-psd-ambrisentan-jul09> [accessed 23 March 2018]

⁶ PBAC, March 2014, <http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2014-03/macitentan-psd-03-2014.pdf> [accessed 23 March 2018]

⁷ PBAC, November 2006, <http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2006-11/SildenafilNov06.pdf> [accessed 23 March 2018]

⁸ PBAC, November 2011 <http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2011-11/Tadalafil ADCIRCA.pdf> [accessed 23 March 2018]



¹⁰ PBAC, March 2006, <http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2006-03/epoprostenol.pdf> [accessed 23 March 2018]

¹¹ PBAC, November 2011, <http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2011-11/Epoprostenol sodium.pdf> [accessed 23 March 2018]

¹² PBAC, March 2016, <http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2016-03/files/selexipag-psd-march-2016.pdf> [accessed 23 March 2018]

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¹⁵ Gaine, S, Simonneau, G. The need to move on from 6-minute walk distance to outcome trials in pulmonary arterial hypertension, European Respiratory Review. 2013, 22:487-494


¹⁷ PBAC, July 2009, <http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2009-07/pbac-psd-ambrisentan-jul09> [accessed 23 March 2018]

¹⁸ PBAC, March 2014, <http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2014-03/macitentan-psd-03-2014.pdf> [accessed 23 March 2018]

¹⁹ PBAC, March 2016, <http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2016-03/files/selexipag-psd-march-2016.pdf> [accessed 23 March 2018]