Pharmaceutical Benefits Scheme

Post-market Review of

Medicines to treat Pulmonary Arterial Hypertension

Executive Summary

Final Report

November 2018

Executive Summary

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Abbreviations

Abbreviation	Full Name / Wording
6MWT	Six minute walk test
6MWD	Six minute walk distance
ACC	American College of Cardiology
AE	Adverse event
AGREE	Appraisal of Guidelines for Research and Evaluation
AHA	American Heart Association
ARD	Absolute risk difference
ARTG	Australian Register of Therapeutic Goods
ASCS	Australian Scleroderma Cohort Study
ASIG	Australian Scleroderma Interest Group
CADTH	Canadian Agency for Drugs and Technologies in Health
CATAG	Council of Australian Therapeutic Advisory Groups
CCB	Calcium channel blocker
CI	Confidence Interval
CTEPH	Chronic thromboembolic pulmonary hypertension
DUSC	Drug Utilisation Sub-Committee
ECHO	Echocardiography
EMA	European Medicines Agency
EQ-5D	EuroQol 5-dimension
EQ-VAS	EuroQol visual analogue scale
ERA	Endothelin receptor antagonist
ERS	European Respiratory Society
ESC	European Society of Cardiology
ESC/ERS guidelines	2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension
FC	Functional class
FDA	United States Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HPAH	Heritable pulmonary arterial hypertension
HR	Hazard ratio
IPAH	Idiopathic pulmonary arterial hypertension
LPH	Living with pulmonary hypertension

Abbreviation	Full Name / Wording
LVF	Left ventricular function
MLHF questionnaire	Minnesota living with heart failure questionnaire
mmHg	millimetre of mercury
mPAP	Mean pulmonary arterial pressure
mRAP	Mean right atrial pressure
PAH	Pulmonary arterial hypertension
PAH-CHD	Pulmonary arterial hypertension associated with congenital heart disease
PAH-CTD	Pulmonary arterial hypertension associated with connective tissue disease
PAH-HIV	Pulmonary arterial hypertension associated with human immunodeficiency virus infection
PAH-PH	Pulmonary arterial hypertension
PASP	Pulmonary artery systolic pressure
PAP	Pulmonary artery pressure
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PDE-5 inhibitor	Phosphodiesterase-5 inhibitor
PH	Pulmonary hypertension
PHAA	Pulmonary Hypertension Association Australia
PHSANZ	Pulmonary Hypertension Society of Australia and New Zealand
Review	Post-market Review
PI	Product information
PICO	Population, Intervention, Comparator and Outcome
PVR	Pulmonary vascular resistance
QoL	Quality of life
RPBS	Repatriation Schedule of Pharmaceutical Benefits
RCT	Randomised controlled trial
RHC	Right heart catheterisation
RR	Relative risk
RVSP	Right ventricular systolic pressure
sGC stimulator	Soluble guanylate cyclase stimulator
SmPC	Summary of product characteristics (European)
SoC	Standard of care
TGA	Therapeutic Goods Administration

Abbreviation	Full Name / Wording
ToR	Term(s) of Reference
TRV	Tricuspid regurgitation velocity
WHO	World Health Organization

Executive Summary

Background and context

Pulmonary Arterial Hypertension (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 (PVR) that, if not treated, ultimately leads to right heart failure and premature death[1]. There is no cure for PAH other than lung transplantation. Symptoms of PAH include shortness of breath, dizziness, chest pain and fatigue[2].

In Europe, PAH prevalence and incidence are in the range of 15–60 subjects per million population and 5–10 cases per million per year, respectively[3]. In February 2015 the Drug Utilisation Subcommittee (DUSC) of the Pharmaceutical Benefits Advisory Committee (PBAC) estimated the prevalent and incident patients receiving PAH treatment as 87.6 and 18.6 per million population, respectively[4].

The clinical severity of PAH is classified according to the World Health Organisation (WHO) system based on functional classes (FC) for patients with pulmonary hypertension.

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.

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.

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.

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.

Source: Galie et al 2015[5]

Figure ES.1 WHO functional classes for PAH

PAH medicines belong to four therapeutical classes based on their mode of action:

- Endothelin receptor antagonists (ERA) reverse the effect of endothelin, a substance in the walls of blood vessels that causes them to narrow.
- Phosphodiesterase type 5 (PDE-5) inhibitors and soluble guanylate cyclase (sGC) stimulators interfere with the nitric oxide pathway and help to relax the pulmonary arteries and lower the pressure within the arteries. PDE-5 inhibitors also inhibit the growth of smooth muscle lining blood vessel walls, a contributing factor in the development of PAH.
- Prostacyclin analogues (or prostanoids) exert its effects by promoting direct arterial vasodilation and inhibiting platelet aggregation.

- Calcium channel blockers (CCBs) are vasodilators which are effective in a small number of patients with idiopathic PAH (IPAH), heritable PAH (HPAH) and drug-induced PAH who demonstrate a response to acute vasodilator testing during right heart catheterisation.

A total of eight medicines are listed on the Pharmaceutical Benefits Scheme (PBS) for the treatment of PAH as detailed in Table ES.1 below.

Table ES.1 PBS listed medicines to treat PAH

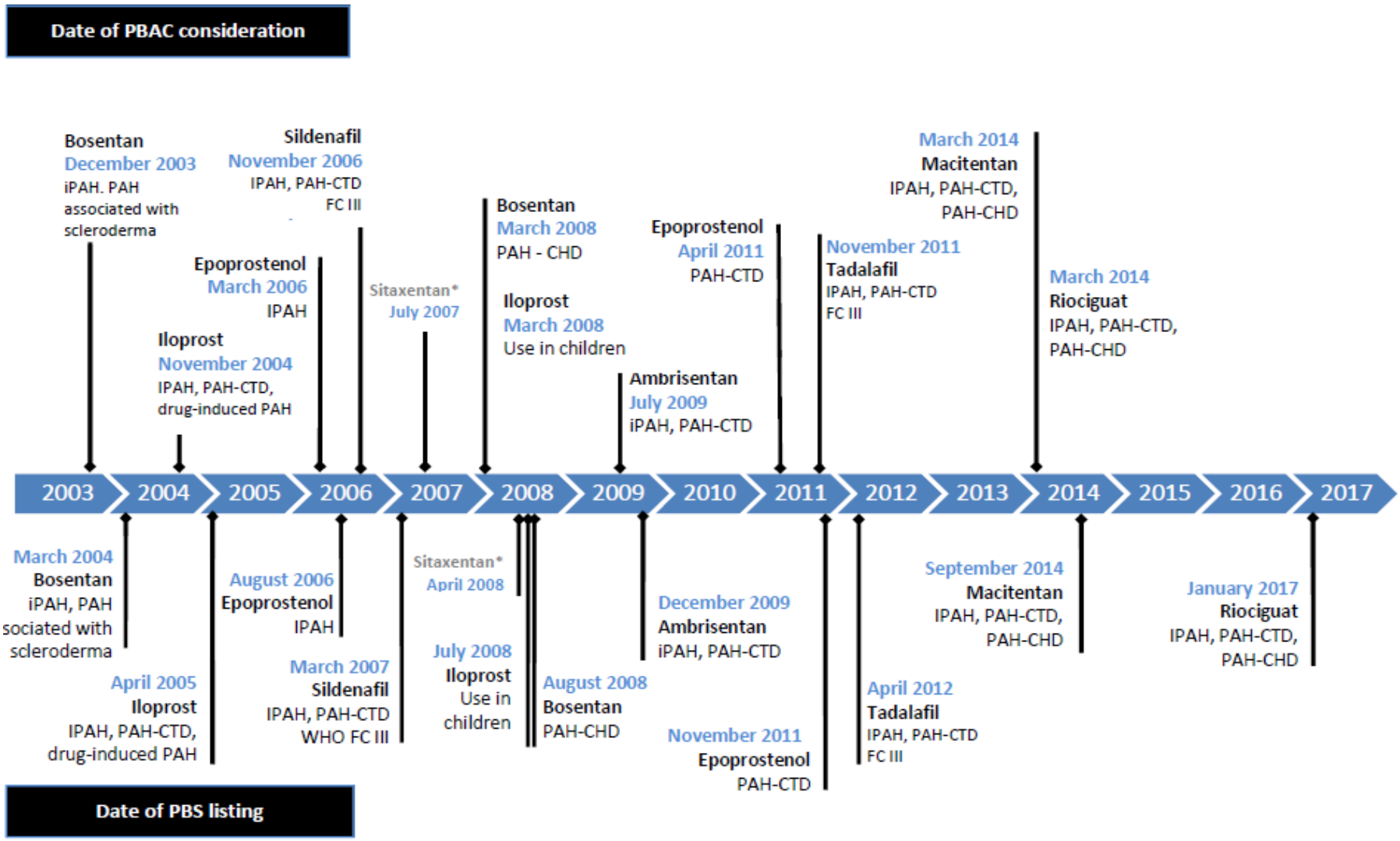
Medicine Class	PBS listed medicines (as of 1 January 2018)
ERAs	bosentan, ambrisentan, macitentan
PDE-5 inhibitors	sildenafil, tadalafil
prostanoids	epoprostenol, iloprost
sGC stimulator	riociguat

ERA=endothelin receptor antagonist, PDE-5=phosphodiesterase type 5, sGC=soluble guanylate cyclase:

The first medicine listed on the PBS for PAH was bosentan in March 2004. Iloprost, epoprostenol, sildenafil, ambrisentan and tadalafil were listed in the following five years. Macitentan and riociguat were listed in 2014 and 2017, respectively. Access to PBS listed PAH medicines are restricted for sole subsidised use according to WHO FC and type of PAH.

In March 2016 and also in March 2017 the PBAC considered a submission for the PBS listing of selexipag. The PBAC did not recommend the listing of selexipag both times. In reaching this conclusion, the PBAC considered that the incremental cost-effectiveness ratios (ICER) presented in the submission were difficult to interpret, and were highly likely to be too high to support the cost-effectiveness of selexipag in the (March 2017) requested listing for triple therapy (or dual therapy, in some situations). Selexipag acts on the same pathway as the prostanoids but is a non-prostanoid prostacyclin receptor agonist.

Refer to Figure ES.2 for the details of the PBS listing of PAH medicines.



*Sitaxentan was delisted on 31 March 2011.
Abbreviations: FC = functional class, iPAH = idiopathic PAH, PAH-CTD = PAH associated with chronic tissue disease, PAH-CHD = PAH associated with congenital heart disease

Figure ES.2 Timeline of PBAC consideration of PAH medicines and date of PBS listing

In 2013, the Pulmonary Hypertension Society of Australia and New Zealand (PHSANZ) requested changes to the then current PBS restrictions for PAH medicines. At its November 2013 meeting, the PBAC considered that "such changes would all require consultation from sponsors and most would require evidence-based submissions regarding maintenance of acceptable cost-effectiveness". The PBAC also noted that requests to make PAH medicines available for patients with WHO FC II disease or for use as part of combination therapy would require a submission to be made to the PBAC, with evidence demonstrating the comparative clinical effectiveness and safety and cost-effectiveness of therapy in such circumstances.

In July 2015, the PBAC considered a submission from the sponsor which identified concerns that the PBS restrictions for PAH medicines are not consistent with currently treatment guidelines and best practice. The PBAC recommended to the Minister for Health that a post-market review (Review) be undertaken on the efficacy and cost‑effectiveness of PAH medicines, including the existing listing for class III and class IV patients, and the additional clinical place of these therapies as recommended in international guidelines.

The Review has the overall aim of reviewing the safety, efficacy and cost-effectiveness of PBS-listed PAH medicines in the context of quality use of medicines and patient access to optimal treatment.

The draft Terms of Reference (ToR) were provided for public consultation between 2 May and 16 May 2016. The PBAC considered the draft Review ToR and comments from stakeholders at the August 2016 PBAC meeting. The Minister for Health approved the final ToR for the Review in December 2016.

Review Terms of Reference

The PMR of PAH Medicines consists of five ToR. This report addresses the first four in full and introduces ToR 5.

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.
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.
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. Collate and evaluate evidence on the comparative effectiveness of PAH medicines, including combination use and use in the WHO FC II patient populations.
5. Following ToR 1-4 consider reviewing the cost-effectiveness of existing PBS listings for PAH medicines, and in treatment of WHO FC II and combination treatment in class III and class IV patients (possible future report).*

*After consideration of the findings from ToR 1-4, the PBAC did not recommend a review of the cost-effectiveness of existing PBS listings for PAH medicines. The PBAC also did not recommend a cost-effectiveness

review in patients with WHO FC II symptoms and/or combination treatment in patients with WHO FC III and class IV patients.

Methodological approach to the technical report

A Reference Group (RG) and academic research units were involved in the preparation of this draft technical report for the PAH Review. Research questions relating to the ToR were developed to guide the review (refer to Background), and approved by the RG Chair. The ToR were addressed through systematic reviews of trial evidence for medicines, reviews of current clinical guidelines and utilisation of PAH medicines in Australia (refer to Table ES.2 and Table ES.3). The PHSANZ and The Australian Scleroderma Interest Group (ASIG) provided information on medicine regimes based on their respective patient registries.

Table ES.2 Methodological approaches to ToR 1, ToR 3, ToR 4 and ToR 5

Methodological approach	Criteria and time period
ToR 1: Compare clinical guidelines for the management of PAH with the PBS restrictions and TGA indications for the use of PAH medicines.	
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.	The search focussed on Australian and European and North American guidelines published from 2010 to August 2016, but considered also earlier publications in the absence of more recent material.
ToR 3: Review of 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.	
A consumer forum was held to answer pre-determined questions on important or clinically relevant outcomes for patients and compared to evidence considered by PBAC.	Consumer forum on 14 October with members of the Pulmonary Hypertension Association Australia, and written submissions from members received between 11 October and 31October 2017.
ToR 4: Review of comparative effectiveness of PAH medicines, including combination use and use in the WHO functional class II patient populations.	
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	The review focussed on evidence that has not previously considered by the PBAC until July 2017.
ToR 5: Following ToR 1-4 consider reviewing the cost-effectiveness of existing PBS listings for PAH medicines, and in treatment of WHO functional class II and combination treatment in class III and class IV patients.	
To be determined by PBAC	

PBAC=Pharmaceutical Benefits Advisory Committee, PBS=Pharmaceutical Benefits Scheme, PICO=Population, Intervention, Comparator and Outcome, PAH=pulmonary arterial hypertension, TGA= Therapeutic Goods Administration, ToR=Terms of Reference, WHO FC=World Health Organization Functional Class

Table ES.3 Methodological approach to ToR 2

Analysis	Data Source	Methodological approach
ToR 2: Utilisation analysis of PAH medicines		
1	Utilisation analysis of PBS/RPBS claims data	• Analysis of PAH Services Australia (formerly the Department of Human Services) date of supply data inclusive of July 2013 to December 2016 • Cohort analysis of de-identified unit record PBS/RPBS prescription dispensing and date of death data
2	PHSANZ registry data analysis	Cross-sectional analysis
3	Australian Scleroderma Cohort Study data analysis	Cross-sectional analysis

PBS= Pharmaceutical Benefits Scheme, PHSANZ= Pulmonary Hypertension Society of Australia and New Zealand RPBS=Repatriation Schedule of Pharmaceutical Benefits,

Stakeholder consultation

Opportunities for stakeholder consultation throughout the PAH Review included:

- Public consultation on the draft ToR - open between 2 May and 16 May 2016.
- Public submissions to the Review - open between 13 February and 27 March 2017.
- Except where requested otherwise, submissions are published on the Review's website.
- Consumer Forum - held in Sydney on 14 October with members of the Pulmonary Hypertension Association Australia (PHAA). The record of discussion from the Consumer Forum is summarised and included in the ToR key findings. A full version of the Consumer Forum Summary is at Appendix F, and on the Review's website.
- Public consultation on the draft report - open from 21 May 2018 to 10 June 2018.

Key findings for ToR 1: Comparison of prescribing restrictions and clinical guidelines

Q1. What are the clinical treatment algorithms recommended in recent Australian, European and North American guidelines for the treatment of WHO FC II, III and IV PAH?

Key findings – Research Question 1

PAH is a rare disease and there are few clinical guidelines aside from a limited number of key documents published by United States (US) and European medical specialist organisations.

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).

Q2. Are the current PBS restrictions for PAH medicines, the TGA-approved indications and the recommendations from clinical guidelines consistent?

Key findings – Research Question 2

The key differences between guideline recommendations and PBS restrictions are:

- The PBS restrictions limit the use of PAH medicines to patients in WHO FC III-IV. Guidelines recommend treatment of patients in WHO FC II-IV. TGA indications for PAH medicines cover WHO FC II-IV.
- Guidelines recommend treatment with initial combination therapy for patients in WHO III-IV with high risk factors. In contrast to the CHEST guideline, the 2015 ERS/ERC guidelines also recommend initial oral combination therapy as an option for patients presenting in WHO FC II. The PBS restrictions limit the use of PAH medicines to monotherapy (the PAH agent is the sole subsidised agent for this condition) in WHO FC III-IV.
- Guidelines also recommend sequential combination therapy for patients with an inadequate clinical response to treatment. Patients continue on their existing medicine and add a second or third medicine as required. TGA listings include combination use for ambrisentan with tadalafil, macitentan with PDE-5 inhibitor or iloprost, and riociguat with ERA or iloprost.
- Response to treatment is defined in guidelines as clinical improvement and/or progress towards therapeutic goals. PBS restrictions define response to treatment as stability or improvement of disease.

- Clinical criteria in PBS restrictions and TGA indications specify both PAH subtype and WHO FC for each PAH medicine, while guideline recommendations are based on medicine class, not individual medicines and make no suggestions as to the line of therapy. In contrast to guidelines prostanoids are neither TGA registered nor PBS-listed for PAH associated with congenital heart disease (PAH-CHD), and PDE-5 inhibitors are not registered or PBS listed for WHO FC IV.
- There are no PBS-listed medicines for certain PAH subtypes: PAH associated with human immunodeficiency virus infection (PAH-HIV), associated with portal hypertension or associated with schistosomiasis.
- The current terminology of PAH sub-types in the TGA indications and PBS restrictions are inconsistent with the latest WHO classifications of pulmonary hypertension (PH) and PAH.
- PBS restrictions mostly fall within TGA-approved indications of PAH medicines, except PBS-listings for drug and toxin induced PAH (PAH-DT), and ambrisentan and iloprost for heritable PAH (HPAH).
- Guidelines recommend vasodilator treatment with calcium channel blockers (CCBs) for patients with IPAH, HPAH and PAH-DT (but not for PAH-CTD) and who also have a positive response to an acute vasoreactivity test during right heart catheterisation (RHC). The PBS restrictions however, require a trial of treatment with CCBs in WHO FC III patients with IPAH, HPAH, PAH-DT and PAH-CTD with a mean right atrial pressure (mRAP) of 8mmHg of less as measured by RHC.
- Guidelines define a positive response to an acute vasoreactivity test during RHC as a decrease in mean pulmonary arterial pressure (mPAP) >10 mm Hg, to a mPAP <40 mm Hg, with no worsening of cardiac output. The PBS restrictions define the criteria for treatment with CCBs as being in FC III with mRAP of 8mmHg of less as measured by RHC. There are safety concerns surrounding treatment with CCBs without a positive response to an acute vasodilator test.
- Treatment with CCBs should lead to dramatic clinical improvements with the first months of treatment. Close follow-up with complete reassessment is recommended after three to four months of therapy (including RHC).
- Guideline recommendations for hypertension referral centres specify annual patient numbers as centres with a high volume of patients tend to obtain the best outcomes.

Q3. Are the current diagnostic and prognostic criteria in PBS restrictions for patients with PAH consistent with Australian and international guidelines?

Key findings – Research Question 3

- Current PBS restrictions specify three diagnostic assessments at baseline and first continuation for PAH treatment subsidy: RHC, six minute walk distance (6MWD) and echocardiography (ECHO).
- Guidelines recommend treatment choices include an assessment of the patient's risk of PAH deterioration. However there is no definitive set of parameters for a patient's risk assessment.
- PAH treatment decisions without RHC are not recommended unless RHC is contraindicated. Where RHC is unavailable or contraindicated the current PBS restriction defines PAH as: right ventricular systolic pressure (RVSP) assessed by ECHO, greater than 40 mmHg with normal left ventricular function. The guidelines recommend measurement of peak tricuspid regurgitation velocity (TRV) as the key cardiographic variable predictive of PAH. PAH is likely if TRV is ≥2.9ms−1 and additional echocardiographic variables suggestive of PH are present, or if TRV is ≥3.4 m·s−1 with no other signs. Other variables include measures for the ventricles, pulmonary artery, inferior vena cava and right atrium, which in the absence of TRV, can also be indicative of PAH (refer to ToR 1, Table 1.9, p.54).

A comparison between PBS restrictions, TGA indications and guideline recommendations is shown in Table ES.4 below.

Table ES.4 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-5i - WHO FC Class II-III ERA - 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-5i - WHO FC III ERA - WHO FC III-IV sGC stimulator - WHO FC III-IV	PDE-5i - WHO FC Class II-III ERA - WHO FC II-IV sGC stimulator - 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)
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 2015 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;	SoC for patients WHO FC II-IV with inadequate response, up to a maximum of three PAH medicines.

Criterion	PBS Listings	TGA Status	PAH Guidelines
		• riociguat + ERA or iloprost	
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 LVF	—	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 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)	Recommended for IPAH, HPAH and PAH-DT patients only.

Criterion	PBS Listings	TGA Status	PAH Guidelines
		However, amlodipine, diltiazem and nifedipine have specific TGA registered indications for hypertension and angina.	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 an 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 to PAH agents	—	Follow-up at ~3 months. Response should show a dramatic improvement or near normalisation to ~WHO FC I
Designated hospitals	>60 centres listed by Services Australia	—	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-5i=phosphodiesterase type 5 inhibitor; ERA=endothelin receptor antagonist; ESC=European Society of Cardiology; ERS=European Respiratory Society; FC=functional class, 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

Stakeholder Views

- Stakeholders consider the 2015 ESC/ERS guidelines to be the most relevant to Australian practice and note they incorporate the latest evidence for combination therapy.
- Stakeholders are concerned that Australians do not have the same access to the range or combination of PAH medicines at an affordable cost, compared to international patients.
- Stakeholders consider that PAH medicines should not be reimbursed based on the cause of PAH or FC, and suggests PAH medicines should be available to all PAH patients regardless of what type, FC or severity of PAH disease.
- Stakeholders suggest the PAH treatment approach should be one of 'disease management' so that patients can achieve a reasonable quality of life for a period before disease progression and that all patients in WHO FC I should have access to medication, irrespective of the triggering event.
- Stakeholders suggested a review of PAH in designated Pulmonary Hypertension centres in Australia and note variations in clinical expertise are leading to a variation in treatment and outcomes. Stakeholders suggested collaboration between centres to improve equity of utilisation of PAH medicines.

Consumer Views

- Consumers understood that they can currently access only one PAH medicine at any one time through the PBS. Consumers were also aware of the requirement to provide test results to support their ongoing treatment with PBS medicines.
- Consumers noted that there are no specific medicines listed on the PBS for children.
- Consumers considered it a priority to get access to:
    - multiple PBS-listed medicines at one time;
    - medicines for FC II to coincide with early diagnosis; and
    - a broader range of PAH medicines.
- Some consumers suggested that earlier treatment and combination therapy led to better health outcomes and questioned why treatment is not available for FC II patients whose health is only going to deteriorate.
- Many consumers were unaware of the international guidelines for the treatment of PAH, but some understood that the guidelines provided information on the classification of PAH and treatments.

Key findings for ToR 2: Utilisation of PAH medicines

An analysis of the utilisation of PAH medicines was undertaken using prescription data and date of death data from the -Services Australia PBS Prescriptions Database. Dispensed prescription data for PAH medicines listed on the PBS/RPBS (Repatriation Schedule of

Pharmaceutical Benefits) 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.

PBS/RPBS Claims Data

- 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.
- 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.
- Combination treatment with PBS-listed PAH medicines was very rare.

Pulmonary Hypertension Society of Australia and New Zealand (PHSANZ) Registry

- The mean age of all PAH patients at time of diagnosis in the PHSANZ cohort (n=1071) was 49.9±20.4 years and 7.8% were aged under 18 years.
- More than two thirds of patients were female.
- Overall 49.8%, 39.8% and 10.4% of patients were prescribed monotherapy, dual therapy and triple therapy respectively.
- ERAs were the most commonly prescribed medicine class amongst monotherapy patients (76.55%).
- ERA + PDE-5 inhibitors accounted for 91% of all dual therapy combinations, with the addition of a prostanoid the most common regimen for triple therapy.
- PHSANZ registry data indicates that approximately 20% of patients in the PAH cohort (those alive and receiving medication in 2017) were diagnosed or presented to PAH centres with symptoms classified in WHO FC II. The majority (67%) of patients entered

the cohort with WHO FC III symptoms and 6% with WHO FC IV symptoms. Information on WHO FC at time of cohort entry was not available in 6.8% of patients.

Australian Scleroderma Interest Group Registry (ASIG)

- The mean age of all patients with connective tissue disease associated PAH (CTD-PAH) in the Australian Scleroderma Cohort Study (ASCS) cohort (n=104) at time of last assessment (index visit) was 67 years and 82% of patients were female.
- Monotherapy, dual therapy and triple therapy was used by 53%, 41% and 6% of patients respectively.
- Macitentan was the most commonly used ERA, used by 55% (57/104) of patients included in the study.

Overall conclusions

- 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 and the both registry data analyses did not provide specific information on the extent of patients being initiated to PAH therapy in 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.

Stakeholder views

- Stakeholders suggested methods for ensuring efficient and effective data capture of PAH medicine utilisation and outcomes, noting PBS prescriptions alone do not reflect the full utilisation of PAH medicines. Stakeholders recommend ongoing post-market surveillance and analysis of registry data to support evidence-based decision making for PAH.
- Some patients and prescribers noted the considerable variation in decision making across Drug Therapeutic Committees, making access to PAH medicines potentially inequitable, and dependant on the patients' location for treatment.
- Riociguat, which was recently PBS listed, is not listed in formularies in any of the jurisdictions which responded to the request by the Council of Australian Therapeutic Advisory Groups (CATAG), nor have there been individual patient requests in those jurisdictions.

Consumer views

- Consumers noted that they accessed medicines through a range (and combination) of avenues, including through the PBS, hospitals, drug trials, compassionate access programs or private funding (often sildenafil).
- Consumers noted the financial burden for themselves, family and friends including cost of PBS co-payments, cost of privately funded medicines and incidental health care items and tests. This is exacerbated by reduced income due to an inability to work.

Key findings for ToR 3: Clinical outcomes relevant to patients and evidence considered by PBAC

- Historically, the Pharmaceutical Benefits Advisory Committee (PBAC) has primarily considered studies that present Six Minute Walk Test (6MWT) results as the main surrogate outcome when assessing PAH (pulmonary arterial hypertension) medicines.
- Clinical trials for PAH medicines may also measure a range of other clinical outcomes such as changes in WHO FC (functional class), 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 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.

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 EQ5, 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.

Key findings for ToR 4: Review of effectiveness and safety

Q1. What is the effectiveness and safety of monotherapy with a PAH medicine, compared to placebo/no treatment or another PAH medicine listed on the PBS, in patients with WHO FC I or II PAH?

Effectiveness and safety of monotherapy in WHO FC I or II PAH

ERA versus placebo

Clinical effectiveness

Four RCTs reported on the effectiveness of an ERA in treating PAH compared with placebo 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.

Overall, the use of an ERA medication to treat patients with WHO FC I/II PAH is likely to be beneficial.

Table ES.5 Summary of the evidence for the clinical effectiveness of an ERA compared with placebo in patients with WHO FC I/II PAH

Outcome	Included trials No. of patients	Summary of evidence
Clinical worsening	EARLY (bosentan) ARIES-1&2 (ambrisentan) SERAPHIN (macitentan) N=375	High quality evidence (GRADE ⊕⊕⊕⊕) [redacted]
All-cause mortality	EARLY (bosentan) SERAPHIN (macitentan) N=256	High quality evidence (GRADE ⊕⊕⊕⊕) [redacted]
Improved WHO FC	ARIES-1&2 (ambrisentan) N=101	Moderate quality evidence (GRADE ⊕⊕⊕⊙) Significantly more patients improved their WHO FC after being treated with an ERA compared with receiving a placebo (ARD = 14.0%; 95% CI 4.4, 23.6)
Worsened WHO FC	ARIES-1&2 (ambrisentan) N=101	Low quality evidence (GRADE ⊕⊕⊙⊙) Fewer patients taking an ERA had worsening of their WHO FC when compared with receiving a placebo but the 95% CI indicates that there may also be an effect in the opposite direction (RR = 0.25; 95% CI 0.03, 2.20)

Outcome	Included trials No. of patients	Summary of evidence
Change in 6MWD from baseline	EARLY (bosentan) ARIES-1&2 (ambrisentan) N=154	Moderate quality evidence (GRADE ⊕⊕⊕⊙) Patients taking an ERA had a larger mean improvement in their 6MWD than those taking a placebo, and the difference was clinically important in 2 out of 3 studies (range 25.7−40.0 m walked further) There was no significant difference in the effectiveness of different ERA medications
Change in haemodynamic parameter from baseline: PVR	EARLY (bosentan) N=156	Low quality evidence (GRADE ⊕⊕⊙⊙) Patients taking an ERA had a larger mean improvement in their PVR than those taking a placebo (MD = 23.1% improvement was a clinically important difference)

6MWD = 6-minute walk distance; ARD = absolute risk difference; CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation1; MD = mean difference; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; RCT = randomised controlled trial; RR = relative risk; WHO = World Health Organization

Safety

There is no evidence to evaluate the comparative safety of an ERA medication versus placebo when used to treat patients with WHO FC I/II PAH.

PDE-5 inhibitor versus placebo

Clinical effectiveness

Three RCTs were identified that reported on the effectiveness of a PDE-5 inhibitor, as monotherapy, when compared to placebo in patients with WHO FC I/II PAH:

- The PHIRST and Mukhopadhyay 2011 trials used tadalafil
- The SUPER-1 trial used sildenafil.

Neither of these trials reported on all-cause mortality for the subgroup of patients with WHO FC I/II PAH. Two cohort studies were identified that reported on the mortality of patients with WHO FC I/II PAH who were treated with either sildenafil or conventional therapy:

- Sun 2013 enrolled patients with Eisenmenger syndrome who were followed for up to 2 years
- Sastry 2007 collected prospectively acquired survival data from a hospital registry for five years for patients with IPAH of WHO FC II-IV being treated with sildenafil.

The evidence provided by these studies is summarised in Table ES.6.

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.

Table ES.6 Summary of the evidence for the clinical effectiveness of a PDE-5 inhibitor versus placebo in patients with WHO FC I/II PAH

Outcome	Included trials No. of patients	Summary of evidence
All-cause mortality	Sun 2013 cohort study (sildenafil) Sastry 2007 cohort study (sildenafil) N=76	Very low quality evidence (GRADE ⊕⊙⊙⊙) Fewer patients died after treatment with a PDE-5 inhibitor compared with placebo, but the 95% CI indicates that there may also be an effect in the opposite direction (pooled RR = 0.32; 95% CI 0.05, 1.90)
Improved WHO FC	Mukhopadhyay 2011 (tadalafil) N=22	Low quality evidence (GRADE ⊕⊕⊙⊙) The same proportion of patients improved their WHO FC taking a PDE-5 inhibitor compared with placebo, but the wide 95% CI indicates that the study was underpowered for this outcome (RR = 1.00; 95% CI 0.07, 15.00)
Worsened WHO FC	Mukhopadhyay 2011 (tadalafil) N=22	Low quality evidence (GRADE ⊕⊕⊙⊙) No patients had worsening of their WHO FC during the study period.
Change in 6MWD from baseline	PHIRST (tadalafil) SUPER-1 (sildenafil) N=73	Low quality evidence (GRADE ⊕⊕⊙⊙) Patients taking a PDE-5 inhibitor had a larger mean improvement in their 6MWD than those taking a placebo, and the difference was clinically important in [redacted] (range [redacted] walked further) No significant difference in the effectiveness of different PDE-5 inhibitors

6MWD = 6-minute walk distance; CI = confidence interval; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation1; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase type 5; RCT = randomised controlled trial; RR = relative risk; WHO = World Health Organization

Safety

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.

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.

sGC stimulator versus placebo

Clinical effectiveness

Only one RCT was identified that reported on the effectiveness of monotherapy with a sGC stimulator in treating PAH compared with placebo 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.

Overall, there is [redacted] as to whether the use of sGC stimulator medication to treat patients with WHO FC I/II PAH [redacted].

Table ES.7 Summary of the evidence for the clinical effectiveness of a sGC stimulator versus placebo in patients with WHO FC I/II PAH

Outcome	Included trials No. of patients	Summary of evidence
Clinical worsening	PATENT-1 (riociguat) N=107	Low quality evidence (GRADE ⊕⊕⊙⊙) [redacted]
All-cause mortality	PATENT-1 (riociguat) N=107	High quality evidence (GRADE ⊕⊕⊕⊕) [redacted]
Hospitalisation due to worsening PAH	PATENT-1 (riociguat) N=107	High quality evidence (GRADE ⊕⊕⊕⊕) [redacted]
Improved WHO FC	PATENT-1 (riociguat) N=107	Moderate quality evidence (GRADE ⊕⊕⊕⊙) [redacted]
Worsened WHO FC	PATENT-1 (riociguat) N=107	High quality evidence (GRADE ⊕⊕⊕⊕) [redacted]
Change in 6MWD from baseline	PATENT-1 (riociguat) N=107	Moderate quality evidence (GRADE ⊕⊕⊕⊙) [redacted]
Change in QoL from baseline: EQ-5Da, LPHb	PATENT-1 (riociguat) N=107	High quality evidence (GRADE ⊕⊕⊕⊕) [redacted]
Change in haemodynamic parameters from baseline: PVR	PATENT-1 (riociguat) N=107	Moderate quality evidence (GRADE ⊕⊕⊕⊙) [redacted]

a EQ-5D utility scores range from −0.59 to 1.00. A higher score represents better QoL.
b LPH total scores range from 0 to 105. A higher score indicates poorer QoL.
6MWD = 6-minute walk distance; ARD = absolute risk difference; CI = confidence interval; EQ-5D = EuroQol 5dimension; ERA = endothelin receptor antagonist; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; LPH = living with pulmonary hypertension; MD = mean difference; PVR = pulmonary vascular resistance; QoL = quality of life; RR = relative risk; sGC = soluble guanylate cyclase; WHO = World Health Organization

Safety

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.

Q2. What is the new evidence concerning the effectiveness and 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, that has not previously been considered by the PBAC?

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

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.

Table ES.8 Summary of evidence for monotherapy in patients with PAH in WHO FC III or IV

PBAC meeting	PBS restrictions	Head-to-head trials / Indirect comparison	Comparison	Summary of evidence
Bosentan				
December 2003	WHO FC III/IV IPAH and PAH associated with scleroderma	[redacted]	[redacted]	[redacted]
March 2008	WHO FC III/IV PAH-CHD	1 head-to-head RCT comparing bosentan with placebo: • BREATHE-5 [5]	Bosentan vs placebo	• Bosentan was superior in terms of effectiveness but inferior in terms of safety, compared with placebo • Bosentan was equivalent, in terms of comparative effectiveness and comparative safety in PAH-CHD, to other PBS-listed PAH aetiology groups, eg IPAH and PAH-CTD
Ambrisentan				
July 2009	WHO FC III/IV IPAH and PAH-CTD	Indirect comparison of 2 RCTs comparing ambrisentan with placebo: • ARIES-1 [6] (WHO FC III/IV subgroup) • ARIES-2 [6] (WHO FC III/IV subgroup) with 2 RCTs comparing bosentan with placebo: • BREATHE-1 [2] • AC-052-351 [4] via placebo as the common reference	Ambrisentan vs bosentan	• Ambrisentan was non-inferior to bosentan in terms of change in 6MWD • There was no statistically significant difference between ambrisentan and bosentan with respect to change in BDI, WHO FC and clinical worsening • The toxicity of ambrisentan appeared non-inferior to bosentan

PBAC meeting	PBS restrictions	Head-to-head trials / Indirect comparison	Comparison	Summary of evidence
Macitentan				
March 2014	WHO FC III/IV IPAH, PAH-CTD and PAH-CHD	Indirect comparison of 1 RCT comparing macitentan with placebo: • SERAPHIN [7] (overall population (ie with or without background therapy consisting of other PAH medicines, regardless of WHO FC) and treatment-naïve WHO FC III/IV subgroup) with 4 RCTs comparing bosentan with placebo: • BREATHE-1 [2, 8] • AC-052-351 [3, 4] • EARLY [9] • STRIDE-2 [10] via placebo as the common reference	Macitentan vs bosentan	• Macitentan was non-inferior to bosentan in terms of improvement in 6MWD • Macitentan was non-inferior in terms of safety when compared to bosentan
Sildenafil				
November 2006	WHO FC III IPAH and PAH-CTD	Indirect comparison of 1 RCT comparing sildenafil with placebo: • SUPER-1 [11] (overall population ie regardless of WHO FC, and WHO III subgroup) with 2 RCTs comparing bosentan with placebo: • BREATHE-1 [2] • AC-052-351 [4] via placebo as the common reference	Sildenafil vs bosentan	• Sildenafil was non-inferior to bosentan in terms of improvement in 6MWD • Sildenafil was no worse than bosentan in terms of toxicity
Tadalafil				
November 2011	WHO FC III IPAH and PAH-CTD	Indirect comparison of 1 RCT comparing tadalafil with placebo: • PHIRST [12-14] (subgroup of no background therapy) with 1 RCT comparing sildenafil with placebo: • SUPER-1 [11, 15-17]	Tadalafil vs sildenafil	• Tadalafil was non-inferior to sildenafil in terms of improvement in 6MWD • There were no statistically significant differences between tadalafil and sildenafil with respect to improvement in FC, clinical worsening and haemodynamic parameters • Tadalafil was non-inferior to sildenafil in terms of safety

PBAC meeting	PBS restrictions	Head-to-head trials / Indirect comparison	Comparison	Summary of evidence
		via placebo as the common reference.		
Iloprost				
November 2004	WHO FC III/IV IPAH, PAH-CTD and drug-induced PAH	[redacted]	[redacted]	[redacted]
Epoprostenol				
March 2006	WHO FC III/IV IPAH	Indirect comparison of 2 RCTs comparing epoprostenol with conventional therapy: • BW-46 [19] • BW-35/36 [20] with 2 RCTs comparing bosentan with placebo: • BREATHE-1 [2] • AC-052-351 [3] via placebo/conventional therapy as the common reference	Epoprostenol vs bosentan	• Epoprostenol was no worse than bosentan in terms of improvement in 6MWD • Epoprostenol was non-inferior to bosentan in terms of safety
November 2011	WHO FC III (as secondary therapy) and FC IV (as first-line therapy) PAH-CTD	Indirect comparison of 1 RCT comparing epoprostenol with conventional therapy: • VA1A4001 [21] with 1 RCT comparing iloprost with placebo: • AIR [18] (overall population (ie regardless of PAH aetiology) and secondary PAH subgroup) via placebo/conventional therapy as the common reference	Epoprostenol vs iloprost Epoprostenol vs bosentan	• Epoprostenol was non-inferior to iloprost in terms of improvement in 6MWD and haemodynamic parameters • Epoprostenol was non-inferior to bosentan in terms of improvement in 6MWD • The comparative safety of epoprostenol with iloprost and bosentan was difficult to assess in the absence of head-to head trial data. However, safety profiles of these PAH medicines were well recognised and the safety of epoprostenol was comparable across all subgroups of PAH patients

PBAC meeting	PBS restrictions	Head-to-head trials / Indirect comparison	Comparison	Summary of evidence
		Indirect comparison of 1 RCT comparing epoprostenol with conventional therapy: • VA1A4001 [21] with 2 RCTs comparing bosentan with placebo: • BREATHE-1 [22] (PAH-CTD subgroup) • AC-052-351 [22] (PAH-CTD subgroup) via placebo/conventional therapy as the common reference		
Riociguat				
March 2014	WHO FC III/IV IPAH, PAH-CTD and PAH-CHD	Indirect comparison of 1 RCT comparing riociguat with placebo: • PATENT-1 [23] (treatment-naïve, WHO FC III/IV subgroup) with 3 RCTs comparing bosentan with placebo: • BREATHE-1 [2] • AC-052-351 [3, 4] • BREATHE-5 [5] via placebo as the common reference	Riociguat vs bosentan	• Riociguat was non-inferior to bosentan in terms of improvement in 6MWD • The safety profiles of riociguat and bosentan were likely to be dissimilar

6MWD = 6-minute walk distance; BDI= Borg Dyspnoea Index; FC = functional class; IPAH = idiopathic pulmonary arterial hypertension; PAH = pulmonary arterial hypertension; PAH-CTD = PAH associated with connective tissue disease; PAH-CHD = PAH associated with congenital heart disease; RCT = randomised controlled trial; WHO = World Health Organization

Source: Relevant Public summary documents and ratified PBAC minutes

Q3. What is the effectiveness and safety of dual combination therapy involving any combination of an ERA, a PDE 5 inhibitor, a prostanoid, or a sGC stimulator, compared to monotherapy, in:

i) PAH patients, irrespective of disease severity or aetiology;

ii) PAH patients with FC III or IV; and

iii) PAH patients with different disease aetiologies?

Effectiveness and safety of dual combination therapy

ERA in addition to PDE-5 inhibitor

Clinical effectiveness

Four RCTs reported on the effectiveness of an ERA in addition to a PDE-5 inhibitor in treating PAH compared with placebo plus a PDE-5 inhibitor in patients with PAH:

- 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).
- There were no statistically significant differences in the effectiveness of treatment for patients receiving initial combination therapy versus monotherapy and patients receiving sequential combination therapy versus monotherapy.
- Two RCTs included a subgroup analysis for patients with WHO FC III/IV PAH.
- Two RCTs included a subgroup analysis for patients with different PAH aetiologies.

The evidence provided by these trials is summarised in Table ES.9.

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.

Table ES.9 Summary of the evidence for the clinical effectiveness of an ERA in addition to a PDE-5 inhibitor, relative to PDE-5 inhibitor monotherapy

Outcome	Included trials No. of patients	Summary of evidence
All PAH patients		
Clinical worsening	EARLY (bosentan/sildenafil) COMPASS-2 (bosentan/sildenafil) SERAPHIN (macitentan/any PDE-5i) AMBITION (ambrisentan/tadalafil) N=1,124	High quality evidence (GRADE ⊕⊕⊕⊕) [redacted]
All-cause mortality	EARLY (bosentan/sildenafil) COMPASS-2 (bosentan/sildenafil) SERAPHIN (macitentan/any PDE-5i) AMBITION (ambrisentan/tadalafil) N=1,124	Moderate quality evidence (GRADE ⊕⊕⊕⊙) [redacted]
Hospitalisation due to worsening PAH	SERAPHIN (macitentan/any PDE-5i) AMBITION (ambrisentan/tadalafil) N=761	High quality evidence (GRADE ⊕⊕⊕⊕) Significantly fewer patients were hospitalised for worsening PAH with combination therapy compared with monotherapy (pooled RR = 0.67; 95% CI 0.45, 0.98) There were no significant differences in treatment effectiveness for the different treatment combinations
Improved WHO FC	COMPASS-2 (bosentan/sildenafil) AMBITION (ambrisentan/tadalafil) N=706	High quality evidence (GRADE ⊕⊕⊕⊕) There was little difference in the proportion of patients whose WHO FC improved with combination therapy compared with monotherapy (pooled RR = 1.10; 95% CI 0.85, 1.42) There were no significant differences in treatment effectiveness for the different treatment combinations
Worsened WHO FC	COMPASS-2 (bosentan/sildenafil) AMBITION (ambrisentan/tadalafil) N=706	High quality evidence (GRADE ⊕⊕⊕⊕) There was no difference in the proportion of patients whose WHO FC worsened with combination therapy compared with monotherapy (pooled RR = 1.00; 95% CI 0.58, 1.73) There were no significant differences in treatment effectiveness for the different treatment combinations
Change in 6MWD from baseline	EARLY (bosentan/sildenafil) COMPASS-2 (bosentan/sildenafil)	Low quality evidence (GRADE ⊕⊕⊙⊙) In 3 out of 4 studies, patients on combination therapy had a larger mean improvement in their 6MWD than those on monotherapy, but the difference was not clinically important (range 17.3 m less to 26.3 m walked further)

Outcome	Included trials No. of patients	Summary of evidence
	SERAPHIN (macitentan/any PDE-5i) AMBITION (ambrisentan/tadalafil) N=1,046	There were no significant differences in treatment effectiveness for the different treatment combinations
Change in QoL from baseline: SF-36 physical component[a]	SERAPHIN (macitentan/any PDE-5i) N=299	High quality evidence (GRADE ⊕⊕⊕⊕) Patients on combination therapy had a larger mean improvement in their QoL than those on monotherapy (MD = 1.4 point improvement; 95% CI 0, 2.9)
Patients with WHO FC III/IV PAH		
Clinical worsening	COMPASS-2 (bosentan/sildenafil) SERAPHIN (macitentan/any PDE-5i) N=351	High quality evidence (GRADE ⊕⊕⊕⊕) [redacted]
All-cause mortality	SERAPHIN (macitentan/any PDE-5i) N=157	High quality evidence (GRADE ⊕⊕⊕⊕) [redacted]
Patients with different PAH aetiologies		
Clinical worsening in IPAH/HPAH	COMPASS-2 (bosentan/sildenafil) N=226	High quality evidence (GRADE ⊕⊕⊕⊕) Fewer patients experienced clinical worsening with combination therapy compared with monotherapy, but the 95% CI indicates that there may also be an effect in the opposite direction (HR = 0.82; 95% CI 0.55, 1.21)
Clinical worsening in PAH CTD	COMPASS-2 (bosentan/sildenafil) AMBITION (ambrisentan/tadalafil) N=231	High quality evidence (GRADE ⊕⊕⊕⊕) Could not calculate RR due to missing numerator in one arm of one study Fewer patients experienced clinical worsening with combination therapy compared with monotherapy, but this did not quite reach statistical significance (pooled HR = 0.59; 95% CI 0.12, 1.07)
Clinical worsening in PAH-CHD	COMPASS-2 (bosentan/sildenafil) N=20	Low quality evidence (GRADE ⊕⊕⊙⊙) Fewer patients experienced clinical worsening with combination therapy compared with monotherapy, but the wide 95% CI indicates that the study was underpowered for this outcome (HR = 0.57; 95% CI 0.10, 3.17)

a SF-36 physical component summary scores range from 0 to 100. A higher score indicates better QoL.
6MWD = 6-minute walk distance; CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation1; HPAH = heritable PAH; HR = hazard ratio; IPAH = idiopathic PAH; MD = mean difference; PAH = pulmonary arterial hypertension; PAH-CHD = PAH associated with congenital heart disease; PAH-CTD = PAH associated with connective tissue disease; PDE-5 = phosphodiesterase type-5; QoL = quality of life; RR = relative risk; SF-36 = short form 36; WHO = World Health Organization

Safety

Three RCTs reported on the comparative safety of treatment with an ERA plus a PDE-5 inhibitor compared with a PDE-5 inhibitor alone in any patient with PAH:

- COMPASS-2, SERAPHIN and AMBITION
- There were no new safety signals identified.

The evidence provided by these trials is summarised in Table ES.10.

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.

Table ES.10 Summary of the evidence for the safety of an ERA in addition to a PDE-5 inhibitor, relative to PDE-5 inhibitor monotherapy

Outcome	Included trials No. of patients	Summary of evidence
All PAH patients		
Any AE	COMPASS-2 (bosentan/sildenafil) N=333	High quality evidence (GRADE ⊕⊕⊕⊕) The proportion of patients who had any AE was the same for both the combination therapy and monotherapy arms (RR = 0.99; 95% CI 0.93, 1.06)
Serious AEs	COMPASS-2 (bosentan/sildenafil) AMBITION (ambrisentan/tadalafil) N=705	High quality evidence (GRADE ⊕⊕⊕⊕) Significantly fewer patients had a serious AE with combination therapy compared with monotherapy (pooled RR = 0.82; 95% CI 0.69, 0.96)
AEs leading to treatment discontinuation	COMPASS-2 (bosentan/sildenafil) AMBITION (ambrisentan/tadalafil) N=705	High quality evidence (GRADE ⊕⊕⊕⊕) More patients had an AE leading to treatment discontinuation with combination therapy compared with monotherapy, but the 95% CI indicates that there could also be an effect in the opposite direction (pooled RR = 1.47; 95% CI 0.81, 2.66)
Patients with IPAH/HPAH		
Any AE in IPAH/HPAH	AMBITION (ambrisentan/tadalafil) N=204	High quality evidence (GRADE ⊕⊕⊕⊕) The proportion of patients who had any AE was the same for both the combination therapy and monotherapy arms (RR = 1.04; 95% CI 0.97, 1.12)
Serious AEs in IPAH/HPAH	AMBITION (ambrisentan/tadalafil) N=204	High quality evidence (GRADE ⊕⊕⊕⊕) Fewer patients had a serious AE with combination therapy compared with monotherapy, but the 95% CI indicates that there could also be an effect in the opposite direction (RR = 0.85; 95% CI 0.58, 1.25)
AEs leading to treatment discontinuation in IPAH/HPAH	AMBITION (ambrisentan/tadalafil) N=204	Moderate quality evidence (GRADE ⊕⊕⊕⊙) The proportion of patients who had an AE leading to treatment discontinuation was the same for both the combination therapy and monotherapy (RR = 0.98; 95% CI 0.44, 2.20)

Outcome	Included trials No. of patients	Summary of evidence
Patients with PAH-CTD		
Any AE in PAH-CTD	AMBITION (ambrisentan/tadalafil) N=143	High quality evidence (GRADE ⊕⊕⊕⊕) The proportion of patients who had any AE was the same for both the combination therapy and monotherapy arms (RR = 1.02; 95% CI 0.96, 1.07)
Serious AEs in PAH-CTD	AMBITION (ambrisentan/tadalafil) N=143	High quality evidence (GRADE ⊕⊕⊕⊕) Fewer patients had a serious AE with combination therapy compared with monotherapy, but the 95% CI indicates that there could also be an effect in the opposite direction (RR = 0.87; 95% CI 0.60, 1.28)
AEs leading to treatment discontinuation in PAH-CTD	AMBITION (ambrisentan/tadalafil) N=143	Moderate quality evidence (GRADE ⊕⊕⊕⊙) Fewer patients had an AE leading to treatment discontinuation with combination therapy compared with monotherapy, but the 95% CI indicates that there could also be an effect in the opposite direction (RR = 0.91; 95% CI 0.37, 2.19)

AE = adverse event; CI = confidence interval; ERA = endothelin receptor antagonist; GRADE = grading of recommendations assessment, development and evaluation1; HPAH = heritable PAH; IPAH = idiopathic PAH; PAH = pulmonary arterial hypertension; PAH-CTD = PAH associated with connective tissue disease; PDE-5 = phosphodiesterase type-5; RR = relative risk

ERA in addition to prostanoid

Clinical effectiveness

Two RCTs reported on the effectiveness of an ERA in addition to prostanoid therapy in treating PAH compared with placebo plus a prostanoid:

- BREATHE-2 enrolled treatment-naïve patients with WHO FC III/IV PAH to receive combination therapy or monotherapy
- Han 2017 enrolled treatment-naïve patients with WHO FC III/IV PAH to receive combination therapy or monotherapy.

The evidence provided by these trials for patients with WHO FC III/IV PAH is summarised in Table ES.11.

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.

Table ES.11 Summary of the evidence for the clinical effectiveness of an ERA in addition to a prostanoid, relative to prostanoid monotherapy

Outcome	Included trials No. of patients	Summary of evidence
Patients with WHO FC III/IV PAH		
All-cause mortality	BREATHE-2 (bosentan/epoprostenol) N=33	Low quality evidence (GRADE ⊕⊕⊙⊙) More patients died from any cause with combination therapy compared with monotherapy, but the wide 95% CI indicates that the study was underpowered for this outcome (ARD = 13.6%; 95% CI −0.7, 28.0)
Improved WHO FC	BREATHE-2 (bosentan/epoprostenol) N=33	Very low quality evidence (GRADE ⊕⊙⊙⊙) More patients improved their WHO FC with combination therapy compared with monotherapy, but the wide 95% CI indicates that the study was underpowered for this outcome (RR = 1.30; 95% CI 0.62, 2.71)
Change in 6MWD from baseline	BREATHE-2 (bosentan/epoprostenol) Han 2017 (bosentan/iloprost) N=47	Very low quality evidence (GRADE ⊕⊙⊙⊙) In 1 out of 2 studies patients on combination therapy had a large clinically important improvement in their 6MWD compared with those on monotherapy (range 6.0 m less to 123.6 m walked further) Two studies were too small to determine whether the two different treatment combinations differ in their treatment effectiveness
Change in QoL from baseline: MLHFa	Han 2017 (bosentan/iloprost) N=14	Very low quality evidence (GRADE ⊕⊙⊙⊙) Patients on combination therapy had a larger mean improvement in their QoL than those on monotherapy (MD = 35.34 point improvement was a clinically important difference)
Change in haemodynamic parameters from baseline: CAI, PVR, mPAP	BREATHE-2 (bosentan/epoprostenol) Han 2017 (bosentan/iloprost) N=47	Very low quality evidence (GRADE ⊕⊙⊙⊙) Patients on combination therapy had a larger mean improvement in their haemodynamic parameters than those on monotherapy and were likely to be clinically important in 1 out of 2 studies (CAI range 10.8−17% improvement; PVR range 9.5−21.5% improvement; mPAP range 6.8−26.3% improvement) The two studies were too small to determine whether the two different treatment combinations differ in their treatment effectiveness
Change in haemodynamic parameters from baseline: mRAP, TPR	BREATHE-2 (bosentan/epoprostenol) N=33	Very low quality evidence (GRADE ⊕⊙⊙⊙) Patients on combination therapy had a larger mean improvement in their haemodynamic parameters than those on monotherapy (mRAP MD = 2.2 mmHg improvement; TPR MD = 13.7% improvement)

a MLHF total scores range from 0 to 105. A higher score indicates poorer QoL.
6MWD = 6-minute walk distance; ARD = absolute risk difference; CAI = cardiac index; CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation1; MD = mean difference; MLHF = Minnesota living with heart failure; mPAP = mean pulmonary artery pressure; mRAP = mean right atrial pressure; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; QoL = quality of life; RR = relative risk; TPR = total pulmonary resistance; WHO = World Health Organization

Safety

Two RCTs reported on the comparative safety of treatment with an ERA plus a prostanoid compared with a prostanoid alone in any patient with PAH:

- BREATHE-2 and Han 2017
- There were no new safety signals identified.

The evidence provided by these trials for patients with WHO FC III/IV PAH is summarised in Table ES.12.

Overall, although there is uncertainty, 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.

Table ES.12 Summary of the evidence for the safety of an ERA in addition to a prostanoid, relative to prostanoid monotherapy

Outcome	Included trials	Summary of evidence
Patients with WHO FC III/IV PAH		
Any AE	Han 2017 (bosentan/iloprost) N=14	Low quality evidence (GRADE ⊕⊕⊙⊙) The proportion of patients who had any AE was similar for both the combination therapy and monotherapy arms, but the 95% CI indicates that there could be an effect favouring either treatment arm (RR = 1.05; 95% CI 0.67, 1.64)
Serious AEs	BREATHE-2 (bosentan/epoprostenol) N=44	Very low quality evidence (GRADE ⊕⊙⊙⊙) Fewer patients experienced a serious AE with combination therapy compared with monotherapy, but the wide 95% CI indicates that the study was likely underpowered for this outcome (RR = 0.75; 95% CI 0.15, 3.85)
AEs leading to treatment discontinuation	BREATHE-2 (bosentan/epoprostenol) N=44	Very low quality evidence (GRADE ⊕⊙⊙⊙) Fewer patients had an AE leading to treatment discontinuation with combination therapy compared with monotherapy, but the wide 95% CI indicates that the study was likely underpowered for this outcome (RR = 0.50; 95% CI 0.03, 7.26)

AE = adverse event; CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation1; PAH = pulmonary arterial hypertension; RR = relative risk; WHO = World Health Organization

PDE-5 inhibitor in addition to ERA

Clinical effectiveness

Five RCTs reported on the effectiveness of a PDE-5 inhibitor in addition to an ERA in treating PAH patients compared with placebo plus an ERA:

- 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)
  - There were no statistically significant differences in outcomes for patients receiving initial combination therapy versus monotherapy and patients receiving sequential combination therapy versus monotherapy.
- Two RCTs included a subgroup analysis for patients with WHO FC III/IV PAH.

- Three RCTs included a subgroup analysis for patients with different PAH aetiologies.

The evidence provided by these trials for all PAH patients is summarised in Table ES.13.

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.

Table ES.13 Summary of the evidence for the clinical effectiveness of a PDE-5 inhibitor in addition to an ERA, relative to ERA monotherapy

Outcome	Included trials No. of patients	Summary of evidence
All PAH patients		
Clinical worsening	AMBITION (tadalafil/ambrisentan) PHIRST (tadalafil/bosentan) Zhuang 2014 (tadalafil/ambrisentan) Vizza 2017 (sildenafil/bosentan) N=694	High quality evidence (GRADE ⊕⊕⊕⊕) Significantly fewer patients experienced clinical worsening with combination therapy compared with monotherapy (pooled RR = 0.53; 95% CI 0.38, 0.73) There were no significant differences in treatment effectiveness for the different treatment combinations, but the point estimate for Vizza 2017 showed the opposite effect
All-cause mortality	AMBITION (tadalafil/ambrisentan) Zhuang 2014 (tadalafil/ambrisentan) Vizza 2017 (sildenafil/bosentan) N=682	Moderate quality evidence (GRADE ⊕⊕⊕⊙) Fewer patients died from any cause with combination therapy compared with monotherapy, but the 95% CI indicates that there could also be an effect in the opposite direction (pooled RR = 0.64; 95% CI 0.18, 2.36) There were no significant differences in treatment effectiveness for the different treatment combinations, but the point estimate for Vizza 2017 showed the opposite effect
Hospitalisation due to worsening PAH	AMBITION (tadalafil/ambrisentan) Zhuang 2014 (tadalafil/ambrisentan) Vizza 2017 (sildenafil/bosentan) N=607	High quality evidence (GRADE ⊕⊕⊕⊕) Significantly fewer patients were hospitalised with combination therapy compared with monotherapy (pooled RR = 0.42; 95% CI 0.25, 0.70) There were no significant differences in treatment effectiveness for the different treatment combinations
Improved WHO FC	AMBITION (tadalafil/ambrisentan) PHIRST (tadalafil/bosentan) Zhuang 2014 (tadalafil/ambrisentan) Vizza 2017 (sildenafil/bosentan) N=691	High quality evidence (GRADE ⊕⊕⊕⊕) There was little difference in the proportion of patients whose WHO FC improved with combination therapy compared with monotherapy (pooled RR = 1.11; 95% CI 0.77, 1.60) The PHIRST study showed a trend favouring the opposite effect to the other 3 studies
Worsened WHO FC	AMBITION (tadalafil/ambrisentan)	High quality evidence (GRADE ⊕⊕⊕⊕) Fewer patients on combination therapy had worsening of their WHO FC compared with monotherapy, but the result did not

Outcome	Included trials No. of patients	Summary of evidence
	PHIRST (tadalafil/bosentan) Zhuang 2014 (tadalafil/ambrisentan) Vizza 2017 (sildenafil/bosentan) N=691	quite reach statistical significance (pooled RR = 0.60; 95% CI 0.34, 1.05) There were no significant differences in treatment effectiveness for the different treatment combinations
Change in 6MWD from baseline	AMBITION (tadalafil/ambrisentan) PHIRST (tadalafil/bosentan) Zhuang 2014 (tadalafil/ambrisentan) Vizza 2017 (sildenafil/bosentan) Mainguy 2013 (sildenafil/PDE-5 inhibitor) N=726	Moderate quality evidence (GRADE ⊕⊕⊕⊙) In 4 out of 5 studies, patients on combination therapy had a larger mean improvement in their 6MWD than those on monotherapy, and the difference could be clinically important in 1 study (range 2.4 m less to 36.1 m walked further) The Vizza 2017 study showed a trend favouring the opposite effect to the other 4 studies, but this difference may not be statistically significant
Change in haemodynamic parameters from baseline: PVR, mPAP	Zhuang 2014 (tadalafil/ambrisentan) N=124	Low quality evidence (GRADE ⊕⊕⊙⊙) Patients on combination therapy had a larger mean improvement in their haemodynamic parameters than those patients receiving monotherapy (PVR MD = 13.9% improvement; mPAP MD = 8.5% improvement)
Patients with WHO FC III/IV PAH		
Change in 6MWD from baseline	PHIRST (tadalafil/bosentan) Zhuang 2014 (tadalafil/ambrisentan) N=109	Moderate quality evidence (GRADE ⊕⊕⊕⊙) Patients on combination therapy had a larger mean improvement in their 6MWD than those patients receiving monotherapy, but the difference was not clinically important (range 13.5−20.1 m walked further) There were no significant differences in treatment effectiveness for the different treatment combinations
Patients with IPAH/HPAH		
Change in 6MWD from baseline	PHIRST (tadalafil/bosentan) Vizza 2017 (sildenafil/bosentan) N=120	Moderate quality evidence (GRADE ⊕⊕⊕⊙) Patients on combination therapy had a larger mean improvement in their 6MWD than those on monotherapy, but the difference was not clinically important (range 8.6−13.6 m walked further) There were no significant differences in treatment effectiveness for the different treatment combinations
Patients with PAH-CTD		
Clinical worsening	AMBITION (tadalafil/ambrisentan) N=147	High quality evidence (GRADE ⊕⊕⊕⊕) Fewer patients experienced clinical worsening with combination therapy compared with monotherapy, but the result just failed to reach statistical significance (HR = 0.51; 95% CI 0.25, 1.01)
Change in 6MWD from baseline	PHIRST (tadalafil/bosentan)	Very low quality evidence (GRADE ⊕⊙⊙⊙) Patients on combination therapy had a wide range of change in their 6MWD compared with those on monotherapy, but the

Outcome	Included trials No. of patients	Summary of evidence
	Vizza 2017 (sildenafil/bosentan) N=55	difference was not clinically important (range 34.1 m less to 20.7 m walked further) There were no significant differences in treatment effectiveness for the different treatment combinations

6MWD = 6-minute walk distance; CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation1; HPAH = heritable PAH; HR = hazard ratio; IPAH = idiopathic PAH; MD = mean difference; mPAP = mean pulmonary artery pressure; PAH = pulmonary arterial hypertension; PAH-CTD = PAH associated with connective tissue disease; PDE-5 = phosphodiesterase type-5; PVR = pulmonary vascular resistance; RR = relative risk; WHO = World Health Organization

Safety

Four RCTs reported on the comparative safety of treatment with a PDE-5 inhibitor plus an ERA compared with an ERA alone in any patient with PAH:

- 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.

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.

Table ES.14 Summary of the evidence for the safety of a PDE-5 inhibitor in addition to an ERA, relative to ERA monotherapy

Outcome	Included trials No. of patients	Summary of evidence
All PAH patients		
Any AE	PHIRST (tadalafil/bosentan) Vizza 2017 (sildenafil/bosentan) N=190	High quality evidence (GRADE ⊕⊕⊕⊕) The proportion of patients who had any AE was similar for both the combination therapy and monotherapy arms (pooled RR = 1.00; 95% CI 0.79, 1.27) There were no significant differences in treatment effectiveness for the different treatment combinations
Serious AEs	AMBITION (tadalafil/ambrisentan) Vizza 2017 (sildenafil/bosentan) N=482	High quality evidence (GRADE ⊕⊕⊕⊕) The proportion of patients who had a serious AE was similar for both the combination therapy and monotherapy arms (pooled RR = 0.99; 95% CI 0.76, 1.29) There were no significant differences in treatment effectiveness for the different treatment combinations
AEs leading to treatment discontinuation	AMBITION (tadalafil/ambrisentan) Zhuang 2014 (tadalafil/ambrisentan) N=503	Moderate quality evidence (GRADE ⊕⊕⊕⊙) More patients had an AE leading to treatment discontinuation with combination therapy compared with monotherapy, but the 95% CI indicates that there could also be an effect in the opposite direction (pooled RR = 1.65; 95% CI 0.35, 7.81) There were no significant differences in treatment effectiveness for the different treatment combinations

Outcome	Included trials No. of patients	Summary of evidence
Patients with PAH-CTD		
Any AE	AMBITION (tadalafil/ambrisentan) N=146	High quality evidence (GRADE ⊕⊕⊕⊕) The proportion of patients who had any AE was similar for both the combination therapy and monotherapy arms (RR = 1.04; 95% CI 0.97, 1.11)
Serious AEs	AMBITION (tadalafil/ambrisentan) N=146	High quality evidence (GRADE ⊕⊕⊕⊕) More patients had a serious AE with combination therapy compared with monotherapy, but the 95% CI indicates that there could also be an effect in the opposite direction (RR = 1.28; 95% CI 0.80, 2.04)
AEs leading to treatment discontinuation	AMBITION (tadalafil/ambrisentan) N=146	High quality evidence (GRADE ⊕⊕⊕⊕) Fewer patients had an AE leading to treatment discontinuation with combination therapy compared with monotherapy, but the 95% CI indicates that there could also be an effect in the opposite direction (RR = 0.75; 95% CI 0.34, 1.65)

AE = adverse event; CI = confidence interval; ERA = endothelin receptor antagonist; GRADE = grading of recommendations assessment, development and evaluation1; PAH = pulmonary arterial hypertension; PAH-CTD = PAH associated with connective tissue disease; PDE-5 = phosphodiesterase type-5; RR = relative risk

PDE-5 inhibitor in addition to prostanoid

Clinical effectiveness

One RCT reported on the effectiveness of a PDE-5 inhibitor in addition to a prostanoid in treating PAH compared with placebo plus a prostanoid:

- PACES-1 enrolled patients receiving long-term intravenous epoprostenol therapy to receive combination therapy with sildenafil plus epoprostenol or epoprostenol alone.

The evidence provided by this trial for all PAH patients is summarised in Table ES.15.

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.

Table ES.15 Summary of the evidence for the clinical effectiveness of a PDE-5 inhibitor in addition to a prostanoid, relative to prostanoid monotherapy

Outcome	Included trials No. of patients	Summary of evidence
All PAH patients		
Clinical worsening	PACES-1 (sildenafil/epoprostenol) N=265	High quality evidence (GRADE ⊕⊕⊕⊕) Significantly fewer patients experienced clinical worsening of their PAH with combination therapy compared with monotherapy (RR = 0.33; 95% CI 0.15, 0.70)
All-cause mortality	PACES-1 (sildenafil/epoprostenol) N=265	High quality evidence (GRADE ⊕⊕⊕⊕) Significantly fewer patients died from any cause with combination therapy compared with monotherapy (ARD = −5.3%; 95% CI −9.2, −1.5)

Outcome	Included trials No. of patients	Summary of evidence
Hospitalisation due to worsening PAH	PACES-1 (sildenafil/epoprostenol) N=265	Moderate quality evidence (GRADE ⊕⊕⊕⊙) Fewer patients were hospitalised with combination therapy compared with monotherapy, but the 95% CI indicates that there may also be an effect in the opposite direction (RR = 0.71; 95% CI 0.30, 1.71)
Change in 6MWD from baseline	PACES-1 (sildenafil/epoprostenol) N=265	Moderate quality evidence (GRADE ⊕⊕⊕⊙) Patients on combination therapy had a larger mean improvement in their 6MWD than those on monotherapy, but the difference was not clinically important (MD = 28.8 m walked further; 95% CI 13.9, 43.8)
Change in haemodynamic parameters from baseline: PVR, mPAP, mRAP	PACES-1 (sildenafil/epoprostenol) N=265	Low quality evidence (GRADE ⊕⊕⊙⊙) Patients on combination therapy had a larger mean improvement in their haemodynamic parameters than those on monotherapy and this improvement may be clinically important PVR and mRAP (PVR MD = 20.8% improvement; mPAP MD = 7.5% improvement; mRAP MD = 2.1 mmHg improvement)

6MWD = 6-minute walk distance; ARD = absolute risk difference; CI = confidence interval; GRADE = grading of recommendations assessment, development and evaluation1; MD = mean difference; mPAP = mean pulmonary artery pressure; mRAP = mean right atrial pressure; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase type-5; PVR = pulmonary vascular resistance; RR = relative risk

Safety

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 identified.

The evidence provided by this trial is summarised in Table ES.16.

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 patients.

Table ES.16 Summary of the evidence for the safety of a PDE-5 inhibitor in addition to a prostanoid, relative to prostanoid monotherapy

Outcome	Included trials	Summary of evidence
All PAH patients		
Any AE	PACES-1 (sildenafil/epoprostenol) N=265	High quality evidence (GRADE ⊕⊕⊕⊕) The proportion of patients who had any AE was similar for both the combination therapy and monotherapy arms (RR = 0.95; 95% CI 0.90, 1.00)
Serious AEs	PACES-1 (sildenafil/epoprostenol) N=265	High quality evidence (GRADE ⊕⊕⊕⊕) Fewer patients had a serious AE with combination therapy compared with monotherapy, but the 95% CI indicates that there could also be an effect in the opposite direction (RR = 0.73; 95% CI 0.48, 1.10)
AEs leading to treatment discontinuation	PACES-1 (sildenafil/epoprostenol) N=265	High quality evidence (GRADE ⊕⊕⊕⊕) Fewer patients had an AE leading to treatment discontinuation with combination therapy compared with monotherapy, but the 95% CI indicates that there could also be an effect in the opposite direction (RR = 0.49; 95% CI 0.20, 1.17)

AE = adverse event; CI = confidence interval; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation1; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase type-5; RR = relative risk; WHO = World Health Organization

Prostanoid in addition to an ERA

Clinical effectiveness

Two RCTs reported on the effectiveness of a prostanoid in addition to an ERA in treating PAH compared with a placebo plus an ERA:

- 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
    - Nearly all included patients had WHO FC III/IV PAH; one patient randomised to monotherapy had WHO FC II PAH

The evidence provided by these trials for patients with WHO FC III/IV PAH is summarised in Table ES.17.

Overall, there is limited evidence to suggest that the use of a prostanoid in addition to an ERA, relative to ERA monotherapy, to treat patients with WHO FC III/IV PAH may be beneficial. This finding would be stronger if it were replicated in additional research.

Table ES.17 Summary of the evidence for the clinical effectiveness of a prostanoid in addition to an ERA, relative to ERA monotherapy

Outcome	Included trials No. of patients	Summary of evidence
Patients with WHO FC III/IV PAH		
Clinical worsening	COMBI (iloprost/bosentan) STEP (iloprost/bosentan) N=105	Very low quality evidence (GRADE ⊕⊙⊙⊙) Fewer patients experienced clinical worsening with combination therapy compared with monotherapy, but the 95% CI indicates that there could also be an effect in the opposite direction (RR = 0.39; 95% CI 0.04, 3.45)
All-cause mortality	COMBI (iloprost/bosentan) STEP (iloprost/bosentan) N=105	Moderate quality evidence (GRADE ⊕⊕⊕⊙) There were no deaths during the study period
Hospitalisation due to worsening PAH	COMBI (iloprost/bosentan) STEP (iloprost/bosentan) N=105	Moderate quality evidence (GRADE ⊕⊕⊕⊙) Fewer patients were hospitalised with combination therapy compared with monotherapy, but the 95% CI indicates that there may also be an effect in the opposite direction (pooled ARD = −5.5%; 95% CI −18.9, 7.8)
Improved WHO FC	STEP (iloprost/bosentan) N=65	Low quality evidence (GRADE ⊕⊕⊙⊙) Significantly more patients improved their WHO FC with combination therapy compared with monotherapy (RR = 5.67; 95% CI 1.36, 23.61)
Worsened WHO FC	STEP (iloprost/bosentan) N=65	Moderate quality evidence (GRADE ⊕⊕⊕⊙) Fewer patients on combination therapy had worsening of their WHO FC compared with monotherapy, but the difference was not statistically significant (ARD = −3.0%; 95% CI −8.9, 2.8)
Change in 6MWD from baseline	COMBI (iloprost/bosentan) STEP (iloprost/bosentan) N=105	Low quality evidence (GRADE ⊕⊕⊙⊙) Patients on combination therapy had a larger mean improvement in their 6MWD than those on monotherapy, but the difference was not clinically important (range 10−26 m walked further)
Change in QoL from baseline: EQ-VAS[a]	COMBI (iloprost/bosentan) N=40	Very low quality evidence (GRADE ⊕⊙⊙⊙) Patients on combination therapy had a larger mean improvement in their QoL than those on monotherapy (MD = 10 point improvement was a clinically important difference)
Change in haemodynamic parameters from baseline: CAI, PVR, mPAP	STEP (iloprost/bosentan) N=65	Moderate quality evidence (GRADE ⊕⊕⊕⊙) Patients on combination therapy had a larger mean improvement in their haemodynamic parameters than those on monotherapy (PVR MD = 30.4% improvement was a clinically important difference; mPAP clinically important MD = 15.6% improvement)

a EQ-VAS scores range from 0 to 100. A higher score represents better QoL.
6MWD = 6-minute walk distance; ARD = absolute risk difference; CAI = cardiac index; CI = confidence interval; EQ-VAS = EuroQoL visual analogue scale; ERA = endothelin receptor antagonist; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation1; MD = mean difference; mPAP = mean pulmonary artery pressure; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; QoL = quality of life; RR = relative risk; WHO = World Health Organization

Safety

Two RCTs reported on the comparative safety of treatment with a prostanoid in addition to an ERA compared with an ERA alone in patients with WHO FC III/IV PAH:

- COMBI and STEP
- There were no new safety signals identified.

The evidence provided by these trials is summarised in Table ES.18.

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.

Table ES.18 Summary of the evidence for the safety of a prostanoid in addition to an ERA, relative to ERA monotherapy

Outcome	Included trials No. of patients	Summary of evidence
Patients with WHO FC III/IV PAH		
Any AE	COMBI (iloprost/bosentan) STEP (iloprost/bosentan) N=107	Very low quality evidence (GRADE ⊕⊙⊙⊙) More patients experienced an AE with combination therapy compared with monotherapy, but the 95% CI indicates there was an effect in the opposite direction (pooled RR = 2.40; 95% CI 0.15, 37.41)
Serious AEs	STEP (iloprost/bosentan) N=67	Moderate quality evidence (GRADE ⊕⊕⊕⊙) Fewer patients had a serious AE with combination therapy compared with monotherapy, but the 95% CI indicates that there could also be an effect in the opposite direction (RR = 0.65; 95% CI 0.23, 1.85)
AEs leading to treatment discontinuation	COMBI (iloprost/bosentan) N=40	Very low quality evidence (GRADE ⊕⊙⊙⊙) More patients had an AE leading to treatment discontinuation with combination therapy compared with monotherapy, but the difference was not statistically significant (ARD = 5.2%; 95% CI −4.8, 15.3)

AE = adverse event; CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation1; PAH = pulmonary arterial hypertension; RR = relative risk; WHO = World Health Organization

sGC stimulator in addition to an ERA

Clinical effectiveness

One RCT reported on the effectiveness of a sGC stimulator in addition to an ERA in treating PAH when compared with a placebo plus an ERA in patients with PAH:

- 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
  - 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.

Overall, there is very limited evidence indicating that the use of a sGC stimulator in addition to an ERA, relative to ERA monotherapy, [redacted] for PAH patients. The evidence for patients with WHO FC III/IV PAH showed a similar [redacted] effect. This finding would be stronger if it were replicated in additional research.

Table ES.19 Summary of the evidence for the clinical effectiveness of a sGC stimulator in addition to an ERA, relative to ERA monotherapy

Outcome	Included trials No. of patients	Summary of evidence
All PAH patients		
Clinical worsening	PATENT-1 (riociguat/ERA) N=167	• Moderate quality evidence (GRADE ⊕⊕⊕⊙) [redacted]
All-cause mortality	PATENT-1 (riociguat/ERA) N=167	• High quality evidence (GRADE ⊕⊕⊕⊕) [redacted]
Hospitalisation due to worsening PAH	PATENT-1 (riociguat/ERA) N=167	• Moderate quality evidence (GRADE ⊕⊕⊕⊙) [redacted]
Improved WHO FC	PATENT-1 (riociguat/ERA) N=167	• Moderate quality evidence (GRADE ⊕⊕⊕⊙) [redacted]
Worsened WHO FC	PATENT-1 (riociguat/ERA) N=167	• Moderate quality evidence (GRADE ⊕⊕⊕⊙) [redacted]
Change in 6MWD from baseline	PATENT-1 (riociguat/ERA) N=167	• Moderate quality evidence (GRADE ⊕⊕⊕⊙) [redacted]
Change in QoL from baseline: EQ-5D[a], LPH[b]	PATENT-1 (riociguat/ERA) N=167	• High quality evidence (GRADE ⊕⊕⊕⊕) [redacted]
Change in haemodynamic parameters from baseline: PVR	PATENT-1 (riociguat/ERA) N=148	• Low quality evidence (GRADE ⊕⊕⊙⊙) [redacted]

Outcome	Included trials No. of patients	Summary of evidence
Patients with WHO FC III/IV PAH		
Clinical worsening	PATENT-1 (riociguat/ERA) N=120	• Moderate quality evidence (GRADE ⊕⊕⊕⊙) [redacted]
All-cause mortality	PATENT-1 (riociguat/ERA) N=120	• High quality evidence (GRADE ⊕⊕⊕⊕) [redacted]
Hospitalisation due to worsening PAH	PATENT-1 (riociguat/ERA) N=120	• Moderate quality evidence (GRADE ⊕⊕⊕⊙) [redacted] • [redacted]
Improved WHO FC	PATENT-1 (riociguat/ERA) N=120	• Moderate quality evidence (GRADE ⊕⊕⊕⊙) [redacted]
Worsened WHO FC	PATENT-1 (riociguat/ERA) N=120	• High quality evidence (GRADE ⊕⊕⊕⊕) [redacted]
Change in 6MWD	PATENT-1 (riociguat/ERA) N=120	• High quality evidence (GRADE ⊕⊕⊕⊕) [redacted]
Change in QoL: EQ-5D[a], LPH[b]	PATENT-1 (riociguat/ERA) N=120	• High quality evidence (GRADE ⊕⊕⊕⊕) [redacted]
Change in haemodynamic parameters: PVR	PATENT-1 (riociguat/ERA) N=103	• Moderate quality evidence (GRADE ⊕⊕⊕⊙) [redacted]

[a] EQ-5D utility scores range from −0.59 to 1.00. A higher score represents better QoL.
[b] LPH total scores range from 0 to 105. A higher score indicates poorer QoL.
6MWD = 6-minute walk distance; ARD = absolute risk difference; CI = confidence interval; EQ-5D = EuroQol 5 dimension; ERA = endothelin receptor antagonist; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; LPH = living with pulmonary hypertension; MD = mean difference; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; QoL = quality of life; RR = relative risk; sGC = soluble guanylate cyclase stimulator; WHO = World Health Organization

Safety

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.

sGC stimulator in addition to a PDE-5 inhibitor

Clinical effectiveness

One RCT reported on the effectiveness of a sGC stimulator in addition to PDE-5 inhibitor in treating PAH when compared with placebo plus a PDE-5 inhibitor:

- 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.

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.

Table ES.20 Summary of the evidence for the clinical effectiveness of a sGC stimulator in addition to a PDE-5 inhibitor, relative to PDE-5 inhibitor monotherapy

Outcome	Included trials No. of patients	Summary of evidence
Patients with WHO FC III/IV PAH		
All-cause mortality	PATENT-PLUS (riociguat/sildenafil) N=18	• Low quality evidence (GRADE ⊕⊕⊙⊙) • No patients died during the study period
Improved WHO FC	PATENT-PLUS (riociguat/sildenafil) N=18	• Low quality evidence (GRADE ⊕⊕⊙⊙) • Fewer patients improved their WHO FC with combination therapy compared with monotherapy, but the wide 95% CI indicates that the study was underpowered for this outcome (RR = 0.50; 95% CI 0.09, 2.73)
Worsened WHO FC	PATENT-PLUS (riociguat/sildenafil) N=18	• Low quality evidence (GRADE ⊕⊕⊙⊙) • No patients had worsening of their WHO FC during the study period
Change in 6MWD from baseline	PATENT-PLUS (riociguat/sildenafil) N=18	• Very low quality evidence (GRADE ⊕⊙⊙⊙) • Patients on combination therapy had a smaller mean improvement in their 6MWD than those on monotherapy, but the difference was not clinically important (MD = 23 m less)

6MWD = 6-minute walk distance; CI = confidence interval; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; MD = mean difference; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase type-5; RR = relative risk; sGC = soluble guanylate cyclase stimulator; WHO = World Health Organization

Safety

One RCT reported on the comparative safety of treatment with a sGC stimulator in addition to a PDE-5 inhibitor, compared with a PDE-5 inhibitor alone, in patients with PAH:

- PATENT-PLUS
- There were no new safety signals identified.

The evidence provided by this trial is summarised in Table ES.21.

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.

Table ES.21 Summary of the evidence for the safety of a sGC stimulator in addition to a PDE-5 inhibitor, relative to PDE-5 inhibitor monotherapy

Outcome	Included trials No. of patients	Summary of evidence
Patients with WHO FC III/IV PAH		
Any AE	PATENT-PLUS (riociguat/sildenafil) N=18	• Low quality evidence (GRADE ⊕⊕⊙⊙) • More patients experienced an AE with combination therapy compared with monotherapy, but the 95% CI indicates that the study was underpowered for this outcome (RR = 1.50; 95% CI 0.85, 2.64)
Serious AEs	PATENT-PLUS (riociguat/sildenafil) N=18	• Low quality evidence (GRADE ⊕⊕⊙⊙) • More patients experienced a serious AE with combination therapy compared with monotherapy, but the 95% CI indicates that the study was underpowered for this outcome (ARD = 16.7%; 95% CI −4.4, 37.8)
AEs leading to treatment discontinuation	PATENT-PLUS (riociguat/sildenafil) N=18	• Low quality evidence (GRADE ⊕⊕⊙⊙) • More patients had an AE leading to treatment discontinuation with combination therapy compared with monotherapy, but the difference was not statistically significant (ARD = 8.3%; 95% CI −7.3, 24.0)

AE = adverse event; ARD = absolute risk difference; CI = confidence interval; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase type-5; RR = relative risk; sGC = soluble guanylate cyclase stimulator; WHO = World Health Organization

sGC stimulator in addition to a prostanoid

Clinical effectiveness

One RCT reported on the effectiveness of a sGC stimulator in addition to a prostanoid when compared with placebo plus a prostanoid in patients with PAH:

- 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.

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.

Table ES.22 Summary of the evidence for the clinical effectiveness of a sGC stimulator in addition to a prostanoid, relative to prostanoid monotherapy

Outcome	Included trials No. of patients	Summary of evidence
All PAH patients		
Clinical worsening	PATENT-1 (riociguat/prostanoid) N=27	• Low quality evidence (GRADE ⊕⊕⊙⊙) [redacted]
All-cause mortality	PATENT-1 (riociguat/prostanoid) N=27	• Low quality evidence (GRADE ⊕⊕⊙⊙) [redacted]
Hospitalisation due to worsening PAH	PATENT-1 (riociguat/prostanoid) N=27	• Low quality evidence (GRADE ⊕⊕⊙⊙) [redacted]
Improved WHO FC	PATENT-1 (riociguat/prostanoid) N=27	• Very low quality evidence (GRADE ⊕⊙⊙⊙) [redacted]
Worsened WHO FC	PATENT-1 (riociguat/prostanoid) N=27	• Low quality evidence (GRADE ⊕⊕⊙⊙) [redacted]
Change in 6MWD from baseline	PATENT-1 (riociguat/prostanoid) N=27	• Low quality evidence (GRADE ⊕⊕⊙⊙) [redacted]
Change in QoL from baseline: EQ-5D[a], LPH[b]	PATENT-1 (riociguat/prostanoid) N=27	• Moderate quality evidence (GRADE ⊕⊕⊕⊙) [redacted]
Change in haemodynamic parameters from baseline: PVR	PATENT-1 (riociguat/prostanoid) N=27	• Very low quality evidence (GRADE ⊕⊙⊙⊙) [redacted]

[a] EQ-5D utility scores range from −0.59 to 1.00. A higher score represents better QoL.
[b] LPH total scores range from 0 to 105. A higher score indicates poorer QoL.
6MWD = 6-minute walk distance; ARD = absolute risk difference; CI = confidence interval; EQ-5D = EuroQol 5 dimension; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; LPH = living with pulmonary hypertension; MD = mean difference; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; QoL = quality of life; RR = relative risk; sGC = soluble guanylate cyclase stimulator; WHO = World Health Organization

Safety

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.

Q4. What is the effectiveness and safety of triple combination therapy involving any combination of an ERA, a PDE 5 inhibitor, a prostanoid, or a sGC stimulator, compared to dual combination therapy, in:

i) PAH patients, irrespective of disease severity or aetiology;

ii) PAH patients with FC III or IV; and

iii) PAH patients with different disease aetiologies?

Effectiveness and safety of triple combination therapy

There was no comparative evidence concerning the effectiveness and safety of triple combination therapy with PBS-listed PAH medicines relative to dual combination therapy in any patients with PAH.

Extended safety assessment

The key findings on the safety assessment of PAH medicines are:

- No clear safety signal has been identified on the basis of the safety data from included trials and studies.
- In paediatric patients, sildenafil had a worse safety profile than placebo. AEs occurring more frequently in patients receiving sildenafil, included pyrexia, increased erection, and upper respiratory tract infections. The occurrence of pyrexia, vomiting, and nausea appeared to be dose-related.
- The proportion of patients with ocular adverse events was generally low and comparable between sildenafil at the recommended dose (ie 20 mg three times a day), and placebo, but with some AEs reported only in patients receiving sildenafil, eg retinal haemorrhage (1.4%).
- Monotherapy with tadalafil was inferior to placebo in terms of safety, with a higher incidence of overall AEs, diarrhoea, nausea, nasopharyngitis, upper respiratory tract infections, myalgia, flushing, dyspepsia and pain in the extremities.
- The included observational studies followed patients for 2 years and above, which reflects the typical prolonged use of PAH medicines in clinical practice. For individual PAH medicines, the safety results from observational studies generally agreed with each other and with the safety results from RCT(s) and post-marketing data included in the product information (PI) documents.
- Limited data from studies in paediatric PAH patients suggested that, for both bosentan and sildenafil, the safety profile in children with PAH was generally consistent with that in adults.

The potential new safety signals identified by comparing the TGA-approved PI with the European Medicines Agency (EMA) Summary of Product Characteristics (SmPC) and the United States Food and Drug Administration (FDA) product label include:

- Use of bosentan in patients with chronic obstructive pulmonary disease (increase in minute ventilation, decreased oxygen saturation and dyspnoea).
- AEs of penile haemorrhage and haematospermia in patients receiving PDE-5 inhibitors (both sildenafil and tadalafil).
- Potential for vaso-occlusive crises in patients receiving sildenafil for PH secondary to sickle cell anaemia.
- Intracerebral haemorrhage in tadalafil-treated patients.
- Increased mortality and serious AEs in patients receiving riociguat in treating PH associated with idiopathic interstitial pneumonias.

There was evidence from a long-term observational study suggesting increased mortality with higher sildenafil doses. Sildenafil is not indicated for use in paediatric patients, according to the TGA PI. The FDA product label communicates an apparently lesser strength of warning: use of sildenafil, particularly chronic use, is not recommended in children (namely there may be situations in which the benefit-risk profile of sildenafil may be acceptable in individual children; for example, when other treatment options are limited and sildenafil can be used with close monitoring). The EMA SmPC states that sildenafil is indicated for the treatment of children aged 1-17 years of age with PAH, but only at a recommended low dose. The international guidelines do not reach consensus regarding the use of sildenafil in paediatric PAH patients.

Stakeholder views

- Decisions regarding combination therapy for WHO FC II patients should be evidence based.
- Stakeholders note the shift to reporting improvements in long term outcomes rather than short term functional changes.
- Composite end points to measure PAH disease progression should include morbidity and mortality measures.
- Stakeholders note there are few RCTs assessing the comparative efficacy and safety of PAH treatments, but provide available evidence for ambrisentan and epoprostenol that is yet to be considered by PBAC, with inclusion of studies pertaining to combination use and use in the FC II patient population.

Consumer views

- Consumers advised they tended to be using various double and triple combinations of endothelin receptor antagonists with PDE-5 inhibitors and prostanoids.

- Some consumers participated in drug trials, including for bardoxolone methyl (Catalyst trial) and oral trepostinil (prostacyclin analogue).
- There were reports of patients in the Pulmonary Hypertension Association Australia using selexipag.
- Consumers advised that they usually stay on the same medicines and add a further medicine to address worsening symptoms.
- Consumers swapped medicines to alleviate side-effects or because they proved ineffective.
- Consumers pointed out that continuous intravenous administration of epoprostenol, while effective, leads to considerable inconvenience and additional cost for accessories and dressings. In addition, there is a risk of catheter-related infection.
- Some consumers reported preferring the nebulised prostanoids which although had more frequent dosing, were less invasive.
- Generally, consumers found that PAH medicines did not impact on other medicines.

Key findings for ToR 5: Cost-effectiveness

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.

Key findings

- 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.
- 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.
- 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 [redacted], and there was no evidence found to support monotherapy use of prostanoids in patients presenting in WHO FC I or II.
- 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 potentially underpowered to report significant differences between treatment arms.
- Several trials [redacted], HAN 2017, COMBI, [redacted] measured change in quality of life in patients (FC II-IV) treated with combinations of: [redacted]; ERA and prostanoids; and [redacted]. All trials reported significant

improvements in quality of life in patients treated with combination therapy compared to monotherapy.

- There was no evidence identified in the systematic review of PBS listed PAH medicines that reported on the effectiveness of triple combination therapy compared to dual combination therapy.
- PBAC has not received a submission requesting subsidised access to PAH specific medicines for patients presenting in WHO FC II.
- The PBAC has considered a submission for selexipag in combination with an ERA and/or PDE-5 inhibitor. PBAC has rejected this submission on two occasions due to high and uncertain cost effectiveness in the requested dual and triple combinations.
- 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.
- 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 result in an additional net cost to the PBS.

PAH Review Options

The Reference Group has considered the evidence review and the stakeholder input and proposes the following options for PBAC to consider. DUSC and ESC has also provided advice on the following review options.

The Reference Group noted that any alteration to the restrictions surrounding the PBS listing of PAH targeted medicines would need to consider the financial impact on the PBS.

PBS options

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.

Current TGA registration/PBS restrictions for PAH medicines in WHO FC II

The following PBS subsidised PAH medicines include: ERAs (macitentan/ambrisentan/bosentan), PDE-5 inhibitors (sildenafil/tadalafil) and sGC stimulators (riociguat). All are TGA registered for use in WHO Functional Class II PAH, however they are not PBS subsidised for use in WHO FC II. The clinical criteria from the PBS restrictions for these medicines referencing WHO Functional Class reads:

- *Patient must have WHO Functional Class III idiopathic pulmonary arterial hypertension (iPAH) or anorexigen-induced PAH or hereditable PAH; OR*

- *Patient must have WHO Functional Class III pulmonary arterial hypertension secondary to connective tissue disease*

Issues for consideration

- The current PBS restrictions do not align with clinical guidelines, limiting the use of PBS subsidised PAH medicines to patients in WHO FC III-IV at the time they initiate treatment. The 2015 ERS/ERC guidelines and the CHEST guideline both recommend monotherapy for patients in WHO FC II with oral medicines (PDE-5 inhibitors, ERAs and sGC stimulators).
- These clinical guidelines consider an assessment of a patient's risk of disease deterioration or prognosis as key to the determination of initial pharmacotherapy. However, PBS restrictions, TGA indications and trial populations are silent on risk. Patients in WHO FC II PAH may be considered to be at low or intermediate risk and ERS/ERC clinical guidelines support initial monotherapy for low risk treatment naïve patients.
- There is no single set of criteria universally recommended to assess PAH risk of disease deterioration.
- The systematic review conducted in TOR 4 identified the following evidence to support the use of PAH medicines in patients presenting in WHO FC I or II:
    - Four RCTs compared ERAs to placebo and all reported ERAs to significantly reduce clinical worsening. Two trials reported improvement in WHO FC following treatment, and two of three trials reported significant improvements in 6MWD. Two trials found no significant difference in all-cause mortality when treated with bosentan or macitentan compared to placebo, however these trials may not have been powered to detect a mortality difference.
    - Three trials and two cohort studies compared PDE-5 inhibitor monotherapy to placebo in WHO FC II and all studies were assessed as low quality. There were no statistically significant improvements in WHO FC or mortality. Two studies reported improvements in 6MWD, and for one study this difference was clinically significant.
    - One RCT compared the use of sGC stimulator medication to placebo in patients with WHO FC I/II PAH. [redacted]
- There was limited evidence available on the comparative safety of monotherapy with PAH medicines versus placebo for WHO FC I or II.

- Option 1 would increase the number of people eligible for PBS-listed PAH medicines, thereby impacting the cost-effectiveness that was originally assessed by the PBAC and the total cost to the PBS.
- To date, the PBAC has not had the opportunity to consider a submission from any industry sponsor to consider the effectiveness and cost-effectiveness of PAH targeted medicines in WHO FC II patients.
- According to the registry data approximately 20% of patients were classified as having WHO FC II symptoms at time of diagnosis. The majority of patients presented in WHO FC III.

Stakeholder views

- There is a demand from patients and prescribers for access to PBS subsidised PAH medicines to treat WHO FC II PAH.

Reference Group views

- The Reference Group supported Option 1. The Reference Group was not supportive of the suggestion to assess cost-effectiveness in this population. The modelling for this disease has been highly uncertain in the past and is unlikely to be significantly different for patients presenting in WHO FC II.
- There is similar evidence of benefit in WHO FCII and FCIII from the same trials (but different sub-groups) for ERAs (EARLY, ARIES-1, ARIES-2, SERAPHIN), PDE-5 inhibitors (PHIRST, SUPER-1) and sGC stimulators (PATENT-1). However, there was little trial evidence to assess the comparative safety of PAH medicines in FCII. Despite this, the Reference Group considered the safety profile in FCII would be similar to patients treated in FC III/IV. In addition, the close monitoring of these patients in clinical practice would ensure that any adverse events are identified and managed appropriately.

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.

Current TGA registration/PBS restrictions for PAH medicines in combination in WHO FC II

The following targeted PAH medicines are TGA approved for add-on or combination therapy:

- ambrisentan plus tadalafil
- macitentan plus PDE-5 or iloprost
- riociguat plus ERA or iloprost.

The current PBS restrictions do not allow for subsidised use of any targeted PAH medicines in WHO FC II PAH.

Issues for Consideration (In addition to Option 3)

- AMBITION was the only trial reporting on the effectiveness of PDE-5 and ERA in initial combination therapy. Outcomes of a sub-group analysis by WHO FC II support combination therapy over monotherapy in regard to clinical failure.
- There were no statistically significant differences in the effectiveness of treatment for patients receiving initial combination therapy versus monotherapy and patients receiving sequential combination therapy versus monotherapy.
- Use of initial combination therapies in general may be contrary to Quality use of Medicine principles, whereby response to a single medicine should be confirmed prior to initiating a second medicine. According to current PBS restrictions if there is no response (i.e. stability or improvement of disease) to the first PAH therapy, the medicine should be ceased.
- To date, the PBAC has not had the opportunity to consider an application from any industry sponsor to assess the cost-effectiveness of the treatment of patients with PAH presenting in WHO FC II with two targeted PAH medicines in either initial or sequential combinations.

Stakeholder views

Consumers suggested that earlier treatment and combination therapy led to better health outcomes and questioned why treatment is not available for FC II patients whose health is only going to deteriorate.

Reference Group views

- The Reference Group considered that Option 3 should be considered before Option 2.
- As for Option 3, the Reference Group supported initial sequential combination therapy in WHO FC II and considered that combination therapy in WHO FC II should be at clinician's discretion around risk of deterioration.

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.

Specific treatment options could include any or all of the following:

- dual combination therapy for patients in FC III-IV (initial and/or sequential)
- dual combination therapy for patients in FC IV (initial and/or sequential)

- triple combination therapy for patient in FC III- IV (initial and/or sequential)
- triple combination therapy for patient in FC IV alone (initial and/or sequential).

Current TGA registration/PBS restrictions for PAH medicines in combination in WHO FC III and IV

The following medicines are TGA registered for use in dual therapy in WHO FC III and IV:

- ambrisentan in combination with tadalafil
- macitentan in combination with a PDE-5 inhibitor or inhaled prostanoids
- riociguat in combination with ERAs or inhaled or subcutaneous prostanoids
- selexipag (not PBS listed) in combination with an ERA and/or a PDE-5inhibitor.

Selexipag is TGA indicated for use in triple therapy with an ERA and/or a PDE-5 inhibitor for patients presenting in WHO FC III and IV.

Issues for Consideration

- The 2015 ERS/ESC guidelines and the CHEST guideline support combination therapy for patients with moderate risk and suggest the overall treatment goal is to achieve a low risk status which is usually associated with good exercise capacity, good quality of life, good RV function and a low mortality risk (WHO FC II). Patients who are stabilised on one PAH medicine or those who improve slightly, can still receive additional PAH medicines if treatment goals are not met.
- The 2015 ERS/ESC guidelines and the CHEST guideline concur that the standard of care for patients WHO FC II-IV with inadequate clinical response to monotherapy is to continue on the current therapy and add a further agent from a different class (up to a maximum of 3 PAH medicines, combinations of PDE-5 inhibitors or sGC stimulators with ERAs and prostanoids are recommended).
- The 2015 ERS/ESC guidelines and the CHEST guideline recommend initial combination therapy for patients presenting with WHO FC III and WHO FC IV assessed with high risk factors.
- Use of initial combination therapies in general is contrary to Quality Use of Medicine principles in Australia, whereby response to a single medicine should be confirmed prior to initiating a second medicine. According to current PBS restrictions if there is no response (i.e. stability or improvement of disease) to the first PAH therapy, the medicine should be ceased.
- According to the literature review in TOR 4, the majority of the available clinical trial evidence to support combination therapy with PAH medicines is in the whole PAH population and not presented according to WHO FC III/IV. The exception was the four

trials that assessed the benefit of adding ERA to a prostanoid or vice versa, that were all conducted in predominantly patients in WHO FC III or IV.

  - In most dual combination PAH therapy trials there was some evidence to suggest benefit from adding a second PAH medicines compared to being treated with monotherapy, noting much of this evidence relied on sub-group analyses for WHO FC III/IV or the whole PAH population.

- Overall in terms of safety, combination therapy could be non-inferior to monotherapy, noting some uncertainty and also paucity of data.
- There is a possible safety concern for serious adverse events (AEs) in the subgroup of patients with PAH-CTD treated with a PDE-5 inhibitor in addition to an ERA.
- 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.

[redacted]

- There were no trials or larger observational studies found that included current PBS PAH medicines that compared triple combination therapy with dual combination therapy in any patients with PAH.

- Registry data identifies that currently about 40% of patients receive dual combination therapy and 10% triple combination therapy.

- The PBAC has considered two submissions for combination therapy; selexipag in combination with and ERA and or PDE-5 (Selexipag Public Summary Documents, 2016 and 2017). Both 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.

- PBAC has in the past noted that cost-effectiveness in the setting of monotherapy cannot necessarily be generalised to cost-effectiveness in the setting of combination therapy (Selexipag Public Summary Document, March 2016).

<u>Stakeholder views</u>

- The majority of consumers and prescribers are supportive of subsidised access to combination PAH therapies.
- Consumers experience anxiety about the continued availability and financial burden of

PAH medicines, especially at the time when particular pharmaceutical access programs or drug trials end.

Reference Group views

- The Reference Group were supportive of subsidising initial sequential combination therapy for patients in WHO FC III and IV and advised that clinicians introduce medicines one at a time, consistent with QUM and the medicines' Product Information. PAH medicines are initiated separately to ensure adverse side effects, if they occur, can be attributed to the correct medicine. However the second PAH medicines is added after a month or six weeks without the requirement for the patient's condition to deteriorate further or have repeated right heart catheterisation.
- The Reference Group noted the DUSC comments and advised that clinicians have tried switching of PAH medicines in the past and experienced poor outcomes for patients. Therefore, clinical trials that compared switching medicines to combination therapy would not be forthcoming.
- Once the PBAC has made recommendations for the Review Options, the current PBS restrictions would need to be redrafted and presented again to the Reference Group and the PBAC. The Reference Group members offered their assistance in this process.
- The Reference Group considered that a reapplication to the PBS would be appropriate for patients who failed therapy in WHO FC II and progressed to WHO FC III, including a full clinical assessment. The Reference Group considered this should not restrict any medicine (group) from being prescribed again for patients in WHO FC III.
- The Reference Group considered that prescribers should be able to determine the particular combination of medicine suitable for their patients, instead of specifying medicine combinations in the PBS restrictions.

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

(1) including a NOTE in the PBS restrictions identifying the need for a positive vasoreactivity test prior to trialling vasodilator (calcium channel blocker) treatment; and

(2) removing the requirement for a trial of vasodilator (calcium channel blockers) for PAH-CTD.

Current PBS restriction criterion

To access PAH medicines, current PBS restrictions require evidence of prior vasodilator treatment (CCBs) in patients as follows:

...Patient must have WHO Functional Class III idiopathic, hereditable, drug-induced PAH or PAH secondary to CTD PAH

AND

Patient must have a mean right atrial pressure of 8 mmHg or less as measured by right heart catheterisation (RHC); …

….Patient must have failed to respond to 6 or more weeks of appropriate vasodilator treatment unless intolerance or a contraindication to such treatment exists, Details of prior vasodilator treatment, including the dose and duration of treatment, must be provided at the time of application. Where the patient has an adverse event to a vasodilator or where vasodilator treatment is contraindicated, details of the nature of the adverse event or contraindication according to the Therapeutic Goods Administration (TGA) approved Product Information must also be provided with the application.

Issues for consideration

- Clinical guidelines identify that vasodilator treatment with high doses of CCBs leads to a favourable response in only a small number of patients with PAH in WHO FC II-III.
- Clinical guidelines only recommend vasoreactivity testing in patients with IPAH, HPAH and PAH to detect patients who can be treated with high doses of a CCB. However, unlike PBS restrictions, guidelines do not recommend a trial of CCBs for treatment of PAH - CTD.
- Clinical guidelines recommend that patients who have not undergone a vasoreactivity study during right heart catherisation (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).

Stakeholder views

Stakeholders suggest a review of the current PBS restriction criteria including the requirement for patients to trial 6 weeks of vasodilator therapy with CCBs.

Reference Group views

- The Reference Group noted that CCBs (typically high dose) are now reserved for the following patients:
    - NYHA Functional Class (FC) II and III patients without right ventricular failure; and
    - idiopathic, anorexigen induced or hereditable PAH; and
    - who have a positive acute vasodilator response (now well defined by Sitbon et al 2005).
- Approximately 5% of these patients overall (50% of the acute responders) have an enduring (years and even decades) response often returning to NYHA FC I or II with normal or near normal haemodynamics. In the soon to be published Nice 2018 Classification this distinct but uncommon phenotype will have a specific designation

within the overall classification. As over 95% of Group 1 (PAH) patients will derive no benefit, suffer harm and/or have effective therapy delayed, the routine use of high dose calcium channel blocker as pulmonary vasodilator therapy is strongly discouraged.

- The Reference Group considered that the present PBS requirement that all PAH patient need to be treated with a CCB for eight weeks (if mean right atrial pressure <8mmHg) is not supported by evidence and should be removed.

Additional comments on PBS Restriction

- The Reference Group considered a right heart catherisation (RHC) essential to the diagnosis of PAH. The Reference Group considered that evidence of consultation with a second expert clinician should be provided by the treating clinician seeking exemption from a RHC for a patient. This requirement could be stipulated in the restriction and evidence of such consultation provided to Services Australia when seeking authorisation to prescribe PAH medicines without RHC results.

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

Current TGA/PBS restriction

- The current PBS restrictions restrict subsidy of PAH medicines by PAH disease subtype, WHO FC and line of treatment.
- There is no PBS subsidised treatment with PAH medicines for the following three PAH subtypes: PAH associated with HIV infection; portal hypertension; and schistosomiasis.
- There are examples of other small PAH sub-groups for whom PAH medicines are not TGA indicated but PBS subsidised, e.g. bosentan, macitentan, ambrisentan, epoprostenol and riociguat for anorexigen-induced PAH.

Alignment of ARTG indications with PBS listings (not accounting for WHO FC)

Treatment	IPAH	HPAH	PAH-CTD	PAH-CHD	Drug induced PAH	Anorexigen induced PAH
Macitentan	☑✚	☑✚	☑✚	☑✚	✖⭘	✖✚
Ambrisentan	☑✚	✖✚	☑✚	✖⭘	✖⭘	✖✚
Bosentan	☑✚	☑✚	☑✚	☑✚	✖⭘	✖✚
Sildenafil[a]	☑✚	☑✚	☑✚	☑⭘	☑⭘	☑✚
Tadalafil[a]	☑✚	☑✚	☑✚	☑⭘	☑⭘	☑✚
Riociguat	☑✚	☑✚	☑✚	☑✚	✖⭘	✖✚
Iloprost	☑✚	✖✚	☑✚	✖⭘	☑✚	☑✚
Epoprostenol	☑✚	☑✚	☑✚	✖⭘	✖⭘	✖✚

☑ = ARTG registered indication; ✖ = not an ARTG registered indication; ✚ = PBS indication; ⭘ = not PBS listed for this indication

a: Sildenafil and tadalafil are indicated for PAH in general (in grey) – efficacy shown only in IPAH and PAH-CTD (in black)

- The PBS subsidises only one PAH medicine for drug-induced PAH (iloprost).
- 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.

Issues for consideration

- The 2015 ESC/ERS Guidelines recommend using all PAH medicines for all of the WHO Group I PAH subtypes irrespective of the subtype or line of treatment.

Stakeholder comments

- Stakeholders strongly believe that PAH medicines should not be reimbursed based on the cause of PAH or FC, and suggests PAH medicines should be available to all PAH patients regardless of what type, FC or severity of PAH disease they have.

Reference Group views

The Reference Group supported extending the PBS restrictions to include the remaining WHO Group I PAH subtypes. These PAH subtypes include very small populations and therefore it is unlikely that clinical data would be forthcoming to support the effectiveness of PAH medicines.

The Reference Group considered that the PBS restriction should not detail the type of PAH as treatment recommendations in the 2015 ESC ERS guidelines apply to all WHO Group I type patients.

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

Current restriction

To access PBS subsidised PAH medicines:

- *…Patient must have been assessed by a physician at a designated hospital…*

- The Department (TAAD, PHIP Supply Program Section) is managing the *Highly Specialised Drugs (HSD) Programme*, which includes access to PAH medicines through PAH Designated Prescribing Centres. This area assesses applications for hospitals to become a PAH Designated Prescribing Centre based on guidelines.

Issues for Consideration

- Current Australian guidelines and criteria for PAH designated prescribing centres do not specify minimum patient numbers. This may be because the Australian population is spread over a large and diverse country.

- The 2015 ESC/ERS Guidelines make specific recommendations on the facilities and skills required for a referral centre. In particular, the ideal number of patients seen by an adult centre each year is recommended to be no fewer than 200, of which at least half have a final diagnosis of PAH. In countries with a population of over 10 million, adult centres should ideally expand to accommodate 300 patients annually.

- The 2015 ESC/ERS Guidelines also recommend that a referral centre, as a minimum, should follow at least 50 patients with PAH or chronic thromboembolic pulmonary hypertension (CTEPH) and receive at least two new referrals per month with documented PAH or CTEPH.

- 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, the number of patients treated with PBS subsidised PAH medicines in 2016 was about 2,400. Therefore on average, each centre would see about 40 patients with PAH annually.

Stakeholder views

- Stakeholders suggested the review should explore what constitutes a designated Pulmonary Hypertension (PH) centre and collaboration between centres to improve equity of access to PAH medicines.

Reference Group views

- The Reference Group supported a review of the PAH Designated Prescribing Centres.

There is concern about the high number of centres, therefore there may be a case for tightening the criteria for treatment centres due to the specific expertise required to treat PAH.

- The Reference Group noted the importance of patient safety and the difficulty of ensuring this while maintaining equity of access in regard to treatment for patients in rural and remote locations. The Reference Group suggested a “hub-and-spoke” model may be the most effective approach.

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