Agenda Item 9.01

Post-market review of Pulmonary Arterial Hypertension Medicines

1 Purpose of Application

1.1 Request that PBAC members: Consider the draft report for the Post-market review of pulmonary arterial hypertension (PAH) medicines (the Review) and make recommendations to the Minister for Health regarding the Pharmaceutical Benefits Scheme (PBS) listings of these medicines and the Review Options.

2 Current PBS listings

2.1 Current PBS listed PAH medicines (as at 1 November 2018) are shown in Table 1.

Table 1: PBS listed PAH medicines (as at 1 November 2018)

Medicine/Sponsor	Strength/form/pack size/PBS item code
Bosentan Sponsor: • Actelion • Alphapharm • Apotex • Arrow Pharma • Dr Reddy's Laboratories • Generic Health • Sandoz • Sun Pharma ANZ	62.5 mg tablet, pack of 60 *(5618Q, 6429J)* 125 mg tablet, pack of 60 *(5619R, 6430K)*
Ambrisentan Sponsor: • GlaxoSmithKline	5 mg tablet, pack of 30 *(5607D, 9648T)* 10 mg tablet, pack of 30 *(5608E, 9649W)*
Macitentan Sponsor: • Actelion	10 mg tablet, pack of 30 *(10134J, 10136L)*
Sildenafil Sponsor: • Pfizer • Accord Healthcare • Amneal • Dr Reddy's Laboratories • Sandoz	20 mg tablet, pack of 90 *(9547L, 9605M)*
Tadalafil Sponsor: • Eli Lilly	20 mg tablet, pack of 56 *(1304P, 1308W)*
Riociguat Sponsor: • Bayer	500 µg tablet, pack of 42 *(11031N, 11040C)* 500 µg tablet, pack of 84 *(11059C, 11058B)* 1.0 mg tablet, pack of 42 *(11028K, 11054T)* 1.0 mg tablet, pack of 84 *(11053R, 11060D)* 1.5 mg tablet, pack of 42 *(11046J, 11047K)* 1.5 mg tablet, pack of 84 *(11048L, 11061E)* 2.0 mg tablet, pack of 42 *(11038Y, 11045H)* 2.0 mg tablet, pack of 84 *(11030M, 11039B)* 2.5 mg tablet, pack of 42 *(11052Q, 11057Y)* 2.5 mg tablet, pack of 84 *(11024F, 11035T)*
Epoprostenol Sponsor: • Actelion (Veletri®) • GlaxoSmithKline (Flolan®)	500 µg injection, 1 vial (Veletri®) *(10111E, 10130E)* 500 µg injections (1 vial) (&) inert substance diluent (2 x 50mL vials) 1 pack (Flolan®) *(11069N, 11090Q)* 1.5 mg injection, 1 vial (Veletri®) *(10117L, 10129D)* 1.5mg injection (&) inert substance diluent (2 x 50mL vials), 1 pack (Flolan®) *(11065J, 11082G)*
Iloprost Sponsor: • Bayer	20µg/2mL inhalation solution, 30x2mL ampoules *(5751Q, 6456T)*

2.2 Table 2 provides information on the economic analyses and comparators considered by the PBAC for PBS listed PAH medicines.

Table 2: Basis of economic analysis for PBS listed PAH medicines

Medicine	Date of PBAC recommendation	PBS listing date	Basis of listing	PBS listing type
bosentan	Dec-03	Mar-04	Cost effective compared to standard care	Authority required
iloprost	Nov-04	Apr-05	Cost-minimisation to bosentan	Authority required
epoprostenol	Mar-06	Aug-06	Cost-minimisation to bosentan	Authority required
sildenafil	Mar-07	Nov-06	Cost-minimisation to bosentan	Authority required
ambrisentan	Jul-09	Dec-09	Cost-minimisation to bosentan	Authority required
tadalafil	Nov-11	Apr-12	Cost-minimisation to sildenafil	Authority required
macitentan	Mar-14	Sept-14	Cost-minimisation to bosentan	Authority required
riociguat	Mar-14	Feb-17	Cost-minimisation to bosentan and sildenafil	Authority required

3 Background

Pulmonary Arterial Hypertension

3.1 PAH is a rare and debilitating chronic disease of the pulmonary vasculature, characterised by vascular proliferation and remodelling of the small pulmonary arteries. This results in a progressive increase in pulmonary vascular resistance that, if not treated, ultimately leads to right heart failure and premature death. There is no cure for PAH other than lung transplantation. Symptoms of PAH include shortness of breath, dizziness, chest pain and fatigue.

3.2 The current restrictions for PBS subsidised PAH medicines include reference to specific subtypes of PAH, and to disease severity.

3.3 The WHO classification of pulmonary hypertension (PH) differentiates between five types of PH. PAH represents Group 1 within the PH classification system and is further divided into four subtypes on the basis of aetiology.

Table 3 WHO classification of Group 1 Pulmonary Hypertension disease subtypes

1. Pulmonary arterial hypertension
1.1 Idiopathic PAH
1.2 Heritable PAH
1.2.1 BMPR2
1.2.2 ALK-1, ENG, SMAD9, CAV1, KCNK3
1.2.3 Unknown
1.3 Drug and toxin induced
1.4 Associated with:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart diseases
1.4.5 Schistosomiasis
1′. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
1″. Persistent pulmonary hypertension of the newborn (PPHN)

3.4 The disease severity of PAH is classified according to a system of WHO functional classes. The current criteria are in Table 4.

Table 4 WHO functional classes (FC) for PAH

WHO FC I – Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain or near syncope.
WHO FC II – Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain or near syncope.
WHO FC III – Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain or near syncope.
WHO FC IV – Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

Background to the Review

3.5 In February 2015 the DUSC conducted a PAH medicines utilisation analysis. The DUSC considered that the PBS restrictions for PAH medicines were not consistent with current treatment guidelines in that they:

- Required failure to respond to 6 or more weeks of appropriate vasodilator treatment for WHO FC III patients with a mean right atrial pressure of 8 millimetre of mercury (mmHg) or less;
- Did not allow treatment of WHO FC II patients; and
- Did not allow combination therapy.

3.6 In July 2015, the PBAC considered a submission from a sponsor which identified concerns that the PBS restrictions for PAH medicines were not consistent with treatment guidelines and best practice.

3.7 The PBAC recommended to the Minister for Health that a post-market review be undertaken on PAH medicines, including the existing medicines listed for class III and class IV patients, and the additional clinical place of these therapies as recommended in international guidelines.

3.8 In August 2016, the PBAC endorsed the final terms of reference (ToR) for the Review. The ToR were approved by the Minister for Health in November 2016.

3.9 The department commissioned independent contractors (University of Adelaide, University of New South Wales) to undertake research to assist in informing the Review's response to the ToR. In addition, the Pulmonary Hypertension Society of Australia and New Zealand and the Australian Scleroderma Interest Group provided information on combined use of PAH medicines in Australia based on their patient registries.

3.10 An independent Reference Group was established to guide and provide advice to the Review. The Reference Group informed the development of the draft report, provided advice on issues raised by stakeholders and considered the evidence provided in the draft report.

3.11 The Review has been conducted according to the published Post-market Review Framework. There were a number of opportunities for stakeholder consultation including:

- the opportunity to comment on the draft ToR
- a public submission process addressing the Review ToR
- a consumer forum with members of the Pulmonary Hypertension Association Australia held in Sydney on 14 October 2017 as part of their Patient and Carers Day
- sponsor consultation on the draft report (2 May to 22 May 2018) and
- a public consultation process on the draft report (consultation period from 21 May to 10 June 2018).

3.12 Stakeholder comments to the review ToR have been published on the Review's **Public Consultation website**, except where requested otherwise.

4 Key findings of the Review

The PBAC noted the key findings under the following four ToR.

4.1 *ToR 1: Review recent clinical guidelines for the management of PAH and compare this to the PBS restrictions and Therapeutic Goods Administration (TGA) indications for the use of PAH medicines.*

4.1.1 A systematic search of relevant evidence-based guidelines or evidence-linked clinical practice guidelines from regulatory/funding/health technology assessment bodies, guidelines databases and other relevant websites for the treatment of WHO FC II, III or IV PAH was undertaken.

4.1.2 The key guidelines of relevance to Australian practice are the:

- 2015 European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines for the diagnosis and treatment of pulmonary hypertension,
- the Pharmacologic Therapy for Pulmonary Arterial Hypertension in Adults: CHEST guideline and expert panel report (American College of Chest Physicians, 2014), and
- Drugs for Pulmonary Arterial Hypertension: Comparative Efficacy, Safety, and Cost-Effectiveness — Recommendations Report (Canadian Agency for Drugs and Technologies in Health 2015).

4.1.3 A comparison between guideline recommendations, TGA indications and PBS restrictions is shown in Table 5 below.

Table 5: Comparison of PBS restrictions, TGA indications and PAH guidelines

Criterion	PBS Listings	TGA Status	PAH Guidelines
WHO FC	Treatment for WHO FC III-IV PAH	Prostanoids - WHO FC Class III-IV PDE-5 inhibitors - WHO FC Class II-III ERAs - WHO FC II-IV sGC stimulators - WHO FC II-IV	Monitoring for WHO FC I Oral agents for WHO FC II Oral agents or prostanoids for WHO FC III-IV
Oral PAH medicines place in therapy	PDE-5 inhibitors - WHO FC III ERAs - WHO FC III-IV sGC stimulator - WHO FC III-IV	PDE-5 inhibitors - WHO FC Class II-III ERAs - WHO FC II-IV sGC stimulators - WHO FC II-IV	Standard of care (SoC) for WHO FC II-III In combination with other oral agents or prostanoids for WHO FC IV No recommendations based on line of therapy (1st line etc)
Prostanoids place in therapy	epoprostenol - 2nd line WHO FC III, 1st line in FC IV iloprost for PAH-DT FC III-IV and FC IV. No prostanoids listed for PAH-CHD	epoprostenol registered for IPAH, HPAH, PAH-CTD iloprost registered for IPAH, PAH-CTD and PAH-DT No prostanoids approved for PAH-CHD.	Recommended for WHO FC III (especially high risk) and WHO FC IV No recommendations based on line of therapy Recommendations for PAH-CHD are consensus based but are otherwise consistent with WHO Group 1 conditions
PAH subtypes	Medicines are PBS-listed by PAH subtype Treatment for IPAH, HPAH, PAH-CTD and PAH-DT Oral medicines - PAH-CHD No listings for PAH-HIV + PAH-PH	Medicines are approved by PAH subtype sildenafil, tadalafil, ambrisentan + tadalafil combination are indicated for Group I PAH Only iloprost approved for PAH-DT No prostanoids approved for PAH-CHD	Treatment recommendations apply to all WHO Group 1 PAH types
Monotherapy	All PBS listings	All TGA registrations	Initial monotherapy recommended for treatment naïve patients without high risk factors (WHO FC II-III)

Criterion	PBS Listings	TGA Status	PAH Guidelines
Initial combination therapy	Not permitted (treatment must be the sole PBS-subsidised PAH agent)	PAH medicine combination registered for combination use: • ambrisentan + tadalafil; • macitentan + PDE-5 inhibitor or iloprost; • riociguat + ERA or iloprost	Recommended for WHO FC III and WHO FC IV with high risk factors. The ESC/ERS guidelines also recommend initial oral combination as an option for WHO FC II patients.
Sequential combination therapy	Not permitted.	PAH medicine combination registered: • ambrisentan + tadalafil; • macitentan + PDE-5 inhibitor or iloprost; • riociguat + ERA or iloprost	SoC for patients WHO FC II-IV with inadequate response, up to a maximum of three PAH medicines.
RHC	One of 3 key assessments to provide a baseline measurement – not always required (with justification)	—	RHC is gold standard for diagnosis of PAH – essential unless explicitly contraindicated. RHC relies on ECHO as preliminary test.
ECHO	One of 3 key assessments to provide a baseline measurement – not always required (with justification)	—	ECHO not recommended for diagnosis of PAH. Recommended as essential part of work-up and decision to proceed to RHC. If RHC is available it is likely that ECHO has been done.
If no RHC	RVSP >40 mmHg by ECHO, with normal LVEF	—	Likelihood of PAH to be based on features suggestive of PAH by ECHO, described in ToR 1 Table 1.10. They do not include RVSP or PASP.
6MWD	One of 3 key assessments to provide a baseline measurement – not always required (with justification)	—	Not diagnostic of PAH. One of a panel of baseline assessments to assess disease status and patient risk of PAH clinical worsening.
Patient risk category	Not mentioned.	Not a feature of approved indications.	A key assessment for determination of clinical management, treatment decisions and monitoring. There is no definitive set of parameters for patient

Criterion	PBS Listings	TGA Status	PAH Guidelines
			risk.
Response to treatment	Response defined as stability or improvement of disease. Patients who fail to demonstrate a response must cease therapy with that agent.	—	Response defined as clinical improvement and/or progress towards therapeutic goals. Unless disease is severe, maintaining clinical status may still be an inadequate response. Patients with inadequate clinical response recommended to continue on current therapy and to add a further agent from a different class.
Timing of follow-up	Each authority approval should provide 6 months of treatment; follow-up required at 5 months to make next application.	—	Follow-up at 3-6 months after change in therapy; or on clinical worsening
Patient age group	Restrictions silent on age group	Only bosentan approved for use in children.	Treatment and diagnostic recommendations broadly the same in children as for adults. 6MWD not prognostic for PAH in children. Dose adjustment required for sildenafil in children.
Trial of CCBs – patients	Required for WHO FC III – IPAH, HPAH, PAH and PAH-CTD Not required for PAH-CHD	Dosing and safety not included in PI for CCBs (diltiazem, nifedipine, amlodipine) However, amlodipine, diltiazem and nifedipine have specific TGA registered indications for hypertension and angina.	Recommended for IPAH, HPAH and PAH-DT patients only. Patients not showing acute vasoreactivity response unsuited to CCBs due to safety concerns and lack of benefit Not recommended: PAH-CTD or PAH-CHD
Trial of CCBs – test criterion	mRAP 8mm Hg or below, by RHC	—	Positive response to acute vasoreactivity test during RHC defined as decrease in mPAP >10 mm Hg, to a mPAP <40 mm Hg, with no worsening of cardiac output
Trial of CCBs – response	Minimum trial of 6 weeks required. Same definition as for response	—	Follow-up at ~3 months. Response should show a dramatic improvement or near normalisation to ~WHO FC I

Criterion	PBS Listings	TGA Status	PAH Guidelines
	to PAH agents		
Designated hospitals	>60 centres listed by DHS. No criteria required for number of cases or RHC procedures.	—	PAH treatment centres should see at least 300 referred patients per year; 50 RHC procedures per year

PBS=Pharmaceutical Benefits Scheme; CCBs=calcium channel blockers; TGA=Therapeutic Goods Administration; PAH=pulmonary arterial hypertension; WHO=World Health Organization; FC=functional class; PDE-5 inhibitor=phosphodiesterase type 5 inhibitor; ERA=endothelin receptor antagonist; ESC=European Society of Cardiology; ERS=European Respiratory Society; SoC=standard of care; PAH-'XXX'=PAH due to (CHD=congenital heart disease; DT=drug or toxin induced; CTD=connective tissue disease; HIV=Human Immunodeficiency Virus; or, PH=portal hypertension); IPAH=idiopathic PAH; HPAH=heritable PAH; RHC=right heart catheterisation; ECHO=echocardiography; RVSP=right ventricular systolic pressure; LVF=left ventricular function; PASP=pulmonary artery systolic pressure; 6MWD=6 minute walk distance; CCB=calcium channel blocker; PI=product information; mRAP=mean right atrial pressure; DHS=Department of Human Services

4.2 *ToR 2: Review the utilisation of PAH medicines in Australia, including sources of data that can provide additional information on clinical use that is not available from PBS data.*

4.2.1 An analysis of the utilisation of PAH medicines was undertaken using prescription data and date of death data from the Department Human Services PBS Prescriptions Database. Dispensed prescription data for PAH medicines listed on the PBS were exacted for the period from 1 July 2013 to 31 December 2016 based on the date of dispensing. The data were extracted in August 2017.

4.2.2 The annual number of PAH medicine dispensings increased from 20,454 in 2014 to 23,375 in 2016; the corresponding PBS benefit paid increased from $53.22 million to $58.75 million. The analysis of PBS data found:

- Endothelin receptor antagonists (ERAs) were the most commonly dispensed medicine class, accounting for 77% of all PBS PAH dispensings in 2016.
- Bosentan was the most commonly dispensed PBS PAH medicine in 2015 and macitentan was the most commonly dispensed PAH medicine in 2016.
- The majority of prevalent patients treated with PAH medicines were female (73% in 2016).
- The incident rate for patients newly treated with PAH medicines remained relatively stable across the study period.
- The highest treated incidence rate with PAH medicines (2014-2016) was in females 75-84 year old, followed by females 65-74 year old. The majority of incident patients started PBS subsidised treatment with 10 mg macitentan (57% of new patients in 2016), followed by 20 mg sildenafil (18.7% of new patients in 2016).
- Switching between PBS-listed PAH medicines was not common. Among a total of 3187 treated patients, 418 (13%) switched medicines between 2013 and 2016. Patients most commonly switched from phosphodiesterase-5 (PDE-5) inhibitors to ERAs.

4.2.3 Cross-sectional analyses of two data sources, the Pulmonary Hypertension Society of Australia and New Zealand (PHSANZ) registry data analysis and the Australian Scleroderma Cohort Study data analysis were also undertaken.

4.2.4 The Review found overall:

- Across all three datasets analysed, ERAs were the most commonly used class of PAH medicines followed by PDE-5 inhibitors.
- In both registries approximately 50% of patients were prescribed monotherapy, 40% dual therapy and 10% triple therapy.
- The utilisation of PBS medicines cannot be determined according to WHO FC as the registry data analyses did not provide specific information on the extent of patients being initiated to PAH therapy in WHO FC II.

- ERA was the most commonly prescribed monotherapy, ERA plus PDE-5 inhibitor was the most commonly prescribed dual therapy combination and ERA plus PDE-5 inhibitor plus prostanoid was the most commonly prescribed form of triple therapy.

4.3 *ToR 3: 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.*

4.3.1 A consumer forum was held to answer pre-determined questions on important or clinically relevant outcomes for patients on 14 October 2017 with members of the Pulmonary Hypertension Association Australia. Written submissions from members were received between 11 October and 31 October 2017. Consumer input was compared to evidence previously considered by the PBAC.

4.3.2 The Review found:

- Historically, the Pharmaceutical Benefits Advisory Committee (PBAC) has primarily considered studies that present Six Minute Walk Distance (6MWD) results as the main surrogate outcome when assessing efficacy of PAH medicines.
- Clinical trials for PAH medicines may also measure a range of other clinical outcomes such as changes in WHO 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 WHO FC status, an improved 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 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. The PBAC reaffirmed their view that composite outcomes where death has the same clinical relevance as hospitalisation made the results difficult to interpret. The translation of morbidity/mortality events prevented into

life-years gained or QALYs would be more informative for PBAC in comparing medicines for PAH.

4.4 *ToR 4: Collate and evaluate evidence on the effectiveness and safety of PAH medicines, including combination use and use in the WHO functional class II patient populations.*

4.4.1 The review focussed on evidence that has not previously considered by the PBAC until July 2017. A systematic literature review was performed; encompassing both the peer-reviewed literature and any additional evidence (published or unpublished) provided by the sponsors in their ToR public consultation submissions. The peer-reviewed literature was screened for clinical studies that consider the effectiveness and safety of monotherapy, dual combination therapy and triple combination therapy in patients with PAH.

4.4.2 The Review findings for the effectiveness and safety of monotherapy of medicines used to treat patients with WHO FC I or II PAH are summarised in Table 6.

Table 6: Summary of evidence: Monotherapy for patients with WHO FC I or II PAH

Medicine used to treat PAH	Clinical Effectiveness Trials identified	Safety Trials identified	Conclusion
Monotherapy for patients with WHO FC I or II PAH			
ERA versus placebo	Four RCTs in patients with WHO FC I/II PAH: • ARIES-1&2 used ambrisentan. • EARLY used bosentan. • SERAPHIN used macitentan. The evidence provided by these trials is summarised in Table ES.5 of the Report.	No evidence to evaluate the comparative safety of an ERA medication versus placebo when used to treat patients with WHO FC I/II PAH.	Overall, the use of an ERA medication to treat patients with WHO FC I/II PAH is likely to be beneficial.
PDE-5 inhibitor versus placebo	Three RCTs in patients with WHO FC I/II PAH: • The PHIRST and Mukhopadhyay 2011 trials used tadalafil. • The SUPER-1 trial used sildenafil. Two cohort studies reporting on all-cause mortality: • Sun 2013 • Sastry 2007 The evidence provided by these studies is summarised in Table ES.6 of the Report.	There was no evidence available to evaluate the comparative safety of PDE-5 inhibitors versus placebo when used to treat patients with WHO FC I/II PAH.	Overall, there is considerable uncertainty as to whether the use of PDE-5 inhibitor medication to treat patients with WHO FC I/II PAH would be beneficial.
Prostanoid versus placebo			There was no evidence available to determine the safety and effectiveness of prostanoids in treating patients with WHO FC I/II PAH.

Medicine used to treat PAH	Clinical Effectiveness Trials identified	Safety Trials identified	Conclusion
Monotherapy for patients with WHO FC I or II PAH			
sGC stimulator versus placebo	One RCT in patients with WHO FC I/II PAH: • The PATENT-1 trial used riociguat. The evidence provided by this trial is summarised in Table ES.7 of the Report.	There was no evidence available to evaluate the comparative safety of a sGC stimulator versus placebo when used to treat patients with WHO FC I/II PAH.	Overall, there is considerable uncertainty as to whether the use of sGC stimulator medication to treat patients with WHO FC I/II PAH is beneficial.

Evidence of effectiveness and safety of monotherapy in WHO FC III or IV PAH not previously considered by the PBAC

4.4.3 There was no new evidence concerning the effectiveness or safety of monotherapy with a PAH medicine, compared to the main comparator accepted by the PBAC, in patients with WHO FC III or IV PAH. The evidentiary basis for PBAC's positive recommendation of the listing of these PAH medicines is summarised in Table ES.8 of the Report.

Effectiveness and safety of dual combination therapy

4.4.4 The Review findings for the effectiveness and safety of dual combination therapy in patients with PAH are summarised in Table 7.

Table 7 Summary of Evidence Dual Combination Therapy for Patients with PAH

Medicine used to Treat PAH	Clinical effectiveness trials identified	Safety trials identified	Conclusion
Dual combination therapy for patients with PAH			
ERA in addition to a PDE-5 inhibitor compared with placebo plus a PDE-5 inhibitor	Four RCTs: • Three trials, (EARLY, COMPASS-2 and SERAPHIN) enrolled patients on stable PDE-5 inhibitor monotherapy (sequential combination therapy). • One trial (AMBITION) enrolled treatment naïve patients (initial combination therapy). The evidence provided by these trials is summarised in Table ES.9 of the Report.	Three RCTs: • COMPASS-2, SERAPHIN and AMBITION The evidence provided by these trials is summarised in Table ES.10 of the Report.	Overall, there is some evidence to suggest that the use of an ERA in addition to PDE-5 inhibitor, relative to PDE-5 inhibitor monotherapy to treat PAH patients is likely to be beneficial. The evidence for patients with WHO FC III/IV PAH and for patients with different PAH aetiologies is more limited, introducing more uncertainty. Overall, use of an ERA in addition to a PDE-5 inhibitor could be non-inferior to PDE-5 inhibitor monotherapy in terms of safety when treating PAH patients. The comparative safety of an ERA plus a PDE-5 inhibitor relative to PDE-5 inhibitor monotherapy in the subgroup of patients with IPAH/HPAH and in the subgroup of patients with PAH-CTD appeared to be largely consistent with the comparative safety in the overall PAH population.
ERA in addition to prostanoid compared with placebo plus a prostanoid	Two RCTs: • BREATHE-2 enrolled treatment-naïve patients with WHO FC III/IV PAH to receive combination therapy or monotherapy.	Two RCTs: • BREATHE-2 and Han 2017 There were no new safety signals identified. The evidence provided by these trials	Overall, there is uncertainty as to whether an ERA in addition to prostanoid therapy, relative to prostanoid monotherapy, is beneficial in patients with WHO FC III/IV PAH. Overall, although there is uncertainty,

Medicine used to Treat PAH	Clinical effectiveness trials identified	Safety trials identified	Conclusion
	• Han 2017 enrolled treatment-naïve patients with WHO FC III/IV PAH to receive combination therapy or monotherapy. The evidence provided by these trials is summarised in Table ES.11 of the Report.	is summarised in Table ES.12 of the Report.	use of an ERA in addition to a prostanoid could be non-inferior to prostanoid monotherapy when treating patients with WHO FC III/IV PAH.
PDE-5 inhibitor in addition to an ERA compared with placebo plus an ERA	Five RCTs: • Four trials (PHIRST, Mainguy 2013, Vizza 2017 and Zhuang 2014) enrolled patients on stable PDE-5 inhibitor monotherapy (sequential combination therapy). • One trial (AMBITION) enrolled treatment naïve patients (initial combination therapy). The evidence provided by these trials for all PAH patients is summarised in Table ES.13 of the Report.	Four RCTs: • PHIRST, AMBITION, Vizza 2017 and Zhuang 2014 There were no new safety signals identified. The evidence provided by these trials for all PAH patients is summarised in Table ES.14 of the Report.	Overall, there is some evidence to suggest that the use of a PDE-5 inhibitor in addition to an ERA to treat PAH patients, relative to ERA monotherapy, is likely to be beneficial. The evidence for patients with WHO FC III/IV PAH, and for patients with either IPAH/HPAH or PAH-CTD is more limited. Overall, the use of a PDE-5 inhibitor in addition to an ERA appears non-inferior to ERA monotherapy when treating PAH patients overall, although there is possible safety concern for serious adverse events (AEs) in the subgroup of patients with PAH-CTD.
PDE-5 inhibitor in addition to a prostanoid compared with placebo plus a prostanoid.	One RCT: • PACES-1 enrolled patients receiving long-term intravenous epoprostenol therapy to receive combination therapy with sildenafil plus epoprostenol or epoprostenol alone.	One RCT reported on the effectiveness of a PDE-5 inhibitor in addition to prostanoid therapy in treating PAH compared with placebo plus a prostanoid: • PACES-1 There were no new safety signals	Overall, the use of a PDE-5 inhibitor in addition to a prostanoid, relative to prostanoid monotherapy, to treat PAH patients is likely to be beneficial. Overall, the use of a PDE-5 inhibitor in addition to a prostanoid is likely to be non-inferior to prostanoid monotherapy in terms of safety when treating PAH

Medicine used to Treat PAH	Clinical effectiveness trials identified	Safety trials identified	Conclusion
	The evidence provided by this trial for all PAH patients is summarised in Table ES.15 of the Report.	identified. The evidence provided by this trial is summarised in Table ES.16 of the Report.	patients.
Prostanoid in addition to an ERA compared with a placebo plus an ERA	Two RCTs: • COMBI enrolled patients with WHO FC III IPAH (who were already being treated with bosentan) to receive combination therapy with the addition of iloprost or continue bosentan monotherapy • STEP enrolled patients with PAH who were already being treated with bosentan to receive combination therapy with the addition of iloprost or continue bosentan monotherapy The evidence provided by these trials for patients with WHO FC III/IV PAH is summarised in Table ES.17 of the Report.	Two RCTs: • COMBI and STEP There were no new safety signals identified. The evidence provided by these trials is summarised in Table ES.18 of the Report	Overall, there is limited evidence to suggest that the use of a prostanoid in addition to an ERA, relative to ERA monotherapy, in treat patients with WHO FC III/IV PAH may be beneficial. This finding would be stronger if it were replicated in additional research. Overall, there is considerable uncertainty as to whether the use of a prostanoid in addition to an ERA is likely to be as safe as ERA monotherapy in patients with WHO FC III/IV PAH.
sGC stimulator in addition to an ERA compared with a placebo plus an ERA	One RCT: • PATENT-1 enrolled WHO FC I-IV PAH patients with or without background ERA or prostanoid therapy, to receive riociguat or placebo. A subgroup analysis for pre-treated patients with WHO FC III/IV PAH was also undertaken.	There is no evidence to evaluate the comparative safety of a sGC stimulator in addition to an ERA, relative to ERA monotherapy, when used to treat patients with PAH.	Overall, there is very limited evidence indicating that the use of a sGC stimulator in addition to an ERA, relative to ERA monotherapy, may be beneficial for PAH patients. The evidence for patients with WHO FC III/IV PAH showed a similar beneficial effect. This finding would be stronger if it were replicated in additional research.

Medicine used to Treat PAH	Clinical effectiveness trials identified	Safety trials identified	Conclusion
	[12/87 (14%) patients in this subgroup were treated with a prostanoid instead of an ERA]. The evidence provided by this trial is summarised in Table ES.19 of the Report.		
sGC stimulator in addition to PDE-5 inhibitor compared with placebo plus a PDE-5 inhibitor	One RCT: • PATENT-PLUS enrolled WHO FC III/IV PAH patients receiving stable sildenafil therapy to additional receive either riociguat or placebo. No subgroup analyses were performed. The evidence provided by this trial is summarised in Table ES.20 of the Report.	One RCT: • PATENT-PLUS There were no new safety signals identified. The evidence provided by this trial is summarised in Table ES.21 of the report.	Overall, there is insufficient evidence to determine whether the use of a sGC stimulator in addition to a PDE-5 inhibitor, relative to PDE-5 inhibitor monotherapy, is likely to be beneficial for PAH. Overall, there is considerable uncertainty whether the use of a sGC stimulator in addition to PDE-5 inhibitor, relative to PDE-5 inhibitor monotherapy, would cause additional harm to PAH patients.
sGC stimulator in addition to a prostanoid	One RCT: • PATENT-1 enrolled PAH patients with or without background ERA or prostanoid therapy, to receive riociguat or placebo. Due to the small size of the sGC stimulator ± prostanoid group, no further subgroup analysis was undertaken. The evidence provided by this trial is summarised in Table ES.22 of the Report.	There is no evidence to evaluate the comparative safety of a sGC stimulator in addition to a prostanoid, relative to prostanoid monotherapy, when used to treat patients with PAH.	Overall, there is considerable uncertainty as to whether the use of a sGC stimulator in addition to a prostanoid, relative to prostanoid monotherapy to treat PAH patients is likely to be beneficial.

Effectiveness and safety of triple combination therapy

4.4.5 The Review found no comparative evidence concerning the effectiveness and safety of triple combination therapy involving PBS listed PAH medicines relative to dual combination therapy in any patients with PAH.

4.5 *Following ToR 1-4, consider reviewing the cost-effectiveness of existing PBS listed PAH medicines, and in treatment of WHO functional class II and combination treatment in class III and class IV patients.*

4.5.1 There was no new clinical evidence identified for the use of PAH medicines in monotherapy reporting mortality or quality of life outcomes to inform a new cost-effectiveness assessment of current PBS listed PAH medicines.

4.5.2 The utilisation review of PBS data indicated that PAH medicines are being used as the sole PBS subsidised PAH therapy, consistent with their current restrictions.

4.5.3 Overall, the use of ERAs is likely to be beneficial for patients in WHO FC II, however there is considerable uncertainty whether the use of PDE-5 inhibitors and sGC stimulators is beneficial, and there was no evidence found to support monotherapy use of prostanoids in patients presenting in WHO FC I or II.

4.5.4 While there is trial evidence to support dual PAH therapy over monotherapy, it varies according to the various combinations, and is overall inconclusive for the sub-groups of patients treated in WHO FC III and IV. However, these sub-groups were small and almost certainly underpowered to report significant differences between treatment arms.

4.5.5 Several trials (SERAPHIN, HAN 2017, COMBI, PATENT-1) measured change in quality of life in patients (WHO FC II-IV) treated with combinations of: ERAs and PDE-5 inhibitors; ERA and prostanoids; and ERA added to sGC stimulator. All trials reported significant improvements in quality of life in patients treated with combination therapy compared to monotherapy.

4.5.6 The PBAC has not received a submission requesting subsidised access to PAH specific medicines for patients presenting in WHO FC II.

4.5.7 The PBAC has considered a submission for selexipag in combination with an ERA and/or PDE-5 inhibitor. The PBAC rejected this submission on two occasions due to high and uncertain cost effectiveness in the requested dual and triple combinations.

4.5.8 Due to patent expiry and movement to Formulary 2, the original PBS prices for bosentan, epoprostenol, sildenafil and tadalafil are now lower than when originally listed and are likely to fall further due to PBS price disclosure mechanisms.

4.5.9 Cost-effectiveness may be acceptable for dual combination therapy involving currently listed PBS PAH medicines noting that PBAC would need to accept the evidence of some clinical benefit and non-inferior safety in dual therapy over monotherapy, as dual therapy would likely result in an additional net cost to the PBS.

5 PBAC Outcome

5.1.1 The PBAC considered the stakeholder submissions to the Review, sponsors' PSCR, pre-PBAC responses, ESC and DUSC advice in addition to the draft Report.

5.1.2 Overall, the PBAC accepted the key findings presented in the PMR of PAH medicines draft Report.

5.1.3 The PBAC considered the six options presented in the Review Report and made the following comments and recommendations.

5.2 Option 1: Extend PBS restrictions for ERA's, PDE-5 inhibitors and sGC stimulators to include monotherapy for patients presenting with WHO functional class II symptoms.

5.2.1 The PBAC recalled that to date, it had not received a submission to PBS list PAH targeted medicines to treat patients presenting with WHO FC II symptoms.

5.2.2 The PBAC noted that the 2015 ERS/ERC guidelines and CHEST guideline recommend oral monotherapy (PDE-5 inhibitors, ERAs and sGC stimulators) for patients with WHO FC II symptoms who are treatment naïve and at low or intermediate risk of disease progression. These medicines are all TGA registered for use in WHO FC II PAH. The PBAC also noted that current PBS restrictions for PAH targeted medicines do not align with clinical guidelines, limiting use of PBS subsidised PAH medicines to patients in WHO FC III-IV at the time they initiate treatment.

5.2.3 However, unlike clinical guidelines, the PBAC is required to consider both clinical effectiveness and cost-effectiveness in making recommendations for subsidy. The differences between TGA registration, PBS restrictions and clinical guidelines create concerns for prescribers and patients, which include inequities in access and potential for use outside PBS restrictions.

5.2.4 The PBAC noted the demand from patients and prescribers for access to PBS subsidised PAH medicines to treat patients presenting in WHO FC II. According to registry data approximately 20% of patients were classified as having WHO FC II symptoms at time of diagnosis, while the majority of patients presented in WHO FC III. The PBAC considered it may be reasonable to initiate therapy in the earlier stage of disease with the intent of delaying progression of symptoms and to improve health outcomes. The PBAC also acknowledged that due to the subjective interpretation of symptom severity, there may already be use of PBS subsidised medicines in patients presenting with WHO FC II symptoms.

5.2.5 The PBAC noted that pre-PBAC responses from all three sponsors supported extension of the PBS restrictions for ERAs, PDE-5 inhibitors and sGC stimulators to include monotherapy for patients presenting with WHO FC II symptoms.

5.2.6 The PBAC considered that ERAs show similar evidence of benefit in WHO FC II and FC III from the same trials (EARLY, ARIES-1, ARIES-2, SERAPHIN) and that

there was better evidence for ERAs in WHO FC II than the other classes of PAH targeted medicines, although there is some evidence of benefit for PDE-5 inhibitors (PHIRST, SUPER-1). There was little trial evidence to assess comparative safety of these medicines in WHO FC II.

5.2.7 The PBAC considered that subsidy of PAH medicines in WHO FC II should be on the basis of medicine class and at the current time, should be restricted to medicines within the ERA and PDE-5 inhibitor classes.

5.2.8 The PBAC agreed that this option to extend monotherapy to WHO FC II would increase the number of patients eligible for PBS-listed PAH medicines and therefore would impact the total cost to the PBS. The PBAC considered the longer survival and persistence with treatment when initiating patients in WHO FC II would increase the prevalent treated population. However, the increase is likely to be small given that only 20% of patients in the registry data present in WHO FC II and that subjective interpretation of WHO FC already occurs.

5.2.9 The Review Reference Group supported Option 1 but did not support economic modelling of the cost-effectiveness in the WHO FC II population. Past modelling for this disease has been highly uncertain and is unlikely to be significantly different to patients presenting in WHO FC III. Two sponsors, Actelion and GSK, agreed that cost effectiveness modelling may not be necessary to establish cost effectiveness for this group of patients.

5.2.10 The PBAC agreed with the ESC's pragmatic view that a full cost-effectiveness analysis was likely not necessary. The PBAC agreed that the benefits of monotherapy in WHO FC II were most likely similar to the benefits of monotherapy in WHO FC III-IV (current listings of ERAs and PDE-5 inhibitors). Therefore, the cost-effectiveness of use in WHO FC II is likely to be acceptable and similar to the cost-effectiveness of use in the WHO III & IV population (at current prices).

5.2.11 The PBAC requested that the department provide modelled estimates of the likely cost impact to the PBS of this change to the restrictions for currently listed ERAs and PDE-5 inhibitors.

5.2.12 Mechanisms such as a cap on subsidy or risk share agreement may also be necessary to manage any uncertainty in the estimates of PBS cost.

5.2.13 Extension of the recommendation to additional classes of PAH medicines other than ERAs and PDE-5 inhibitors with less evidence of clinical benefit in WHO FC II may be possible should sponsors be able to provide additional evidence of their effectiveness.

Recommendation:

5.2.14 The PBAC was of a mind to recommend the extension of PBS restrictions to patients in WHO FC II for monotherapy with targeted PAH medicines. Subsidy should be on the basis of medicine class and based on the evidence provided in the PMR report, should be restricted to PBS listed medicines within the ERA and PDE-5 inhibitor classes. The PBAC requested the revised PBS

restrictions for ERAs and PDE-5 inhibitors be presented to the PBAC again prior to a final recommendation. The estimates of cost to the PBS associated with the revised restrictions should also be provided.

5.3 Option 2: Extend PBS restrictions for specific combinations of ERA's, PDE-5 inhibitors, sGC stimulators and prostanoids to include dual combination therapy for patients presenting with WHO functional class II symptoms.

5.3.1 The PBAC recalled that to date it had not considered a submission from sponsors to subsidise dual combination therapy with targeted PAH medicines (initial or sequential combination) to treat patients with WHO FC II symptoms.

5.3.2 The PBAC noted that clinical guidelines (CHEST & ERS/ERC) recommend treatment with initial combination therapy for patients with WHO FC III-IV symptoms with high risk factors, while the ERS/ERC guidelines recommend initial oral combination therapy as an option for patients presenting with WHO FC II symptoms. Guidelines also recommend sequential combination therapy for patients with an inadequate clinical response to treatment.

5.3.3 The PBAC recalled that current PBS restrictions do not allow for subsidised use of any targeted PAH medicines in WHO FC II PAH, while some PAH targeted medicines (ambrisentan + tadalafil, macitentan + PDE-5 inhibitor or iloprost, riociguat + ERA or iloprost) are TGA approved for add on or combination therapy across WHO FC II-IV.

5.3.4 The PBAC agreed with the DUSC that the evidence to support clinical effectiveness and safety of combination therapy in the PAH subgroups was limited compared to evidence across all WHO FC subgroups. This makes it difficult to determine whether there is more benefit associated with combination therapy initiated in WHO FC II over WHO FC III. The trials presented did not adequately demonstrate that the addition of a second medicine (dual therapy) was superior to switching monotherapy.

5.3.5 AMBITION (tadalafil + ambrisentan) was the only trial that supported initiation of combination therapy in patients with WHO FC II. A subgroup analysis of WHO FC II patients showed greater benefit of combination therapy versus monotherapy in regard to clinical failure events compared to WHO FC III patients.

5.3.6 The PBAC agreed with the ESC that, while combination therapy may be safe and efficacious for some patients in WHO FC II, the trial evidence is insufficient to inform a cost-effectiveness analysis of combination therapy.

5.3.7 However, the PBAC noted that across both patient registries, approximately 40% of patients were prescribed dual therapy, and a further 10% triple therapy. Neither registry analyses provided specific information on the extent of patients being initiated to PAH therapy in WHO FC II.

5.3.8 The PBAC also noted the Reference Group's support for sequential combination therapy in WHO FC II when patients were generally at lower risk

of deterioration. Consumers suggested that earlier treatment and access to combination therapy led to better health outcomes.

5.3.9 All three sponsors supported combination therapy for WHO FC II patients with PAH targeted medicines in their pre-PBAC responses. Two sponsors (Bayer and GSK) supported initial and sequential combination therapy, while the third (Actelion) supported sequential combination therapy only, emphasising the use of initial combination therapy is not consistent with QUM principles. Actelion also put forward a pricing proposal for combination therapy (macitentan + sildenafil) for patients in WHO FC II and WHO FC III.

Recommendation:

5.3.10 Overall, the PBAC considered there was limited evidence to support dual combination therapy compared to monotherapy and did not recommend extending PBS restrictions to include dual combination therapy for patients presenting with WHO FC II symptoms.

5.4 Option 3: Extend PBS subsidised access to combination (initial combination and/or sequential combination) therapy with various combinations of ERAs and PDE-5 inhibitors, sGC stimulators and prostanoids for patients with PAH in WHO FC III-IV.

5.4.1 The PBAC recalled that it had considered two submissions for combination therapy, selexipag in combination with an ERA and/or PDE-5 inhibitor (March 2016, March 2017). The submissions were rejected because the magnitude and clinical relevance of any benefit remained unclear, and the cost-effectiveness analysis presented a high and uncertain ICER. During consideration of the March 2016 submission, the PBAC noted that cost-effectiveness in the monotherapy setting cannot be generalised to cost-effectiveness in the combination therapy setting.

5.4.2 The PBAC noted that the 2015 ERS/ESC guidelines and CHEST guidelines support combination therapy for patients with moderate risk and suggest the overall treatment goal is to achieve low risk status (usually WHO FC II). Patients stabilised on monotherapy can receive additional medicines if treatment goals are not met. For WHO FC II-IV patients with inadequate response to monotherapy, both guidelines agree a further agent from an additional class (ERAs, PDE-5 inhibitors, prostanoids) can be added, up to a maximum of three PAH targeted medicines.

5.4.3 The 2015 ERS/ESC guidelines and CHEST guidelines recommend initial combination therapy for patients with WHO FC III-IV presenting with high risk factors. The PBAC noted that sequential use of medicines, where response to a single medicine is confirmed prior to an addition of a second medicine, as opposed to initial combination therapy, is most consistent with good prescribing practice in this clinical area.

5.4.4 In terms of safety, the PBAC considered that combination therapy could be similar to monotherapy, although available data was limited. Uncertainties include whether a prostanoid added to an ERA is likely to be as safe as ERA monotherapy in patients with WHO FC III/IV, and possible safety concerns in

the subgroup of PAH patients with connective tissue disease treated with a PDE-5 inhibitor in addition to an ERA.

5.4.5 The ESC noted there was limited comparative data on which to base a cost-effectiveness model of combination therapy versus monotherapy in WHO FC III/IV, as most trial outcomes lose significance when split by WHO FC.

5.4.6 The PBAC agreed with ESC that PBS subsidised combination therapy would shift the cost of medicines currently funded through other sources to the PBS. An accurate estimate of the net cost to government would need to be included in any further consideration by the PBAC to recommend combination therapy.

5.4.7 The PBAC was also mindful of the potential for use outside PBS restriction in patients with WHO FC II symptoms should combination therapy be extended to WHO FC III patients.

5.4.8 The PBAC considered that a recommendation for dual combination therapy should be for a medicine class not for individual medicines. Based on the available clinical effectiveness data dual combination therapy should be restricted to medicines within the ERA and PDE-5 inhibitor classes. Registry data indicates that over 90% of patients on combination therapy combine an ERA with a PDE-5 inhibitor.

5.4.9 The PBAC were mindful that limiting combination therapy to the ERA and PDE-5 inhibitor classes did not address clinician demand for use of a prostanoid in combination with an ERA or PDE-5 inhibitor in patients in WHO FC IV.

5.4.10 Due to PBS Statutory price reductions, the prices for some medicines in the ERA and PDE-5 inhibitor classes have fallen since the time of initial PBS-listing. Taking a pragmatic view, the PBAC considered that if dual combination therapy is likely superior in efficacy and similar in safety to monotherapy, then a small price premium over the price of monotherapy (at the current PBS price) may be acceptable.

5.4.11 The PBAC discussed the difficulties in making class-based recommendations for combination therapy due to the different individual drug prices within and between classes. The committee noted the pre-PBAC responses and suggested a stakeholder meeting with sponsors may be an appropriate way forward to establish acceptable prices of dual combination therapy.

5.4.12 The PBAC noted the Reference Group supported the PBS subsidy of early combination therapy for patients in WHO FC III-IV, suggesting that addition of the second medicine could occur after 4-6 weeks of monotherapy. A repeat right heart catheterisation or further deterioration in the patient's condition should not be required ahead of commencing the second PAH targeted therapy.

5.4.13 The PBAC acknowledged that revision of the existing complex PAH targeted medicine PBS restrictions would be required and that the Reference Group

expressed willingness to assist with any revision of PBS restrictions as recommended by the PBAC as part of the Review.

5.4.14 Stakeholders and consumers were supportive of PBS-subsidised access to combination PAH therapies. The financial burden and uncertainty associated with the continued availability of PAH targeted medicines through non-PBS avenues is a cause of stress and anxiety for consumers.

5.4.15 All three pre-PBAC responses from sponsors supported combination therapy for WHO FC III-IV patients with PAH targeted medicines.

5.4.16 Bayer's pre PBAC response highlighted that as the effective price of riociguat is below macitentan, and as bosentan is in formulary 2 (F2), riociguat + bosentan (PATENT-1) may be an acceptable dual therapy as an alternative option to the ERA + PDE-5 inhibitor combination.

5.4.17 GSK's pre-PBAC response highlighted that AMBITION (macitentan + tadalafil) showed a benefit for initial combination therapy in WHO FC II and WHO FC III patients. GSK also requested a stakeholder meeting.

5.4.18 Actelion supported combination therapy for macitentan (with PDE-5 inhibitor or iloprost) and ambrisentan (with tadalafil). Actelion's pre-PBAC response put forward a pricing proposal for macitentan and sildenafil combination therapy. Actelion maintained that there was a lack of evidence to support the benefit of bosentan + PDE-5 inhibitor combination therapy and highlighted the known drug interaction between bosentan and PDE-5 inhibitors.

Recommendation:

5.4.19 The PBAC was of a mind to recommend initial combination therapy with PBS subsidised ERA and PDE-5 inhibitor medicines for patients with WHO FC III/IV symptoms with increased risk factors, and sequential combination therapy with ERA and add on PDE-5 inhibitor medicine for patients with WHO FCIII/IV symptoms with demonstrated inadequate response to monotherapy. Accordingly, the PBAC suggests a stakeholder meeting be held with sponsors to progress PBS restrictions and prices for dual combination PAH therapy.

5.5 Option 4: To align PBS restrictions for PAH medicines with clinical treatment guidelines, consider:

- **including a NOTE in the PBS restrictions identifying the need for a positive vasoreactivity test prior to trialling vasodilator (calcium channel blocker) treatment; and**
- **removing the requirement for a trial of vasodilator (calcium channel blockers) for PAH-CTD.**

5.5.1 The PBAC noted that clinical guidelines:

- Identify that vasodilator treatment with high doses of calcium channel blockers (CCBs) leads to a favourable response in only a small number of patients with PAH in WHO FC II-III.

- Only recommend vasoreactivity testing in patients with IPAH, HPAH and PAH to detect patients who can be treated with high doses of a CCB.
- Recommend that patients who have not undergone a vasoreactivity study during RHC or those with a negative study should not be started on CCBs because of potential severe side effects (e.g. hypotension, syncope and RV failure).

5.5.2 The PBAC noted the Reference Group did not support the routine use of high dose CCBs and that stakeholders were also supportive of a review of the current PBS restriction criteria.

5.5.3 The PBAC considered that inclusion of the requirement to trial vasodilator treatment in the PAH medicine PBS restrictions may be confusing and not useful for clinicians. The PBAC considered that clinicians can best determine which patients may respond to a trial of CCBs.

5.5.4 The PBAC considered that PAH centres of excellence should play a major role in diagnosis of this condition. The PBAC noted the ESC advice and Reference Group's comment and agreed that RHC is essential for the correct diagnosis of PAH and monitoring treatment response, as echocardiogram results are potentially unreliable and are operator dependent. The PBS restrictions for PAH medicines could stipulate that 'evidence of consultation with a second expert clinician be provided by the treating clinician if seeking exemption from a RHC for a patient'.

Recommendation:

5.5.5 The PBAC recommended that the current requirement for patients to 'have failed to respond to 6 or more weeks of appropriate vasodilator treatment unless intolerance or a contraindication to such treatment exists' be removed from the PBS restrictions for all PAH medicines.

5.5.6 The PBAC also recommended that treating clinicians seeking an exemption from RHC in specific patients, be required to provide a second opinion from an expert cardiologist or PAH physician to reconfirm the reasons why a RHC should not be performed.

5.6 Option 5: Extend PBS restrictions to include the remaining WHO Group I PAH subtypes associated with HIV infection; portal hypertension; and schistosomiasis in WHO FC III/IV.

5.6.1 The PBAC noted that:

- The ESC/ERS Guidelines recommend PAH medicines for all WHO Group I PAH subtypes irrespective of the subtype or line of treatment.
- Clinical criteria in PBS restrictions and TGA indications specify both PAH subtype and WHO FC for each PAH medicine.
- A small number of medicines and combinations (sildenafil, tadalafil, ambrisentan plus tadalafil) are TGA registered for the treatment of all of WHO Group I PAH.

- The current terminology of PAH sub-types in the TGA indications and PBS restrictions are inconsistent with the latest WHO classifications of pulmonary hypertension and PAH.
- There are no PBS-listed medicines for certain PAH subtypes: PAH associated with HIV, associated with portal hypertension or associated with schistosomiasis.

5.6.2 The ESC and DUSC agreed that there would be difficulties obtaining further evidence on the effectiveness of PAH medicines for these small population sub-types of PAH. The DUSC advised that expanding the PBS restrictions to include these subtypes was also unlikely to significantly increase the number of patients treated or the net cost to the PBS.

5.6.3 The Reference Group supported extending the PBS restrictions to include the remaining WHO Group I PAH subtypes.

5.6.4 The PBAC considered that all reference to WHO Group 1 PAH subtypes should be removed from the PBS restriction criteria for PAH medicines. However, a NOTE in the restrictions should define the subtypes currently included in WHO Group 1 PAH.

Recommendation:

5.6.5 The PBAC recommended extending the PBS restrictions for all PAH medicines to include the remaining WHO Group 1 PAH subtypes associated with HIV infection; portal hypertension; and schistosomiasis.

5.7 Option 6: Request the Department of Health to review the guideline for PAH Designated Prescribing Centres in regard to specific recommendations on patient numbers.

5.7.1 The PBAC noted that:

- The Department manages the Highly Specialised Drugs (HSD) Programme and assesses applications for hospitals to become a PAH Designated Prescribing Centre based on guidelines. Patients are assessed by a physician at a designated hospital prior to accessing PBS subsidised PAH medicines.
- Current Australian guidelines and criteria for PAH Designated Prescribing Centres do not specify minimum patient numbers, while the ESC/ERS Guidelines make specific recommendations on the facilities, skills required, and the ideal number of patients seen annually at a referral centre.
- There are over 60 PAH Designated Prescribing Centres in Australia and 77 per cent of the centres are located in metropolitan areas. Based on PBS prescription data, on average, each centre would see about 40 patients with PAH annually.

5.7.2 The PBAC noted ESC and DUSC supported reviewing the guideline/criteria for PAH designated prescribing centres, noting the high number of centres is not

consistent with building centres of excellence and may cause variation in patient outcome. The DUSC also raised the importance of access and equity in regard to treatment, particularly for patients in rural and remote areas.

5.7.3 The PBAC discussed that amalgamation of clinics and the formal adoption of a 'hub and spoke' location model may be effective in concentrating clinical expertise and improving patient outcomes. For example, right heart catheterisation is best undertaken by experienced centres and clinicians.

5.7.4 The PBAC also noted the clinical advice received on these issues from stakeholders and the Reference Group and acknowledged Australia's lower population levels and geographical vastness compared to international settings. For rural and remote patients, the challenge is to balance patient safety while maintaining equity of access to treatment.

5.7.5 The PBAC considered that increased collaboration between PAH Designated Prescribing Centres and improved data collection and systems for sharing data would promote consistency in treatment approaches and better patient outcomes.

Recommendation:

5.7.6 The PBAC recommended a review of the guidelines/criteria for establishing PAH Designated Prescribing Centres, particularly with regard to annual numbers of patients and available clinical expertise. Where possible, the criteria should match international clinical guidelines.

5.8 Following ToR 1-4, consider reviewing the cost-effectiveness of existing PBS listed PAH medicines, and in treatment of WHO functional class II and combination treatment in class III and class IV patients.

Refer to PBAC consideration under options 1, 2 & 3.

Recommendation:

5.8.1 The PBAC did not recommend further economic modelling of the cost-effectiveness of existing PBS listed PAH medicines in the treatment of patients presenting with WHO FC II symptoms or for dual combination treatment in patients with WHO FC class III/IV symptoms.