Pharmaceutical Benefits Scheme

Post-market Review of

Medicines to treat Pulmonary Arterial Hypertension

Background and ToR 1

Final Report

November 2018

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Abbreviations

Abbreviation	Full Name / Wording
6MWT	6 minute walk test
6MWD	Six minute walk distance
ACC	American College of Cardiology
ARTG	Australian Register of Therapeutic Goods
ATC	Anatomical Therapeutic Chemical (code)
AusPAR	Australian public assessment report
BNP	B-type natriuretic peptide
CADTH	Canadian Agency for Drugs and Technologies in Health
CATAG	Council of Australian Therapeutics Advisory Groups
CCB	Calcium channel blocker
CI	Cardiac index
CO	Cardiac output
CPET	Cardiopulmonary exercise testing
CTEPH	Chronic thromboembolic pulmonary hypertension
DPMQ	Dispensed price for maximum quantity
DLco	Diffusing capacity of lung for carbon monoxide
DTC	Hospital drugs and therapeutics committee
DUSC	Drug Utilisation Sub Committee
EMA	European Medicines Agency
EPAR	European public assessment report
ERA	Endothelin receptor antagonist
ERS	European Respiratory Society
ESC	European Society of Cardiology
FC	Functional class
FDA	United States Food and Drug Administration
GP	General practitioner
HPAH	Heritable pulmonary arterial hypertension
ICER	Incremental cost-effectiveness ratio
IPAH	Idiopathic pulmonary arterial hypertension
IV	Intravenous

LVF	Left ventricular function
mPAP	Mean pulmonary arterial pressure
mRAP	Mean right atrial pressure
MRI	Magnetic resonance imaging
MTD	Maximum tolerable dose
NHS	National Health Service (United Kingdom)
NICE	National Institute for Health and Care Excellence
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
PAH	Pulmonary arterial hypertension
PAH-CHD	PAH associated with congenital heart disease
PAH-CTD	PAH associated with connective tissue disease
PAH-HIV	PAH associated with human immunodeficiency virus
PAH-PH	PAH associated with portal hypertension
PASP	Pulmonary artery systolic pressure
PAP	Pulmonary artery pressure
PAWP	Pulmonary artery wedge pressure
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PCWP	Pulmonary capillary wedge pressure
PDE-5 inhibitor	Phosphodiesterase type 5 inhibitor
PH	Pulmonary hypertension
PHAA	Pulmonary Hypertension Association Australia
PHSANZ	Pulmonary Hypertension Society of Australia and New Zealand
PI	Product information
PMR	Post-market Review
PPH	Primary pulmonary hypertension
PPHN	Persistent pulmonary hypertension of the newborn
PSD	Public summary document
PVR	Pulmonary vascular resistance
RA	Right atrial/atrium
RAP	Right atrial pressure

REVEAL registry	Registry to Evaluate Early And Long-term PAH Disease Management
RHC	Right heart catheterisation
RR	Relative risk
RVEF	Right ventricular ejection fraction
RVSP	Right ventricular systolic pressure
SC	Subcutaneous
sGC stimulator	Soluble guanylate cyclase stimulator
SmPC	Summary of product characteristics (European)
SoC	Standard of care
SvO_2	Mixed venous oxygen saturation
TGA	Therapeutic Goods Administration
ToR	Term(s) of Reference
TRV	Tricuspid regurgitation velocity
TAPSE	Tricuspid annular plane systolic excursion
TSANZ	Thoracic Society of Australia and New Zealand
US/USA	United States/United States of America
VE/VCO_2	Minute ventilation/carbon dioxide production
VO_2	Oxygen uptake
WHO	World Health Organization

Report Structure

This Report is presented in six separate parts, as briefly outlined below. The Report has been structured in this way to address the Terms of Reference (ToR) of the Review.

Background	Provides the context and objectives of the Review, a brief description of PAH and its prevalence in Australia, the listing history for PBS listed PAH medicines and their prescribing restrictions, and the ToR for the review.
Section 1	ToR 1: Reviews recent clinical guidelines for the management of PAH and compare this to the Pharmaceutical Benefits Scheme (PBS) restrictions and Therapeutic Goods Administration (TGA) indications for the use of PAH medicines.
Section 2	ToR 2: Reviews 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.
Section 3	ToR 3: Reviews 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 Pharmaceutical Benefits Advisory Committee (PBAC).
Section 4	ToR 4: Collates and evaluates evidence on the comparative effectiveness of PAH medicines, including combination use and use in the World Health Organization (WHO) functional class (FC) II patient populations.
Section 5	ToR 5: Summarises the evidence considered in ToR 1-4 and presents options for the PBAC to determine if a cost-effectiveness review of existing PBS listings for PAH medicines is required, including for treatment of WHO FC II and combination treatment in FC III and FC IV patients.

Background

B.1 Post-market monitoring

The Post-Market Review (PMR) program is a systematic approach to monitoring medicines subsidised by the PBS. PMRs were initiated under the 2011-12 Budget measure 'Improving sustainability of the PBS through enhanced post-market surveillance'.

PMRs are established under the quality use of medicines objective of the National Medicines Policy framework; promoting the safe and effective use of medicines, with the aim to improve health outcomes for all Australians.

The PMR program contributes to the following:

- Improved patient safety through better understanding of adverse events and medicine-related harms.
- Ensuring the ongoing viability of the PBS through targeted medicines usage and avoiding preventable wastage or inappropriate prescribing.
- A better understanding of medicines utilisation, to review intended clinical benefit and inform medicines evaluation processes.
- Ongoing cost-effectiveness, including through better management of clinical and economic uncertainty.
- Overall improvements to the quality use of medicines and education for patients and prescribers.

Post-market reviews can be initiated when concerns related to the quality use of a medicine, cost-effectiveness, clinical effectiveness, higher than predicted utilisation and/or international differences are raised. A full post-market review will only proceed following PBAC agreement and Ministerial approval.

B.2 Context of the Review

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 March 2014, when considering the submission for macitentan, the PBAC noted that "the PBS restrictions for the PAH agents have not been updated for some time and note that terminology and clinical guidelines have since changed". The PBAC recommended that the restrictions for the

PAH medicines be reviewed to reflect current clinical guidelines on the proviso that the resultant change does not create any additional expenditure for the Commonwealth.

In February 2015 the Drug Utilisation Sub Committee (DUSC) of the PBAC conducted a PAH medicines utilisation analysis. The DUSC considered that the PBS restrictions for PAH medicines were not consistent with current treatment guidelines in that:

- It required failure to respond to 6 or more weeks of appropriate vasodilator treatment for WHO FC III patients with a mean right atrial pressure of 8 mmHg or less;
- It did not allow treatment of WHO FC II patients; and
- It did not allow combination therapy.

These issues were also noted in a submission from the sponsors of bosentan, epoprostenol and macitentan that requested amending the current 'continuing treatment' restriction of PAH medicines. At the July 2015 meeting, the PBAC considered that there were a number of issues around PAH medicines including:

- A lack of evidence to support the cost-effectiveness of combined therapy with two or more PAH medicines;
- A lack of evidence to support the cost-effectiveness of PAH medicines for use in WHO FC II patients; and
- Difficulty in identifying the population of patients who would derive the most benefit from these medicines (bosentan, epoprostenol and macitentan, Public Summary Document (PSD), July 2015 PBAC meeting).

The PBAC recommended that a PMR should be undertaken of medicines for the treatment of PAH, including the existing listed medicines for FC III and IV patients, and a review of the clinical place of these therapies as recommended in international guidelines.

B.3 Review Process

B.3.1 Purpose of the Review

The purpose of the PMR of PAH Medicines is to review 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

B.3.2 Review Reference Group

A Reference Group is formed to assist in the review of the evidence and information for each of the Review's terms of reference, and to ensure that the perspectives of stakeholders are considered in its preparation of the final report to the PBAC. The Reference Group may provide the PBAC with options to address key findings. Members of the Reference Group are appointed as either individuals or organisational representatives. Representation includes clinical experts,

health economists and representatives of relevant health professional and consumer organisations. The Reference Group for the Review was appointed on 9 May 2017.

B.3.3 Review Terms of Reference

The Review's draft Terms of Reference (ToR) were open to public consultation between 2 May and 16 May 2016. Fourteen submissions on the draft ToR were received, including seven from individuals, two from industry; and five from health professional peak bodies, consumer groups and health professionals. Public submissions were published on the PAH Review Public Consultation website, except where requested otherwise.

The PBAC considered the draft ToR and comments from stakeholders in August 2016. In December 2016, the Minister for Health approved the final Review ToR. Research questions relating to the ToR were developed to guide the technical review. The final ToR and research questions, approved by the Reference Group Chair, are listed below.

Term of Reference 1

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

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?

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

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

Term of Reference 2

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

Q1. What is the prevalence and incidence of PBS-listed PAH medicine use?

Q2. If and how has the prevalence and incidence of PAH medicine use changed over time during July 2013 to December 2016?

Q3. What is the length of time on treatment according to individual PAH medicines, as well as overall length of time on treatment with any PBS-listed PAH medicine?

Q4. Based on co-prescribed PBS-listed PAH medicines, is there evidence of combination treatment with two or more individual PAH medicines among prevalent and incident users?

Q5. What is the prevalence of switching between PAH medicines taking into account length of treatment?

Q6. What is the extent of combination treatment in data collected in the PHSANZ registry and the Australian Scleroderma Cohort Study?

Term of Reference 3

ToR 3: Review the clinical outcomes that are most important or clinically relevant to patients with PAH, and the extent to which these outcomes are included in the evidence previously considered by PBAC.

Through a consumer forum:

Q1. How have PAH medicines made a difference to your symptoms and daily life?

Q2. What changes in health do you value the most?

Q3. Are important changes in your health reflected in clinical measures such as the six-minute walk distance (6MWD) or rates of hospitalisation?

Q4. Are there side effects from PAH medicines that impact negatively on your daily activities and quality of life?

Q5. Are there any other clinical outcomes that should be highlighted to the PBAC when they consider the effectiveness of PAH medicines?

Term of Reference 4

ToR 4: Collate and evaluate evidence on the comparative effectiveness of PAH medicines, including combination use and use in the WHO FC II patient populations.

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?

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?

Q3. What is the effectiveness and safety of dual combination therapy involving any combination of an endothelin receptor antagonist (ERA), a phosphodiesterase type 5 (PDE-5) inhibitor, a prostanoid, or a soluble guanylate cyclase (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?

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?

Term of Reference 5

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.

B.3.4 Public submissions

Public submissions to the Review were open for seven weeks from 13 February to 27 March 2017. This process provided stakeholders with an opportunity to identify relevant issues, evidence or data that may inform the Review. Seven submissions were received from health professional peak bodies, pharmaceutical companies and a health professional. Public submissions were published on the PAH Review Public Consultation website unless requested otherwise.

B.3.5 Consumer Forum

A Consumer Forum for the Post-market Review of PAH Medicines was held in Sydney on 14 October 2017, as part of the Pulmonary Hypertension Association Australia (PHAA) Members & Carers Day. Attendees were provided with a background discussion paper prior to the meeting. The discussion paper included information on the Review ToR, and identified key issues and questions for discussion. A brief overview of the review process was provided during the Forum. Focus questions were posed to prompt discussion and there was also an opportunity for open discussion not directly related to the focus questions. The Consumer Outcome Statement from the Forum is presented in ToR 3 Appendix 3A and is also available on the PAH Review website. Key findings from the Consumer Forum are presented under ToR 3, and where appropriate, summarised, under other ToR.

The Reference Group decided not to hold a stakeholder forum.

B.3.6 Public consultation on the draft Report

The draft PMR of PAH Report was made available for public comment on the PAH Review website between 21 May and 10 June 2018. Pharmaceutical sponsor companies were also provided with the opportunity to comment on the draft report prior to consideration by the DUSC and the Economic Sub-Committee of the PBAC, and again to comment on the sub-committees advice prior to PBAC consideration of the report in November 2018.

B.4 Pulmonary Arterial Hypertension in Australia

B.4.1 Description of the condition

PAH is a rare, progressive 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[1]. PAH medicines may help improve symptoms and slow the progress of pulmonary hypertension (PH).

B.4.2 Prevalence of PAH

There are no published nationwide data on the prevalence of PAH in Australia. In a community-based observational cohort study in Western Australia (population of 165,450), Strange et al (2012)[2] estimated an indicative prevalence of 151 cases per million population for PAH. This equates to over 3,700 Australians (based on the Australian population as at 30 June 2017). It was noted that the prevalence rate from the study by Strange et al (2012) was much higher than previous reports in other western countries. Peacock et al[3] reported a PAH prevalence rate of 15 to 52 cases per million population, using three sources, one from France and two from Scotland. Jansa et al[4] reported PAH prevalence estimates of between 15 and 26 cases per million adults based on data from Czech Republic, Scotland, France, Spain, Switzerland and the US.

Previous reports have assessed prevalence using patient referrals to specialist centres and thus probably underestimate the true prevalence of PAH within the community. In addition, the wide range in the reported prevalence of PAH is probably due to differences in the methods/criteria used to make a diagnosis and to differences in the selected patient populations.

No Australian data were available on the incidence of PAH. The incidence rate varied from 2.4 to 10.7 case per million population in other countries[3, 4].

The February 2015 DUSC Review of PAH medicines utilisation estimated the prevalent and incident patients receiving PAH treatment, using the Services Australia (formerly the Department of Human Services) Authority Approvals data. This included data on the total number of patients treated with a PAH medicine and the number of patients initiating a PAH medicine for the first time, as well as the total Australian population as at 30 June 2013. The estimated prevalence and incident rates of PAH treatment are 87.6 and 18.6 per million population, respectively. Based on these estimates, the Australian prevalent data reported by Strange et al (2012) (151 cases per million population) and the DUSC Review, it appears the PAH prevalence and incidence rates in Australia are higher than the rates reported in other countries.

Based on the PHSANZ Registry data on incident cases of primary PAH (including idiopathic, heritable and drug-induced PAH) diagnosed between 2012 and 2016[5], the 1-year and 3-year estimated survival rates were 96% and 77%, respectively. In comparison, the US Registry to

Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL) found 1-year and 3-year survival rates of 91% and 74%, respectively, for idiopathic/heritable PAH enrolled between 2006 and 2009[6]. In an older incident cohort of primary PAH patients diagnosed between 2002 and 2003 from the French Registry database, the survival was 86% at Year 1 and 55% at Year 3[7].

Survival differs between primary and secondary PAH aetiologies/subtypes (see Classification below). The REVEAL study reported that, compared with idiopathic/heritable PAH, the 3-year survival rate was higher for PAH associated with congenital heart disease (PAH-CHD) and PAH associated with human immunodeficiency virus infection (PAH-HIV) (81% and 75% vs 74%), but lower for PAH associated with connective tissue disease (PAH-CTD) and portopulmonary hypertension (57% and 52% vs 74%)[6].

In children, PAH usually presents as idiopathic PAH (IPAH), heritable PAH (HPAH) or PAH-CHD[8].

B.4.3 WHO classification and functional classes

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

B.4.3.1 WHO classification of pulmonary hypertension

The WHO classification of pulmonary hypertension (PH) is determined at the meetings of the World Symposium on Pulmonary Hypertension.

The current classification of PH and PAH from the 2013 Nice symposium is given in Table B.1[9]. PAH represents Group 1 within the PH classification system. PAH is further divided into four subtypes on the basis of aetiology. PH and PAH are not interchangeable terms though sometimes they are used to mean the same thing in the literature. The term Primary Pulmonary Hypertension was previously used for Group 1 conditions. Some subtypes previously in Group 1 have been moved to other groups within the classification (Persistent Pulmonary Hypertension of the Newborn, PPHN), and have not been considered in this review.

Table B.1 WHO classification of PH and Group 1 PAH disease subtypes

1. Pulmonary arterial hypertension 1.1 Idiopathic PAH 1.2 Heritable PAH 1.2.1 BMPR2 1.2.2 ALK-1, ENG, SMAD9, CAV1, KCNK3 1.2.3 Unknown 1.3 Drug and toxin induced 1.4 Associated with: 1.4.1 Connective tissue disease 1.4.2 HIV infection 1.4.3 Portal hypertension 1.4.4 Congenital heart diseases 1.4.5 Schistosomiasis **1′. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis** **1″. Persistent pulmonary hypertension of the newborn (PPHN)**
2. Pulmonary hypertension due to left heart disease 2.1 Left ventricular systolic dysfunction 2.2 Left ventricular diastolic dysfunction 2.3 Valvular disease 2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
3. Pulmonary hypertension due to lung diseases and/or hypoxia 3.1 Chronic obstructive pulmonary disease 3.2 Interstitial lung disease 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern 3.4 Sleep-disordered breathing 3.5 Alveolar hypoventilation disorders 3.6 Chronic exposure to high altitude 3.7 Developmental lung diseases
4. Chronic thromboembolic pulmonary hypertension (CTEPH)
5. Pulmonary hypertension with unclear multifactorial mechanisms 5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy 5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders 5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

Source: WHO Classification of PH[9]

4.3.2 WHO functional classes

The clinical severity of PAH is classified according to a system of functional classes originally developed for heart failure by the New York Heart Association (NYHA) and then modified by the WHO for patients with PH at the 1998 meeting of the World Symposium. The current criteria[8] are in Table B.2.

Table B.2 WHO functional classes for PAH

Class 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.
Class 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.
Class 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.
Class 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[8]

B.4.4 Description of the intervention

B.4.4.1 Pharmacological management of PAH

In the past, medicines such as anticoagulants (e.g. warfarin), vasodilators (e.g. calcium channel blockers), digoxin, diuretics and supportive care such as supplemental oxygen were prescribed as specific treatments for PAH. While still described as supportive treatment in PAH literature to manage PAH and associated symptoms, and unlike targeted PAH medicines, these medicines have broader uses and are not TGA approved/PBS-listed specifically for treatment of PAH.

Calcium channel blockers such as diltiazem, or dihydropyridine derivatives (mainly nifedipine) were in common use for PAH before targeted PAH medicines became available (see for example the 2004 PAH European guideline[10]) and continue to be indicated as vasodilators for a small sub-set of PAH patients.

B.4.4.2 Targeted PAH medicines

Targeted PAH medicines (PAH agents, PAH therapies) belong to four therapeutic classes based on the medicine's mode of action:

<u>Endothelin Receptor Antagonists</u>

Bosentan, macitentan and ambrisentan are endothelin receptor antagonists (ERAs). An ERA reverses the effect of endothelin, a substance in the walls of blood vessels that causes them to narrow. Bosentan was one of the first PAH-specific medicines on the market in both Australia and overseas, and also the first PAH medicine available as a tablet. Another ERA, sitaxentan (Thelin®), was withdrawn globally by Pfizer in 2010 due to reported cases of acute liver failure[11].

<u>Phosphodiesterase type 5 inhibitors</u>

Sildenafil and tadalafil are phosphodiesterase type 5 (PDE-5) inhibitors. A PDE-5 inhibitor works by opening the blood vessels in the lungs to allow blood to flow through more easily. The advent of PDE-5 inhibitors for PAH treatment introduced a second class of oral agents in addition to ERAs,

but with comparatively fewer toxicity issues. Sildenafil and tadalafil are marketed as brands specific for PAH (Revatio®and Adcirca®, respectively) to distinguish them from those registered for erectile dysfunction (Viagra® and Cialis®). The strengths and pack sizes are different for Revatio® and Adcirca® compared to Viagra®and Cialis®. The same separation of brands and indications also applies to the generic versions registered for each molecule. An injectable form of sildenafil is registered in Australia for use in PAH patients but is not PBS-listed.

Prostanoids

Iloprost and epoprostenol are prostanoids (or prostacyclin analogues). A prostanoid exerts its effects by promoting direct arterial vasodilation and inhibiting platelet aggregation. The prostanoids epoprostenol and iloprost are short-acting which necessitates continuous administration via infusion and frequent nebulisation respectively.

These features of delivery are considered inconvenient by prescribers and patients. There is reportedly limited use of epoprostenol and iloprost in Australia[12-14] and of prostacyclins available overseas[15]. Treprostinil was recommended for PBS listing by the PBAC in November 2005, but was never listed and was withdrawn from the Australian market in 2016.

Selexipag, which is currently not listed on the PBS, acts on the same pathway as the prostanoids but is a non-prostanoid prostacyclin receptor agonist. The PBAC rejected submissions for PBS listing of selexipag in March 2016 and in March 2017.

Guanylate cyclase stimulator

Riociguat is a soluble guanylate cyclase (sGC) stimulator. A sGC stimulator increases the activity of guanylate cyclase, which interacts with nitric oxide in the lungs and other parts of the body and leads to an increased production of cyclic guanosine monophosphate. This helps to relax the pulmonary arteries and lower the pressure within the arteries. Riociguat is the most recently listed medicine for PAH on the PBS.

Calcium channel blockers

In addition to the four classes of targeted PAH medicines above, calcium channel blockers (CCBs) are effective in a small number of patients with IPAH, HPAH and drug-induced PAH who demonstrate a response to acute vasodilator testing.

B.4.4.3 PAH medicines registered for use in Australia

The PAH medicines currently approved for use in Australia are listed in Table B.3 (grouped by therapeutic class). With the exception of the prostanoids (epoprostenol and iloprost), these medicines are oral dosage forms (tablets). Any reference to ‘oral PAH medicines’ in this report does not include the oral prostanoids available overseas.

Further details of registered brands, sponsors and Australian Register of Therapeutic Goods (ARTG) registration dates for PAH medicines are listed in Appendix 1. (Table B.7). The TGA registered indications extracted from the Product Information (PI) for PAH medicines are presented in Table 1.14.

In addition to PBS listed PAH medicines, information is included where relevant for treprostinil (previously recommended by the PBAC but never listed) and selexipag (recently considered by PBAC but twice rejected).

Table B.3 PAH medicines TGA registered in Australia

Non-proprietary Name	Therapeutic class	ATC	Dosage Forms	PI Recommended Dosage	Route of admin.	ARTG Date[a]
Endothelin receptor antagonists						
Bosentan	ERA	C02KX01	62.5, 125 mg tablet	Initial: 62.5 mg twice daily for 4 weeks Maintenance: 125 mg twice daily (dose adjustment for paediatric use)	Oral	20 November 2002
Sitaxentan	*ERA*	*C02KX03*	*100 mg tablet*	*No longer registered* *(100 mg per day – from sitaxentan PSD)*	*Oral*	*15 March 2007 Withdrawn 10 December 2010*
Ambrisentan	ERA	C02KX02	5, 10 mg tablet	5 mg once daily Additional benefit may be obtained by increasing the dose to 10 mg In combination with tadalafil, the starting dose of 5 mg should be titrated to 10 mg once daily	Oral	24 November 2008
Macitentan	ERA	C02KX04	10 mg tablet	10 mg once daily	Oral	5 February 2014
Prostanoids						
Epoprostenol	Prostanoid	B01AC09	500 µg, 1.5 mg; powder for injection vial	Starting dose 2 ng/kg/min infusion, increase by 2 ng/kg/min until MTD reached. Long-term infusion at MTD less 4 ng/kg/min, increasing based on tolerability / clinical need	I.V. continuous infusion via central line indwelling catheter	15 February 2002
Iloprost	Prostanoid	B01AC11	20 µg/2 mL inhalation solution	Initial 2.5 µg inhaled dose, increased to 5. µg 6-9 inhaled doses per day	Inhalation (nebulised)	21 January 2004
Treprostinil	*Prostanoid*	*B01AC21*	*1.0, 2.5, 5.0, 10.0 mg/mL in 20mL vial*	*No longer registered*	*I.V. or S.C continuous infusion via indwelling catheter*	*31 May 2004*
Phosphodiesterase type 5 inhibitors						
Sildenafil	PDE-5 inhibitor	G04BE03	20 mg tablet 10 mg/12.5 mL or 40 mg/50 mL vial	20 mg *tid*	Oral I.V. injection	14 August 2006
Tadalafil	PDE-5 inhibitor	G04BE08	20 mg tablet	40 mg (2 x 20 mg) taken once daily	Oral	10 August 2011

Non-proprietary Name	Therapeutic class	ATC	Dosage Forms	PI Recommended Dosage	Route of admin.	ARTG Date[a]
Soluble guanylate cyclase stimulator						
Riociguat	sGC stimulator	C02KX05	0.5, 1.0, 1.5, 2.0, 2.5 mg tablet	Starting dose 1.0 mg *tid* for 2 weeks Increase by 0.5 mg increments to a maximum of 2.5 mg *tid* maintenance dose	Oral	14 April 2014
Non-prostanoid prostacyclin receptor agonist						
Selexipag	*Non-prostanoid prostacyclin receptor agonist*	*B01AC27*	*200, 400, 600, 800, 1000, 1200, 1400, 1600 µg tablets*	*Starting dose 200 µg twice daily* *Titration in increments of 200 µg twice daily at weekly intervals to maximum 1600 µg twice daily*	*Oral*	*24 March 2016*

Abbreviations: ATC = Anatomical Therapeutic Chemical code; ARTG = Australian Register of Therapeutic Goods; IV = intravenous; MTD = Maximum Tolerable Dose; PI = Product Information; PSD = Public Summary Document; SC = subcutaneous; *tid* = three times daily

[a] Corresponding to date of first registration where there is more than one brand on the market

Source: Relevant product information documents and PBAC public summary documents

B.4.4.4 Reports of combination use of PAH medicines in Australia

The PBAC has previously acknowledged that the combination use of PAH medicines occurs in current clinical practice in Australia. The concurrent use of second and third PAH medicines (i.e. in addition to PBS subsidised monotherapy) is funded through sources outside the PBS. Submissions from the Council of Australian Therapeutic Advisory Groups (CATAG), the Thoracic Society of Australia and New Zealand (TSANZ) and PHSANZ to this PMR and the published literature[14,16,12,13,17] confirmed that sources of medicines include compassionate access through hospitals or the pharmaceutical industry schemes, pharmaceutical company sponsored clinical trials, self-funding and hospital funding.

The CATAG submission to the Review described survey responses sought from hospital drugs and therapeutic committees (DTCs) nationwide about the use and funding of PAH medicines over a two year period (December 2014 – December 2016). Survey responses indicated that hospital formulary listings provide for combination use in a number of cases, typically with either tadalafil or sildenafil in combination with ERAs. Where the formulary listing did not permit combination use, individual patient use exemptions were employed to allow access to combination PAH medicines.

CATAG commented that some managed access and compassionate use programs are managed through community pharmacies, outside the hospital system entirely and thus as a result, patient numbers managed through the hospitals were unexpectedly low.

B.4.5. Pulmonary Arterial Hypertension medicines on the PBS

B.4.5.1 PBS listing history

Currently, eight PAH medicines are subsidised through the PBS according to the specific subtypes of PAH, and to disease severity.

The first targeted PBS-listed medicine for PAH was bosentan in March 2004. Sitaxentan, iloprost, epoprostenol, sildenafil, ambrisentan and tadalafil were listed in the next five years, with macitentan and riociguat following in 2014 and 2017 respectively. Sitaxentan was de-listed in 2011 due to safety concerns.

The date of PBS listing of individual PAH medicines and the indications for PBS subsidy are shown in Table B.4. A summary of all PBAC considerations to date for PAH medicines (including recommendations and rejections) and information on the Dispensed Price for Maximum Quantity (DPMQ), authority types and treatment phases for PAH medicines are in Appendix 1.

Table B.4 Date of first PBS listing and PBS subsidised indication for PAH medicines

Medicine	Date of PBAC meeting	PBS Indication(s) (WHO FC III/IV unless specified)	Date first PBS-listed
Endothelin receptor antagonists			
bosentan	December 2003	IPAH and PAH associated with scleroderma	1 March 2004
	March 2008	PAH-CHD	1 August 2008
sitaxentan	*July 2007*	*No longer listed (de-listed 31 March 2011)*	*1 April 2008*
ambrisentan	July 2009	IPAH and PAH-CTD	1 December 2009
macitentan	March 2014	IPAH, PAH-CTD and PAH-CHD	1 September 2014
Prostanoids			
iloprost	November 2004	IPAH, PAH-CTD and drug-induced PAH	1 April 2005
	March 2008	Removal of 'adult' from restrictions to permit use in children (minor submission)	1 July 2008
epoprostenol	March 2006	IPAH	1 August 2006
	November 2011	PAH-CTD (WHO FC III second line; WHO FC IV first line)	1 April 2011
Phosphodiesterase type 5 inhibitors			
sildenafil	November 2006	IPAH and PAH-CTD (WHO FC III only)	1 March 2007
tadalafil	November 2011	IPAH and PAH-CTD (WHO FC III only)	1 April 2012
Soluble guanylate cyclase stimulator			
riociguat	March 2014	IPAH, PAH-CTD and PAH-CHD	1 February 2017

Source: compiled for this review

The basis for the economic analysis as considered by the PBAC in making the recommendation to list the each of the currently PBS subsidised PAH medicines, and the corresponding equi-effective doses, are shown in Table B.5.

Table B.5 The Economic analyses and equi-effective doses considered by the PBAC in recommending PBS listing of PAH medicines

Date of PBAC consideration	Active ingredient *Brand name and strength*	Basis of economic analysis[a]	Equi-effective doses recommended[a]
December 2003	**bosentan** Tracleer® 62.5 mg and 125 mg	[redacted]	N/A
November 2004	**iloprost** Ventavis® 10 µg in 2mL ampoule	[redacted]	[redacted]
March 2006	**epoprostenol** Flolan® 1.5 mg injection and 500 µg injection	CMA compared with bosentan	epoprostenol, commencing at an average dose of 11.9 ng/kg/min over the first 3 months of treatment and escalating linearly in steps to an average dose of 27.2 ng/kg/min at 3 years bosentan 125 mg twice daily
November 2006	**sildenafil** Revatio® 20 mg	CMA compared with bosentan	sildenafil 20 mg three times daily bosentan 62.5 mg twice daily for 4 weeks then 125 mg twice daily as the maintenance dose
March 2008[b]	**bosentan** Tracleer® 62.5 mg and 125 mg	Economic analysis not presented[c]	N/A
July 2009	**ambrisentan** Volibris® 5 mg and 10 mg	CMA compared with bosentan	ambrisentan 5 mg once daily bosentan 125 mg twice daily
November 2011	**tadalafil** Adcirca® 20 mg	CMA compared with sildenafil	tadalafil 40 mg once daily sildenafil 20 mg three times daily
November 2011[b]	**epoprostenol** Flolan® 1.5 mg injection and 500 µg injection	CMA compared with bosentan and sildenafil	epoprostenol, commencing at a dose of 2.2 ng/kg/min, with an average dose of 11.2 ng/kg/min at week 12, increasing linearly in steps to an average dose of 47.4 ng/kg/min at 3 years bosentan 62.5 mg twice daily for 4 weeks, then a maintenance dose of 125 mg twice daily iloprost 2.5-5 µg nebulised 6-9 times per day, giving a mean of 7.5 x 20 µg ampoules consumed per day
March 2014	**macitentan** Opsumit® 10 mg	CMA compared with bosentan	macitentan 10 mg once daily bosentan 62.5 mg twice daily for 4 weeks, then a maintenance dose of 125 mg twice daily
March 2014	**riociguat** Adempas® 500 µg,1 mg, 1.5 mg, 2 mg and 2.5 mg	CMA compared with bosentan and sildenafil	riociguat individually titrated (1 mg three times daily to 2.5 mg three times daily bosentan 62.5 mg twice daily or 125 mg twice daily sildenafil 20 mg three times daily

CEA = cost-effectiveness-analysis; CMA = cost-minimisation analysis; PAH = pulmonary arterial hypertension; PBS = Pharmaceutical Benefits Scheme
[a] Taken from public summary documents, except for those highlighted (sourced from submissions or PBAC minutes)
[b] For extension of PBS listing
[c] An economic evaluation for bosentan in PAH associated with congenital heart disease was not presented, as the sponsor argued that the cost-effectiveness of bosentan in this population is likely to be similar to that previously demonstrated for idiopathic PAH.

B.4.5.2 PBS prescribing restrictions

The PBS-listed PAH medicines cover most sub-types of PAH, except for PAH associated with PAH-HIV infection, portal hypertension and schistosomiasis.

The current PBS listed PAH medicines and subsidised indications are summarised in Table B.6, described in terms of PAH type and WHO Functional Class. PBS subsidised use of PAH medicines does not include treatment of WHO FC II patients or combination or add-on use of PAH medicines.

Table B.6 Overview of PBS-listed PAH medicines by PAH type and WHO Functional Class

Type of PAH	Bosentan	Ambrisentan	Macitentan	Tadalafil	Sildenafil	Iloprost	Epoprostenol	Riociguat
IPAH or Anorexigen-induced PAH or HPAH	Class III, IV	Class III, IV	Class III, IV	Class III	Class III	Class IV Class III 2° line	Class IV Class III 2° line	Class III, IV
Drug-induced PAH	–	–	–	–	–	Class III, IV	–	–
PAH-CTD	Class III, IV	Class III, IV	Class III, IV	Class III	Class III	Class IV	Class IV Class III 2° line	Class III, IV
PAH assoc. congenital systemic-to-pulmonary shunt (incl. Eisenmenger physiology)	Class III or IV	–	Class III or IV	–	–	–	–	Class III or IV

HPAH = heritable pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; PAH = pulmonary arterial hypertension; PAH-CTD = pulmonary arterial hypertension associated with connective tissue disease
Source: www.pbs.gov.au

B.4.5.3 Recent amendments to PBS Restrictions for PAH medicines

Recent amendments to the restrictions have been made to maintain currency with guideline criteria. The DUSC 2015 report provides a summary of 2014 changes to terminology and restrictions. These were updated from 1 August 2014 following a request from the PHSANZ:

- The existing single term "Primary Pulmonary Hypertension" was replaced by the terms "Idiopathic Pulmonary Arterial Hypertension (IPAH), anorexigen-induced PAH and hereditable PAH".
- The term "pulmonary capillary wedge pressure (PCWP)" was replaced by "Pulmonary Artery Wedge Pressure" and the cut-point for this parameter was lowered from <18mmHg to <15mmHg to comply with International Guidelines.
- The reference to an mPAP >30mmHg on exercise was removed as part of the definition of Pulmonary Hypertension.

As of 1 September 2014, the restrictions included an explicit criterion “sole PBS-subsidised agent for this condition”.

In July 2015, the PBAC considered a minor submission from PHSANZ to amend the assessments required for continuing treatment (PSD, July 2015 PBAC meeting). The PAH listings were all amended such that the assessments required to demonstrate patient response were retained only for the ‘first continuing’ treatment restriction. A new ‘subsequent continuing’ treatment restriction was added for subsequent applications that required no provision of test results and which could be obtained as a telephone authority.

Current restrictions

All PAH medicines are authority required listings. Authority required listings require the prescriber to obtain approval from the Services Australia prior to prescribing a PBS subsidised medicine. To be eligible for PBS subsidised treatment with a PAH medicine, a patient must be assessed by a physician at a designated hospital, the medicine must be the sole PBS-subsidised PAH medicine and the patient must meet strict clinical criteria.

Refer to Appendix 1.C Published treatment and diagnostic algorithms for the PBS restrictions for PAH medicines in full.

ToR 1: Concordance between prescribing restrictions and clinical guidelines

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.

1.2 Key findings for ToR 1

1.2.1 Key findings for research question 1

Research Question 1: 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?

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).

1.2.2 Key findings for research question 2

Research Question 2: Are the current PBS restrictions for PAH medicines, the TGA-approved indications and the recommendations from clinical guidelines consistent?

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 initial 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 in WHO FC II. The PBS restrictions limit the use of PAH medicines to one PAH medicine at any a time (the PAH agent is the sole subsidised agent for this condition) in FC III-IV.
- Guidelines also recommend sequential combination therapy for patients with an inadequate clinical response to treatment. Patients continue on their existing agent

and add another agent as sequential combination, up to three medicines. 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 recommendation, for example, prostanoids are neither TGA registered nor PBS-listed for PAH-CHD, and PDE-5 inhibitors not for WHO FC IV.
- There are no PBS-listed medicines for certain PAH subtypes: PAH-HIV, associated with portal hypertension or associated with schistosomiasis.
- The current terminology of PAH types in the TGA indications and PBS restrictions are inconsistent with the latest WHO classification scheme for pulmonary hypertension 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 HPAH.
- Guidelines recommend vasodilator treatment with 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 catherisation (RHC). The PBS restrictions however, require vasodilator 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 mmHg, to an mPAP <40 mmHg, with no worsening of cardiac output. The PBS restrictions define the criteria for vasodilator treatment with CCBs as being in FC III with mRAP of 8mmHg of less as measured by RHC. There are safety concerns surrounding vasodilator treatment with CCBs without a positive response to an acute vasodilator test.
- Vasodilator 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). The PBS restrictions require a detail from a trial of minimum six weeks duration.
- Guideline recommend additional therapy with PAH medicines, if the patient does not show an adequate response to treatment with CCBs, defined as being in WHO-FC I-II and with a marked haemodynamic improvement (near normalisation).
- Guideline recommendations for hypertension referral centres specify annual patient numbers as centres with a high volume of patients tend to obtain the best outcomes.

1.2.3 Key findings for research question 3

Research Question 3: Are the current diagnostic and prognostic criteria in PBS restrictions for patients with PAH consistent with Australian and international guidelines?

- Current PBS restrictions specify three diagnostic assessments at baseline and first continuation for PAH treatment subsidy: RHC, 6MWD and echocardiography.

  Based on guideline recommendations, the assessments that form the basis of treatment choices would include an assessment of the patient's risk of PAH deterioration based on a suite of parameters taken at baseline, and which provide the basis for monitoring and follow-up. However there is no definitive set of parameters for patient risk assessment (Table 1.1).

- 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 echocardiography (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, the pulmonary artery and the inferior vena cava and right atrium. In the absence of TRV, clinical feature suggestive of PAH are given in Table 1.9.

The alignment between PBS restrictions, TGA indications and guideline recommendations is summarised in Table 1.1.

Table 1.1 Summary of PBS-TGA-PAH Guidelines alignment

Criterion	PBS Listings	TGA Status	PAH Guidelines
WHO functional class	Subsidy: WHO FC III-IV No subsidy: WHO FC I-II Status is unspecified following improvement to WHO FC I-II (from more advanced disease)	Prostanoids: WHO FC Class III-IV only PDE-5i: WHO FC Class II-III only ERAs, riociguat: WHO FC II-IV	Monitoring for WHO FC I (except if status reached following improvement of more advanced disease) Oral agents for WHO FC II Oral agents (including PDE-5i) or prostanoids for WHO FC III-IV
Oral PAH medicines place in therapy	PDE-5 inhibitors - WHO FC III ERAs - WHO FC III-IV sGC stimulator - WHO FC III-IV	As for WHO FC. See Table 1.16. PDE-5i - WHO FC Class II-III ERA - WHO FC II-IV sGC stimulator - WHO FC II-IV	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	See Table 1.16. 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	Subsidy: IPAH, HPAH, PAH-CTD, PAH-DT Subsidy – oral agents only: PAH-CHD No subsidy: PAH-HIV, PAH-PH	See Table 1.16. Sildenafil, tadalafil and ambrisentan+tadalafil combination indications for Group 1 PAH Only iloprost specifically approved for PAH-DT No prostanoids approved for PAH-CHD	Treatment recommendations apply to all WHO Group 1 conditions
Monotherapy	All restrictions including after disease progression	See Table 1.16. Ambrisentan mono: IPAH, HPAH only	Initial monotherapy recommended for treatment naïve patients without high risk factors (WHO FC II-III)

Criterion	PBS Listings	TGA Status	PAH Guidelines
Initial combination therapy	Not permitted (treatment must be the sole PBS-subsidised PAH agent)	PAH medicines approved for add-on or combination use: • Ambrisentan + tadalafil • Macitentan +PDE-5 inhibitors or iloprost • Riociguat +ERAs or iloprost	Recommended for WHO FC III and WHO FC IV with high risk factors (2015 ESC/ERS Guidelines also recommends initial oral combination as an option for WHO FC II)
Sequential combination therapy	Not permitted (as for initial combination, also patients who fail to respond must cease therapy with that agent)	As for initial combination therapy.	SoC for patients WHO FC II-IV with inadequate response, up to a maximum of 3 PAH medicines
RHC	One of 3 key assessments to provide a baseline measurement – not always required (with justification)	—	RHC is gold standard for diagnosis of PAH – essential unless explicitly contraindicated. RHC relies on ECHO as preliminary test
ECHO	One of 3 key assessments to provide a baseline measurement – not always required (with justification)	—	ECHO alone not recommended for diagnosis of PAH. Recommended as essential part of work-up and decision to proceed to RHC
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 Table 1.9 Guideline diagnostic recommendations for PAH (does 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 add a further agent from a different class

Criterion	PBS Listings	TGA Status	PAH Guidelines
Timing of follow-up	Each authority approval should provide 6 months' 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. Age appropriate forms of bosentan + sildenafil available in EU/USA but not Australia	Treatment and diagnostic recommendations broadly the same in children as for adults. 6MWD not prognostic for PAH in children. Dose adjustment required for sildenafil in children
Trial of CCBs – patients	Required for WHO FC III – IPAH, HPAH, PAH and PAH-CTD Not required for PAH-CHD	Dosing and safety not included in PI for CCBs (diltiazem, nifedipine, amlodipine) However, amlodipine, diltiazem and nifedipine have specific TGA registered indications for hypertension and angina.	Recommended for IPAH, HPAH and PAH-DT patients only Patients not showing acute vasoreactivity response unsuited to CCBs due to safety concerns and lack of benefit Not recommended: PAH-CTD or PAH-CHD
Trial of CCBs – test criterion	mRAP 8 mmHg or below, by RHC	—	Positive response to acute vasoreactivity test during RHC defined as decrease in mPAP >10 mmHg, to an mPAP <40 mmHg, 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; 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 drugs at an affordable cost, compared to international patients.
- Stakeholders consider that PAH medicines should not be reimbursed based on the cause of PAH or the functional class (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 (PH) centres in Australia and notes variations in clinical expertise are leading to a variation in treatment and outcomes, and that the PHSANZ reported significant differences in mortality between treatment centres. 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 understood that patients in FC II are not eligible for PAH medicines under the PBS. There was some confusion over continuing eligibility requirements, with some patients believing that the PBS PAH medicines would no longer be available to them if/when the medicines led to an improvement in their health which saw them reclassified from FC III to FC II.
- Consumers noted that there are no specific medicines listed on the PBS for children and expressed a need for specific drugs and treatment regimens to be available for children.
- Consumers expressed frustration on the limited number of medicines available on the PBS (currently 8 medicines) in comparison to other countries such as Japan where they understood there to be up to 14 medicines available for PAH.
- 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 broad 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. They also suggested that earlier treatment could be more cost-effective.
- 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.

1.3 Methodology

1.3.1 Guidelines search

Searches were conducted according to the agreed protocol for this review.

Guidelines were considered distinct from descriptive reviews of PAH clinical practice. Selected review articles with directly relevant findings are cited throughout this report where appropriate. Recent reviews describing Australian clinical practice including commentary on accessing PBS-subsidised PAH medicines have been described as part of the Background.

As outlined in the protocol, criteria for including clinical practice guidelines in this review are based on PIPOH criteria[17]. The PIPOH criteria for the review of clinical guidelines on the treatment of PAH are summarised in Table 1.2.

Table 1.2 PIPOH guideline selection criteria

Parameter	Inclusion criteria
Population	Patients with WHO FC II, III or IV PAH
Interventions	Pharmaceutical treatments listed on the PBS for PAH
Professionals/Patients	GPs, pulmonologists, cardiologists, rheumatologists, physicians or other referred specialists
Outcomes	Recommendations and clinical indications (diagnostic/prognostic criteria) for PAH treatment, clinical treatment algorithms (if provided)
Health care setting	Primary (*e.g.* GP), secondary (*e.g.* outpatient) and tertiary (*e.g.* hospital) health care settings
Publication type	Evidence-based or evidence-linked clinical practice guidelines
Language	English, or has been translated into English

FC = Functional class; GP = general practitioner; PAH = pulmonary arterial hypertension; WHO = World Health Organization

Accordingly, guidelines not included in this review were those that addressed pulmonary hypertension in patients with the following conditions, or other circumstances:

- Non 'Group 1' PH e.g. PPHN; CTEPH; PH due to interstitial lung disease; due to left heart disease
- Various topics in anaesthesia; pregnancy; pre-eclampsia

- Acute care/intensive care topics for preterm infants
- Treatment of high altitude sickness; pulmonary embolism
- Systemic hypertension
- Sickle cell disease; thalassaemia; cystic fibrosis
- Guidelines for non-OECD countries / healthcare systems such as China, Turkey
- Guidelines published prior to 2010.

As there were few identifiable guidelines, searches were conducted with alternative, less stringent terms ('pulmonary hypertension' or 'arterial hypertension' or 'hypertension'; 'guidance' or 'recommendations'). The majority of results, regardless of search platform, were for the documents already identified (Table 1.4) or were for other types of PH. Searches were aided by the availability of older (pre-2010) guidelines – focused searches were done to identify updates to those documents using PubMed, Google and organisation websites. Searches also looked for other PAH recommendations published by the specialist organisations in Table 1.3.

Table 1.3 Specialist groups targeted in search strategy

Country	Specialist groups
Australia; New Zealand	Pulmonary Hypertension Society of Australia and New Zealand (PHSANZ) The Cardiac Society of Australia and New Zealand Lung Foundation Australia The Thoracic Society of Australia and New Zealand
UK	British Thoracic Society British Cardiovascular Society
Europe	European Society of Cardiology European Respiratory Society
USA	American Thoracic Society American College of Cardiology American Heart Association American College of Chest Physicians

The quality of the identified guidelines was rated according to the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument[18]. The results of the critical appraisal were included in the summary table (Table 1.4).

Of the guidelines identified, the CHEST guideline (US), the 2015 ESC/ERS guidelines (European) and the CADTH guideline (Canada) were the three guidelines with higher quality. Thus recommendations from these documents were given more credence than the other lower-scoring guidelines. The lower scores were primarily due to low scores in domains of "Rigour of Development" and "Applicability" of the AGREE II instrument.

1.3.2 Current clinical guidelines identified

Overall, only nine guidelines were considered relevant, covering diagnosis and treatment of PAH, the international classification scheme and recommendations for paediatric patients (Table 1.4). There are no guidelines specifically for Australia or New Zealand. As such, this report assumes that European and US guideline recommendations are applicable to Australia, except for certain aspects (recommendations regarding drugs not on the market in Australia such as treprostinil).

Published reviews on PAH from various national/regional specialists organisations indicate that the 2015 European Society of Cardiology /European Respiratory Society joint guidelines[8] (the 2015 ESC/ERS guidelines) are considered definitive not just for Europe but in other regions. This guideline serves, alongside the equivalent US guideline from the American College of Chest Physicians (i.e. the CHEST guideline[19]), as guidance for other countries – including Australia.

Two further guidelines were identified from the US; one, a guideline on PAH treatment by the American College of Cardiology and the American Heart Association[20] – but which dates from 2009 and has not been updated – and a guideline on diagnostic imaging criteria for PAH from the American College of Radiology[21]. In the US, a joint 2015 guideline by the American Heart Association and the American Thoracic Society covers all types of PH in children (for this review, only those recommendations for PAH were considered)[22]. The current PH classification guideline from the World Symposium on PAH is fundamental to definition of the eligible patient populations even though it makes no treatment recommendations[9]. Also from the World Symposium, two consensus based guidelines were relevant (one for treatment of PAH in children[23] and a second regarding PAH diagnostics[24]). The CHEST guideline defers all recommendations regarding treatment of children with PAH to the Ivy et al[23] document.

Guidelines published before 2010 were not included, with the exception of MacLaughlin *et al* 2009[20] primarily because this was the most recent version and US authors continue to cite it. It did not inform many of the treatment pathways developed for this review. Guidelines identified in the search dating from before 2010 are available as updated versions, or did not cover newer PAH medicines macitentan and riociguat.

A review by the Canadian Agency for Drugs and Technologies in Health (CADTH) from March 2015 was considered partially relevant[25]. Although it is driven by the costs and constraints of the Canadian healthcare system (as well as different prostanoids being available in Canada), it contains some informative, evidence-based recommendations on therapy choices, particularly combination/add-on treatments. A similar review by the National Institute of Health and Care Excellence (NICE) in the United Kingdom was in development but was halted at the protocol stage as the National Health Service (NHS) had already issued commissioning guidance for PAH medicines[26]. NHS commissioning guidance

for PAH[27] in turn was not relevant as it is driven by cost arrangements existing between manufacturers and the NHS and the availability of low cost sildenafil.

The PBS restrictions include some specific haemodynamic variables. To develop an informed view of guideline requirements for these aspects, it was necessary to draw on both PAH and interventional guidelines, as well as recent review articles. However, an exhaustive search was not conducted to identify all potentially relevant interventional guidelines (namely echocardiography and cardiac catheterisation).

A 2010 guideline on echocardiography of the right heart by the American Society of Echocardiography (endorsed by its counterpart European Association of Echocardiography) was used to address some of these questions[28]. This is cited in the 2015 ESC/ERS Guidelines for this purpose. A report from the Working Group on Diagnosis and Assessment of the 2013 Nice World Symposium contained further information[24].

Table 1.4 Guidelines relevant to this review

Date	Type	Organisation(s)	Title	Quality appraisal
2016	Clinical guidance	American College of Radiology	ACR Appropriateness Criteria suspected pulmonary hypertension[21]	Low-to-moderate
2015	Clinical guidance	American Heart Association American Thoracic Society	AHA/ATS Guideline: Pediatric Pulmonary Hypertension[22] **NOTE: hybrid of both evidence-based and consensus based recommendations**	Moderate
2015	Clinical guidance	European Society of Cardiology (ESC) European Respiratory Society (ERS)	2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension[8]	Moderate-to-high
2015	Health technology assessment	Canadian Agency for Drugs and Technologies in Health	Drugs for Pulmonary Arterial Hypertension: Comparative Efficacy, Safety, and Cost-Effectiveness — Recommendations Report[25]	Moderate-to-high
2014	Clinical guidance	American College of Chest Physicians	Pharmacologic therapy for pulmonary arterial hypertension in adults: CHEST guideline and expert panel report[19] **NOTE: hybrid of both evidence-based and consensus based recommendations**	Moderate-to-high
2013	Classification guideline	WHO 5th World Symposium on Pulmonary Hypertension in Nice, France (2013)	Updated Clinical Classification of Pulmonary Hypertension[9] **NOTE: includes no treatment recommendations – no quality assessment performed**	N/A
2013	Consensus statement	Pediatric Task Force of the WHO 5th World Symposium on Pulmonary Hypertension in Nice, France (2013)	Pediatric Pulmonary Hypertension. (Discussions and recommendations from the Pediatric Task Force of the 5th World Symposium on Pulmonary Hypertension (WSPH) in Nice, France (2013))[23]	Low-to-moderate

Date	Type	Organisation(s)	Title	Quality appraisal
2013	Meeting report	WHO 5th World Symposium on Pulmonary Hypertension in Nice, France (2013), working group on diagnosis and assessment	Definitions and Diagnosis of Pulmonary Hypertension (Discussions and recommendations from the working group on diagnosis and assessment at the 5th World Symposium on Pulmonary Hypertension (WSPH) in Nice, France (2013))[24] **NOTE: includes no treatment recommendations – no quality assessment performed**	N/A
2009	Consensus statement	American College of Cardiology (ACC) American Heart Association	ACCF/AHA 2009 Expert Consensus Document on Pulmonary Hypertension[20]	moderate

1.4 Overview of current clinical guidance

1.4.1 Guidelines overview

PAH guideline recommendations are aimed at specialist physicians with substantial experience in treating PH and PAH patients. There are principles recommended but specific details are left to the judgement of the treating physician, and/or to be based on the clinical features of the individual patient.

Recommendations are broadly similar across the PAH subtypes, including those for children.

There were few recommendations on dosage.

There were essentially no recommendations on switching between PAH medicines.

Recommendations were based on class, not individual agents and made no suggestions as to line of therapy.

Many of the recommended diagnostic assessments inform differential diagnoses which have not formed part of this review. This report focuses on tests that will have been performed for all patients with a PAH diagnosis and that are necessary to manage response to treatment.

RHC and Doppler echocardiography are two essential tests for PAH, but there is an irreducible array of other assessments that must also be considered essential to inform this diagnosis but that may vary between patients. Each prior test will inform the next assessment and the choice parameters investigated in that next test – this will depend in turn on features of the patient's disease.

Some recommendations did not have specific criteria or definitions attached to them:

- Recommendations are presented for choice and frequency of monitoring tests to follow response to treatment but there is no formal definition of what constitutes a response or a change in these parameters as multiple factors are likely to be relevant.
- There is no formal definition of clinical worsening.
- Parameters for assessment of patient prognosis/risk factors are indicative, not definitive.

1.4.2 PAH treatment algorithm

The guideline recommendations are summarised as pharmacotherapy pathways for patients receiving monotherapy in Table 1.5 PAH pharmacotherapy – patient groups receiving monotherapy and those receiving combination or add-on treatment in Table 1.6 PAH pharmacotherapy – patient groups receiving combination therapy.

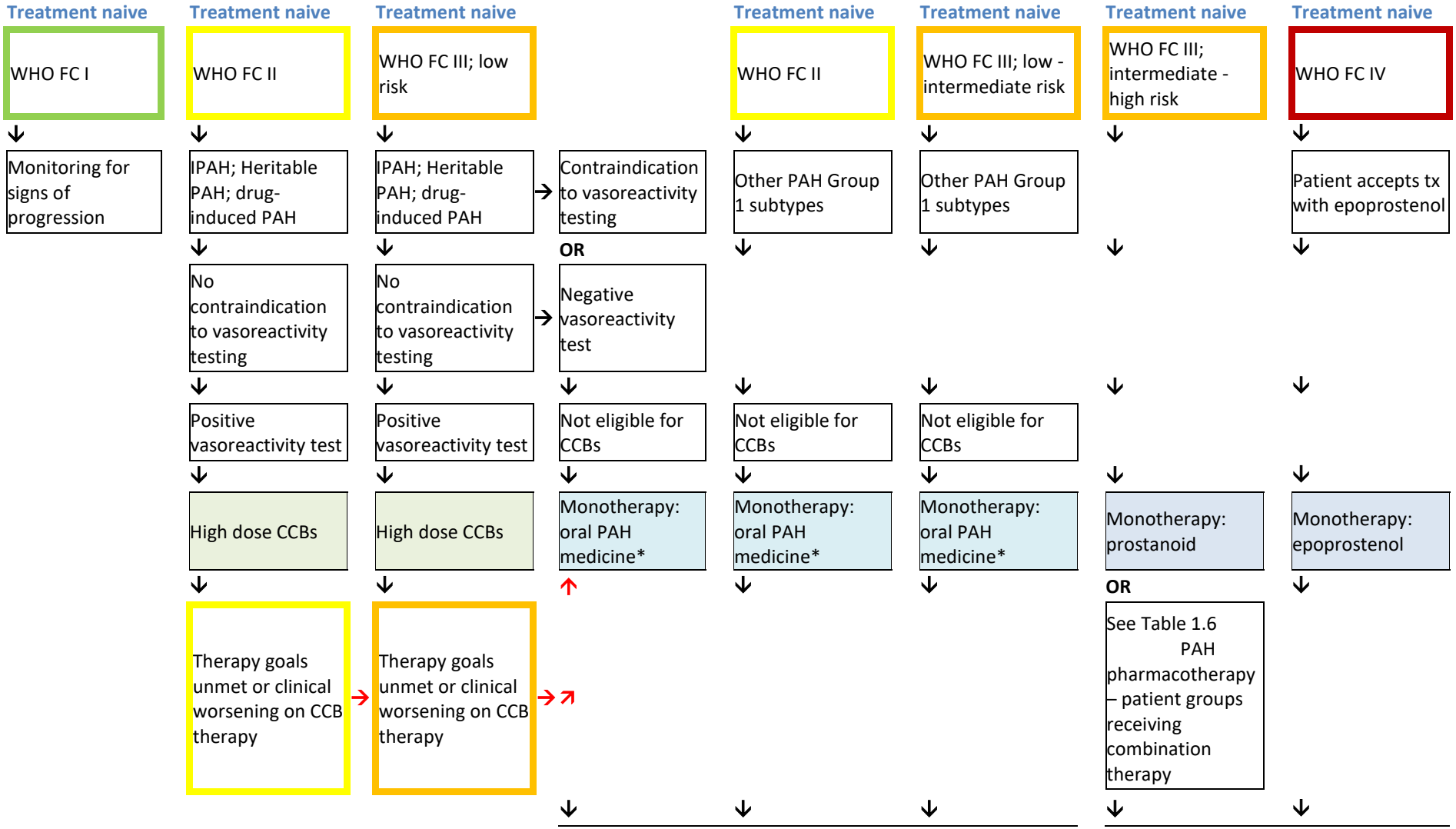
Note: The split between these two types of treatment has been made for reasons of space, to illustrate the options for treatment, but should not be taken as a suggestion that there are two obviously different groups of patients.

Steps are omitted that would appear in a true treatment algorithm such as diagnostics and monitoring; pulmonary rehabilitation; anticoagulants and supplemental oxygen, and others. This focuses on the current recommendations for PAH medicine choices.

The individual pathways are based primarily on the CHEST guideline[19], which provided the best coverage or options for patients in the different risk categories. The overall patient flow follows the algorithm presented in 2015 ESC/ERS Guidelines[8].

These treatment pathways follow the logic of the published algorithms (below) in that patients are triaged according to PAH subtype, risk features and WHO FC status. The specific recommendations from the CHEST guideline[19] and the 2015 ESC/ERS guidelines[8] are summarised in Table 1.7 Guideline recommendations supporting the therapy pathways and Table 1.8 Guideline recommendations regarding high dose CCBs. A key difference between these two documents is that the recommendations in the 2015 ESC/ERS guidelines suggest either initial monotherapy or initial oral combination therapy in patients with WHO FC II-III. The CHEST guideline instead suggests reserving initial combination treatment for those patients with higher risk features. The latter, more conservative approach is reflected here, noting that patients with inadequate response to monotherapy on follow-up are recommended to receive an additional agent according to both guidelines.

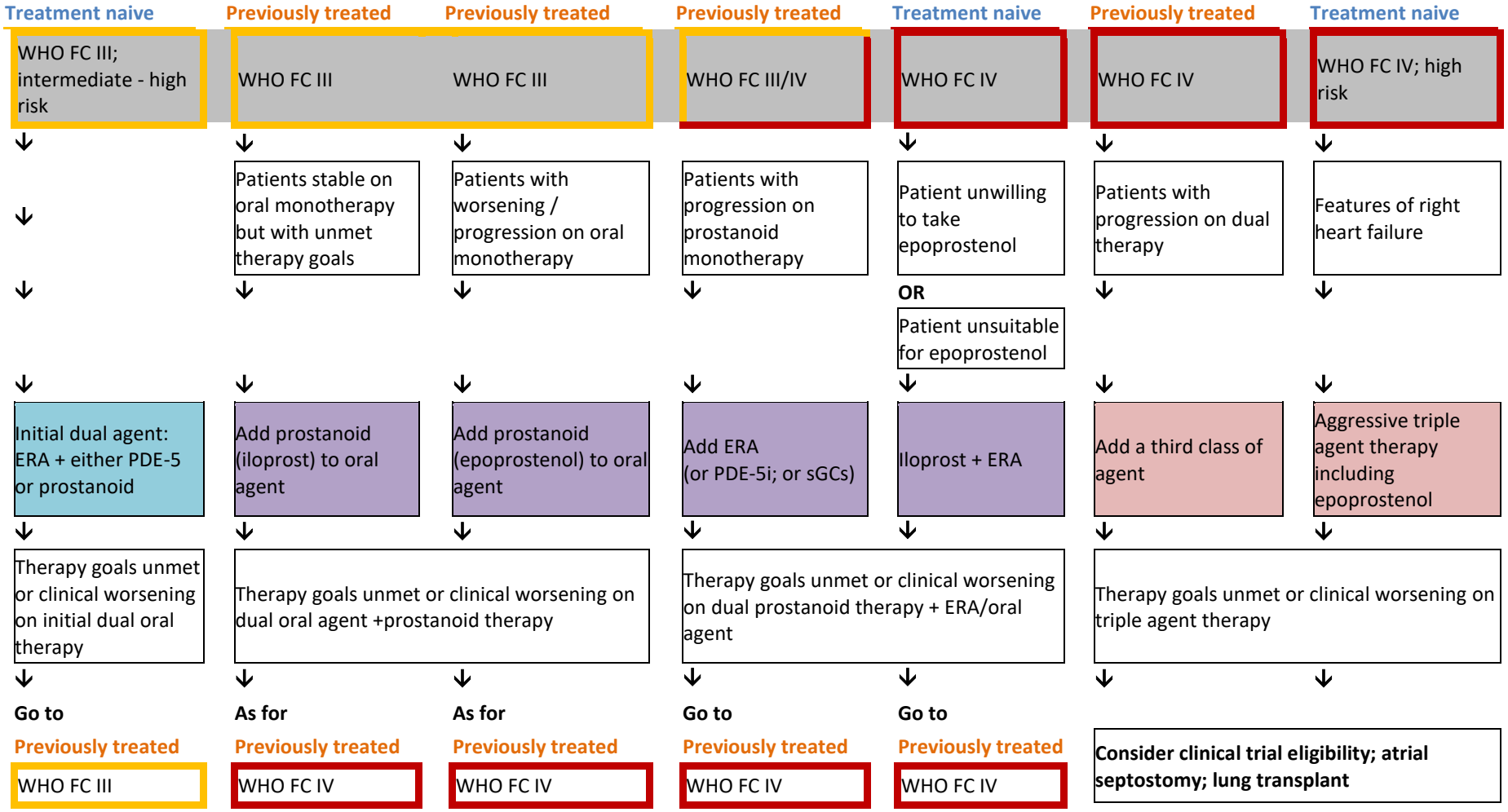
Table 1.5 PAH pharmacotherapy – patient groups receiving monotherapy



Treatment naive	**Treatment naive**	**Treatment naive**	**Treatment naive**	**Treatment naive**	**Treatment naive**	**Treatment naive**
			Therapy goals unmet or clinical worsening on oral monotherapy – See Table 1.6 PAH pharmacotherapy – patient groups receiving combination therapy		Therapy goals unmet or clinical worsening on prostanoid monotherapy – See Table 1.6 PAH pharmacotherapy – patient groups receiving combination therapy	

*If on ambrisentan 5 mg with unmet therapy goals only, first increase to 10 mg
Note: Medicines not available in Australia are not included here, thus oral medicine only includes ERAs, PDE-5 inhibitors and riociguat; prostanoid only includes epoprostenol and iloprost.
Source: Guideline recommendations from sources in Table 1.1.

Table 1.6 PAH pharmacotherapy – patient groups receiving combination therapy



Source: Guideline recommendations in Table 1.7 Guideline recommendations supporting the therapy pathways; from sources in Table 1.1.

Table 1.7 Guideline recommendations supporting the therapy pathways

Patient Group	CHEST Guideline[19]	2015 ESC/ERS Guidelines[8]
General comments		
Choice of medicine – monotherapy	*"Direct comparisons of available oral therapies for PAH monotherapy for treatment-naive patients have not been performed, and we do not make recommendations or suggestions of one medicine, or class of medicine, over another. Rapid onset of action and titratability of this form of therapy to the severity of the class IV patient's disease make this preferable over oral PAH-specific therapies."*	*"If initial monotherapy is chosen, since head-to-head comparisons among different compounds are not available […] the choice of the drug may depend on […] labelling, route of administration, side-effect profile, potential interaction with background therapies, patient preferences, co-morbidities, physician experience and cost"*
Choice of medicine – high risk/WHO FC IV	*"Most experts in the field consider IV epoprostenol the therapy of choice for WHO FC IV patients based on extensive clinical experience and the findings of improved survival in a single study"*	*"In non-vasoreactive and treatment-naive patients at high risk, initial combination therapy including i.v. prostacyclin analogues should be considered. I.V. epoprostenol should be prioritised since it has reduced the 3-month rate of mortality in high-risk PAH patients also as monotherapy"*
Treatment response	*"The therapy is considered adequate only if the targets are met […] patients who are stabilised, or even those who improve slightly, can still receive additional therapy if treatment goals are not met"* *"The goal-oriented treatment strategy utilises different targets, including WHO-FC I or II, and the near-normalization of resting CI and/or of NT-proBNP (*N-terminal pro-B-type natriuretic peptide) *plasma levels"*	*"Achievement/maintenance of an intermediate-risk profile should be considered an inadequate treatment response for most patients with PAH"*
Treatment naïve		
WHO FC I	*"For treatment naive PAH patients with WHO FC I symptoms, we suggest continued monitoring for the development of symptoms that would signal disease progression and warrant the initiation of pharmacotherapy"*	WHO FC I patients are not included in the guideline algorithm or the tabulated drug therapy recommendations; nor is there discussion about management of patients at this stage.

Patient Group	CHEST Guideline[19]	2015 ESC/ERS Guidelines[8]
WHO-FC I-III, all symptomatic patients without high risk factors	*"Patients with PAH who, in the absence of right-heart failure or contraindications to CCB therapy, demonstrate acute vasoreactivity according to consensus definition, should be considered candidates for a trial of therapy with an oral CCB blocker"* [Note: elsewhere in this Guideline, targeted PAH medicines rather than CCBs are recommended for WHO FC III with poor prognosis/risk factors or WHO FC IV]	*"Initiation of specific PAH therapy is recommended in patients in WHO-FC III or IV (or those without marked haemodynamic improvement (near normalization) after high doses of CCBs)"* From the guideline algorithm: An acute vasoreactivity test should be administered to patients with IPAH/heritable PAH/drug induced PAH only, and CCBs trialled in those who are vasoreactive. Tabulated recommendations for monotherapy include CCBs for those meeting the subtypes and vasoreactivity criteria and who are WHO FC II or III – per the guideline algorithm this would not include WHO FC III with high risk factors.
WHO FC II – not eligible for CCBs	*"For treatment naive PAH patients with WHO FC II symptoms who are not candidates for CCB therapy, we advise monotherapy with an ERA, PDE-5 inhibitor or riociguat"*	*"Non-responders to acute vasoreactivity testing who are at low or intermediate risk can be treated with either initial monotherapy or initial oral combination therapy"* (per the guideline algorithm, this only applies to WHO FC II or III). The tabulated recommendations for monotherapy indicate ERAs, PDE-5 inhibitors and riociguat, (also selexipag) in WHO FC II and III.
WHO FC II – all	*"Parenteral or inhaled prostanoids [should] not be chosen […] for treatment naive PAH patients with WHO FC II symptoms"*	Tabulated recommendations for monotherapy excludes all prostanoids for WHO FC II; WHO FC II also excluded from all initial combination therapy recommendations.
WHO FC III – not eligible for CCBs	*"For treatment-naive PAH patients with WHO FC III symptoms who are not candidates for CCB therapy, we advise monotherapy be initiated with an ERA, a PDE-5 inhibitor, or riociguat"*	From the guideline algorithm: Low or intermediate risk WHO FC II–III should receive EITHER initial monotherapy OR initial oral combination. Tabulated recommendations for monotherapy indicate ERAs, PDE-5 inhibitors and riociguat, (also selexipag) in WHO FC II and III.

Patient Group	CHEST Guideline[19]	2015 ESC/ERS Guidelines[8]
WHO FC III – high risk / poor prognosis	*"For treatment naive PAH patients with WHO FC III symptoms who have evidence of rapid progression of their disease, or other markers of a poor clinical prognosis, we advise consideration of initial treatment with a parenteral prostanoid"*	*"In non-vasoreactive and treatment-naive patients at high risk, initial combination therapy including i.v. prostacyclin analogues should be considered"* Tabulated recommendations for monotherapy are for oral medicines and prostanoids in WHO FC III and IV, but especially epoprostenol in Class IV. From the guideline algorithm: Initial combination including i.v. prostacyclin analogue for high risk WHO FC IV (also WHO FC III).
WHO FC IV	*"For treatment naive PAH patients in WHO FC IV, we advise initiation of monotherapy with a parenteral prostanoid agent"* *"For treatment naive PAH patients in WHO FC IV who are unable or do not desire to manage parenteral prostanoid therapy, we advise treatment with an inhaled prostanoid in combination with an ERA"*	Tabulated recommendations for monotherapy are for oral agents and prostanoids in WHO FC III and IV, but especially epoprostenol in Class IV. From the guideline algorithm: Initial combination including i.v. prostacyclin analogue for high risk WHO FC IV (also WHO FC III).
WHO FC III or IV	*"In PAH patients initiating therapy with IV epoprostenol, we suggest against the routine simultaneous initiation of bosentan"*	Tabulated recommendations for monotherapy are for oral agents and prostanoids in WHO FC III and IV, but especially epoprostenol in Class IV.
Previously treated		
WHO FC II –failed CCBs	*"For PAH patients with WHO FC II symptoms who have failed CCB therapy, we advise monotherapy with an ERA, PDE-5 inhibitor or riociguat"*	[As for WHO FC III – failed CCBs, below]
WHO FC III – failed CCBs	*"For PAH patients with WHO FC III symptoms who have failed CCB therapy, we advise monotherapy be initiated with an ERA, a PDE-5 inhibitor, or riociguat"*	*"Initiation of specific PAH therapy is recommended in patients in WHO-FC III or IV or those without marked haemodynamic improvement (near normalization) after high doses of CCBs"*

Patient Group	CHEST Guideline[19]	2015 ESC/ERS Guidelines[8]
WHO FC III – high risk / poor prognosis	*"For PAH patients in WHO FC III who have evidence of progression of their disease, and/or markers of poor clinical prognosis despite treatment with one or two classes of oral agents, we advise consideration of the addition of a parenteral or inhaled prostanoid."*	From the guideline algorithm: Initial combination including i.v. prostacyclin analogue for WHO FC IV (also high risk WHO FC III).
WHO FC III or IV	*"For WHO FC III or IV PAH patients with unacceptable clinical status despite established PAH-specific monotherapy, we advise addition of a second class of PAH therapy to improve exercise capacity:* *- on ERA or PDE-5 inhibitor; add iloprost* *- on IV epoprostenol, add sildenafil or titrate up epoprostenol dose* *- on ERA or iloprost, add riociguat* *- on PDE-5 inhibitor or iloprost; add macitentan"*	*"In case of inadequate clinical response to initial combination therapy or initial monotherapy, sequential double or triple combination therapy is recommended. In case of inadequate clinical response with sequential double combination therapy, triple combination therapy should be attempted"* From the guideline algorithm: Double or triple sequential combination to follow initial therapy.
WHO FC III or IV – high risk / poor prognosis	*"For WHO FC III or IV PAH patients with unacceptable or deteriorating clinical status despite established PAH-specific therapy with two classes of PAH pharmacotherapy, we suggest addition of a third class of PAH therapy* *[A]ddition of a third class of PAH medication usually indicates poor functional status. In this setting, we believe that treatment with a parenteral prostanoid therapy must be considered."*	As above – addition of a PAH medicine to existing therapy, up to triple combination.
On approaching maximum drug therapy options	*"[E]scalation of therapy and referral for lung transplantation evaluation should occur when a patient has evidence of disease progression on combination therapy"*	*"Consider eligibility for lung transplantation after an inadequate clinical response to the initial monotherapy or initial combination therapy and to refer the patient for lung transplantation soon after the inadequate clinical response is confirmed on maximal combination therapy"*

Table 1.8 Guideline recommendations regarding high dose CCBs

Issue	Chest Guideline[19]	2015 ESC/ERS Guidelines[8]
Indication for CBBs	*Patients with PAH who, in the absence of right-heart failure or contraindications to CCB therapy, demonstrate acute vasoreactivity according to consensus definition, should be considered candidates for a trial of therapy with an oral CCB.*	*High doses of CCBs are recommended in patients with IPAH, heritable PAH and drug induced PAH who are responders to acute vasoreactivity testing.*
Recommendation for vasoreactivity testing	*Patients with PAH, in the absence of contraindications, should undergo acute vasoreactivity testing using a short-acting agent at a center with experience in the performance and interpretation of vasoreactivity testing.* *No other clinical characteristic or baseline hemodynamic feature predicts those patients who will respond.*	*Vasoreactivity testing is recommended in patients with IPAH, HPAH and PAH associated with drugs use to detect patients who can be treated with high doses of a CCB.* *Only a small number of patients with IPAH who demonstrate a favourable response to acute vasodilator testing at the time of RHC do well with CCBs.*
Positive acute response definition	*The consensus definition of acute vasoreactivity is a fall in mPAP >10 mmHg, to an mPAP <40 mmHg, with an unchanged or increased CO.* This guideline defers to a separate document for PAH in children. Other guidance defines a positive response in children is defined as ≥20% decrease in PAP and PVR with no decrease in cardiac output[22, 23].	*A positive response to vasoreactivity testing is defined as a reduction of mean PAP ≥10 mmHg to reach an absolute value of mean PAP ≤40 mmHg with an increased or unchanged cardiac output.*
CCB dosage	*Although the optimal dose remains uncertain, the typical dosage used is amlodipine 20-30 mg/day, nifedipine 180-240 mg/day, or diltiazem 720-960 mg/day.*	*The daily doses of these drugs that have shown efficacy in IPAH are relatively high: 120–240 mg for nifedipine, 240–720 mg for diltiazem and up to 20 mg for amlodipine.*
Follow-up	*Patients who respond to CCB therapy show dramatic clinical improvements within the first few months of treatment.*	*Close follow-up with complete reassessment after 3–4 months of therapy (including RHC) is recommended in patients with IPAH, heritable PAH and drug induced PAH treated by high doses of CCBs.* *If the patient does not show an adequate response, defined as being in WHO-FC I or II and with a marked haemodynamic improvement (near normalization), additional PAH therapy should be instituted.*

Issue	Chest Guideline[19]	2015 ESC/ERS Guidelines[8]
Contraindications	*CCBs should not be used empirically to treat PAH in the absence of demonstrated acute vasoreactivity.* *Contraindications to acute vasoreactivity testing include a low systemic blood pressure, low cardiac output or the presence of FC IV symptoms.*	*High doses of CCBs are not indicated in patients without a vasoreactivity study or non-responders unless standard doses are prescribed for other indications (e.g. Raynaud's phenomenon).* *The use of CCBs is not recommended in patients with Eisenmenger syndrome.*
Potential adverse effects	*The use of CCBs in patients with PAH can cause systemic hypotension producing reflex tachycardia, sympathetic stimulation, and right ventricular ischemia. Reports of serious adverse events when CCBs are used inappropriately underscore that CCBs need to be used with caution.*	*Patients who have not undergone a vasoreactivity study 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).*

This distillation of treatment recommendations summarises the guidance. This does not take into account updated data on the effectiveness of individual medicines to achieve different outcomes (improvement in 6MWD or WHO Functional class, delay in clinical worsening etc). These are included (where available) in the assessment for TOR 4.

Treatment and diagnostic algorithms from the published guidelines and selected authoritative reviews are given in Appendix 1.

Figure 1.2 Treatment algorithm for PAH 2015 ESC/ERS Guidelines

Figure 1.3 Treatment algorithm from McLaughlin *et al* (2015)

Figure 1.6 Treatment algorithm for Paediatric PAH (World Symposium)

Figure 1.4 Diagnostic algorithm for PAH, 2015 ESC/ERS Guidelines

Figure 1.5 Diagnostic algorithm for PAH

Figure 1.7 Diagnostic algorithm for Paediatric PAH

The CHEST guideline[19] did not include a treatment algorithm. The algorithm in the ACC/AHA 2009 consensus statement has been omitted as it was simplified and missing several new oral PAH medicines. The lead author of that consensus statement recently co-authored a review with several other PAH key opinion leaders that includes an algorithm which has been included for comparison[29] (Figure 1.3). A useful diagnostic algorithm has also been included from a literature review on echocardiography[30] as it reflects the interventions recommended in the various guidelines.

The best evidence-based assessment was found in the CADTH review[25]. CADTH evaluated evidence for monotherapy across WHO FC I-IV and found that *"the available drugs used in monotherapy are similarly efficacious for improving the key trial outcomes of FC worsening and clinical worsening"* (PDE-5 inhibitors were recommended based on cost). The review goes on to state that there was *"no evidence to guide the duration of treatment […] before changing to or adding another drug. The decision to change from or add to initial therapy […] should be based on patient-specific factors and response".*

Regarding treatment of patients with PAH-CTD, or PAH-CHD or drug and toxin induced PAH there are no fundamental differences to be highlighted in the proposed pharmacotherapy pathways as this is focusing on choice of PAH medicine only. The clinical features in those different subtypes may however affect the prognostic factors and drive different treatment strategies. For example, patients with scleroderma (systemic sclerosis) tend to progress more quickly and have poorer survival. There were no specific recommendations for HIV infection or patients with portal hypertension either. ERAs remain indicated for the latter in spite of the hepatotoxicity risk, noting that macitentan and ambrisentan have a better safety profile for this endpoint in principle but have not been studied to the same extent as bosentan[8].

The 2015 ESC/ERS guidelines state that *"The medical treatment strategy for patients with PAH associated with [congenital heart disease], and in particular for subjects with Eisenmenger syndrome, is mainly based on the clinical experience of experts rather than being formally evidence-based".* Regarding children, it states that "*The general scheme of the diagnostic algorithm for adult patients may also be adopted in children, with some adaptation related to the different epidemiology"*[8].

1.4.3 Diagnostic and monitoring recommendations

Right heart catheterisation (RHC)

Pulmonary hypertension is defined as a resting mPAP of 25 mmHg or more by RHC. RHC is the gold standard for PAH diagnosis and is used to measure this and other parameters such as RAP, other dimensions of the right heart and cardiac performance. RHC is recommended as essential prior to making treatment decisions, unless contraindicated (Table 1.9 Guideline diagnostic recommendations for PAH). RHC should be performed once the non-invasive assessments have been completed.

Transthoracic Echocardiography

A chest echocardiogram is the key non-invasive method to determine if PAH is suspected and whether RHC is indicated. PAP cannot be measured directly using echocardiography and must be inferred from peak tricuspid regurgitation velocity (TRV) and mean right atrial pressure (mRAP). The tricuspid valve lies between the right atrium and the right ventricle. Regurgitation results from the leaking tricuspid valve allowing blood flow back into the right atrium, instead of the blood flowing as it should (right atrium –> right ventricle –> pulmonary artery).

This method is less effective in patients with mild PAH as regurgitation may not be apparent, or in those who have underlying lung disease. If TRV is not measurable, the other signs of PAH on echocardiography become key to determining the likelihood of PAH (Table 1.9) and a decision to proceed to RHC. The lack of reliably measureable TRV in some patients rules out echocardiography as the key diagnostic test.

Risk categories and prognostic characteristics

An essential component of PAH diagnosis and treatment decisions is the suite of baseline characteristics to provide a measure of risk of PAH disease deterioration or prognosis, and then for monitoring of response.

Current treatment recommendations are informed by considering patient risk factors based on their symptoms and other clinical features – several different approaches are described in Table 1.10, referring to examples of recommended risk factor assessments in Table 1.11, Table 1.12 and Figure 1.1.

Table 1.9 Guideline diagnostic recommendations for PAH

Issue	Details
Right Heart Catheterisation (RHC)	
Haemodynamic definition of PAH	Pulmonary hypertension is defined as an increase in mean pulmonary artery pressure (mPAP) ≥25 mmHg at rest as assessed by right heart catheterisation (RHC). This is in comparison to a normal mPAP, which at rest is 14±3 mmHg with an upper limit of normal of approximately 20 mmHg[21, 24]. The patient should be confirmed to have normal pulmonary artery wedge pressure (PAWP) ≤15 mmHg (as an indication of left ventricular pressure) and a pulmonary vascular resistance (PVR) of >3 Wood units in the absence of other causes of precapillary PH such as PH due to lung diseases or CTEPH. In children, the definition is the same except PVR should be >2 Wood units[22].
Contraindications for RHC	Absolute contraindications: Mechanical tricuspid or pulmonic valve Right heart masses (thrombus or tumour) Right-sided endocarditis Relative contraindications: Coagulopathy Pacemaker Bioprosthetic tricuspid or pulmonic valve Left bundle branch block Arrhythmias Skin site infections Source: Rosenkranz *et al* 2015[31]
Parameters for RHC	For diagnosis of PAH, RHC should include measurement of cardiac output, mixed venous oxygen saturation (SvO_2), PAP, PAWP, RAP and right ventricular pressure. Parameters calculated from these measurements include the transpulmonary pressure gradient, diastolic pressure gradient, PVR and cardiac index[24, 31].
Safety of RHC	The 2015 ESC/ERS Guidelines[8] observe that *"when performed at expert centres, [RHC] should have low morbidity (1.1%) and mortality (0.055%) rates."* On the other hand, with inexpert administration, balloon inflation can result in ruptured pulmonary arteries[24].
RHC in children	RHC requires general anaesthesia or conscious sedation in most children under 15 years[22]. *[S]erial echocardiography and serial RHC are […] indicated as they are in adults to monitor initial response and potentially on clinical worsening to look for evidence of right heart deterioration[22].*
Echocardiography	
Methodology/ equipment	Specifically, continuous wave Doppler transthoracic echocardiography should be performed, conducted in a patient at rest in line with current guidance on cardiac imaging. Either 2D or 3D methods can be used, though 3D is superior in evaluation of right ventricular volumes and ejection fraction according to the American College of Radiology PAH imaging guidance[21].

<table>
<tr><th>Issue</th><th>Details</th></tr>
<tr><td>Indication</td><td>The 2015 ESC/ERS Guidelines state[8] “Echocardiography should always be performed when PAH is suspected. […] When treatment of PAH itself is being considered, echocardiography alone is not sufficient to support a treatment decision and cardiac catheterization is required.”</td></tr>
<tr><td>Key parameter – Tricuspid Regurgitation Velocity (TRV)</td><td>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[8]; described in more detail in Grunig at al 2015[32].
The 2015 ESC/ERS Guidelines[8] state that “given the inaccuracies of RAP estimation and the amplification of measurement errors by using derived variables, we recommend using the continuous wave Doppler measurement of peak TRV as the main variable for assigning the echocardiographic probability of PH”.</td></tr>
<tr><td>Other signs of PAH on echocardiography (than TRV)</td><td>
<table>
<tr><th>A: The ventricles</th><th>B: Pulmonary artery</th><th>C: Inferior vena cava and right atrium</th></tr>
<tr><td>Right ventricle/ left ventricle basal diameter ratio >1.0</td><td>Right ventricular outflow Doppler acceleration time <105msec and/or midsystolic notching</td><td>Inferior cava diameter >21mm with decreased inspiratory collapse (<50% with a sniff or <20% with quiet inspiration)</td></tr>
<tr><td>Flattening of the interventricular septum (left ventricular eccentricity index >1.1 in systole and/or diastole)</td><td>Early diastolic pulmonary regurgitation velocity >2.2m/sec</td><td>Right atrial area (end-systole) >18cm^2</td></tr>
<tr><td></td><td>PA diameter >25 mm</td><td></td></tr>
</table>
Notes: Echocardiographic signs from at least two different categories (A/B/C) from the list should be present to alter the level of echocardiographic probability of pulmonary hypertension.
Source: Galie et al 2015[8]</td></tr>
<tr><td>Whether to estimate mRAP</td><td>The method to estimate RAP can be clinical estimation from jugular venous pressure; using a fixed value from 5mmHg to 10mmHg; or (most commonly) using the diameter and collapse of the inferior vena cava during spontaneous respiration[28]. As a result, the mRAP value can vary depending on the approach used and leads to variable estimates of PAP.</td></tr>
</table>

Table 1.10 Monitoring recommendations and other patient assessments for PAH

Issue	Details
Risk Factors	
Different approaches to risk / prognostic factors	*The 2015 ESC/ERS guidelines[8] divide patients into risk categories according to the summary in Table 1.11.* *McLaughlin et al 2015[29] provided a suggested list of patient risk factors (Table 1.12).* *The US REVEAL risk calculator assigns weighted values for a list of clinical features given in Figure 1.1[33].*
Risk factors – children	Regarding PAH risk factors in children, the 2015 ESC/ERS guidelines state that "*As in adults, clinical evidence of RV failure, progression of symptoms, WHO-FC III/IV and elevated B-type natriuretic peptide (BNP) levels are recognized as being associated with higher risk of death. In children, failure to thrive, haemodynamic parameters such as the mPAP:systemic artery pressure ratio, RAP >10 mmHg and PVR index >20 Wood Units/m^2 have also been associated with a higher risk of death, while the 6MWD was not a prognostic parameter."*
Treatment response (per 2015 ESC/ERS guidelines[8])	
Assessments	*"It is recommended to evaluate the severity of PAH patients with a panel of data derived from clinical assessment, exercise tests, biochemical markers and echocardiographic and haemodynamic evaluations"* – see Table 1.13. The assessments are the same as those to determine risk factors.
Frequency	*"It is recommended to perform regular follow-up assessments every 3–6 months in stable patients"* – see Table 1.13. *"In children, it is recommended RHC should be repeated within 3 to 12 months after initiation of therapy to evaluate response or upon clinical worsening; and thereafter at regular follow-up intervals or upon clinical worsening. In general, follow-up should be made, at a minimum, every 3 to 6 months, or more frequently visits for children with advanced disease or if PAH changing medication"[22, 23].*
Objectives	*"Achievement/maintenance of a low-risk profile is recommended as an adequate treatment response for patients with PAH".* *"Achievement/maintenance of an intermediate-risk profile should be considered an inadequate treatment response for most patients with PAH".*
Clinical worsening	*Clinical worsening is the main indicator of a change in PAH disease status. Time to clinical worsening is frequently included as a secondary endpoint in PAH clinical trials[34](discussed further in TOR4). The guidelines refer to clinical worsening but without offering a definition for use in clinical practice (c.f. clinical trials). Change in exercise capacity and signs of right heart failure will be dependent on frequency of assessment and the margin that is defined as clinically meaningful.*
Treatment goals	*"The goal-oriented treatment strategy utilises different targets, including WHO Functional Class I or II, and the near-normalisation of resting cardiac index and/or of NT-proBNP plasma levels."*

Issue	Details
	Choice of further goals or measures is left to the judgement of the treating physician and is not covered by the guidelines. However, as an illustration, suggested treatment goals for PAH are summarised in McLaughlin et al 2015[29]: Target to reach: WHO Functional Class I or II • Echocardiography/Cardiac MRI normal or near-normal RV size and function • Haemodynamics: normal indexes of RV function, RAP <8 mmHg and cardiac index >2.5 to 3.0 L/min/m^2) • 6MWD distance >380 to 440 m • Cardiopulmonary exercise testing: peak oxygen uptake >15 mL/min/kg and ventilatory equivalents for CO_2 <45 L/min • BNP level: “normal” (determined by local laboratory cut-off values).

There is no single set of criteria recommended to assess PAH risk factors, but the various approaches suggested are similar. These risk factors include parameters determined by RHC (such as cardiac output, mixed venous oxygen saturation (SvO_2) and RAP and by echocardiography (such as tricuspid annular plane systolic excursion (TAPSE) which is a measure of right ventricular function shown to be prognostic for PAH patients[28]).

Table 1.11 Clinical features of high risk vs low risk PAH patients (2015 ESC/ERS Guidelines)

Determinants of prognosis (estimated 1-year mortality)	Low Risk Patients (<5% in 1-year mortality)	Intermediate risk 5–10%	High Risk Patients (>10% 1-year mortality)
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope	Repeated syncope
WHO Functional Class	I, II	III	IV
6MWD	>440m	165-440m	<165m
Cardiopulmonary exercise testing	Peak VO_2 >15 mL/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 mL/min/kg (35–65% pred.) VE/VCO_2 slope 36–44.9	Peak VO_2 < 11 mL/min/kg (<35% pred.) VE/VCO_2 slope ≥45
BNP (ng/L) plasma levels	BNP <50 ng/L NT-proBNP <30 0ng/L	BNP 50–300 ng/L NT-proBNP 300–1400 ng/L	BNP >300 ng/L NT-proBNP >1400 ng/L
Imaging	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No/minimal, pericardial effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 L/min/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 L/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI ≥2.5 L/min/m^2 SvO_2 <60%

BNP = B-type natriuretic peptide; CI = Cardiac Index; NT = N-terminal; Pred. = predicted; RA = right atrial; SvO_2 = mixed venous oxygen saturation; VE/VCO_2 = minute ventilation/carbon dioxide production; RAP = Right Atrial Pressure; VO_2 = Oxygen uptake
Source: 2015 ESC/ERS Guidelines[8]

Table 1.12 Clinical features of high risk PAH patients (USA)

Items	Clinical features of high risk
Syncope	Yes
NYHA/WHO class	IV
6MWD	<300 m
CPET Peak oxygen uptake	<12 mL/kg/min
Echocardiographic findings – Pericardial effusion	Yes
Echocardiographic findings – TAPSE	<1.5 cm
Hemodynamics – RAP	>15 mmHg
Hemodynamics – Cardiac index	≤2 L/min/m^2
Cardiac MRI RVEF	<35%

6MWD = 6-minute walk distance; CPET = cardiopulmonary exercise testing; NYHA = New York Heart Association; RAP = right atrial pressure; RVEF = right ventricular ejection fraction; TAPSE = tricuspid annular plane systolic excursion
Source: McLaughlin et al 2015[29]

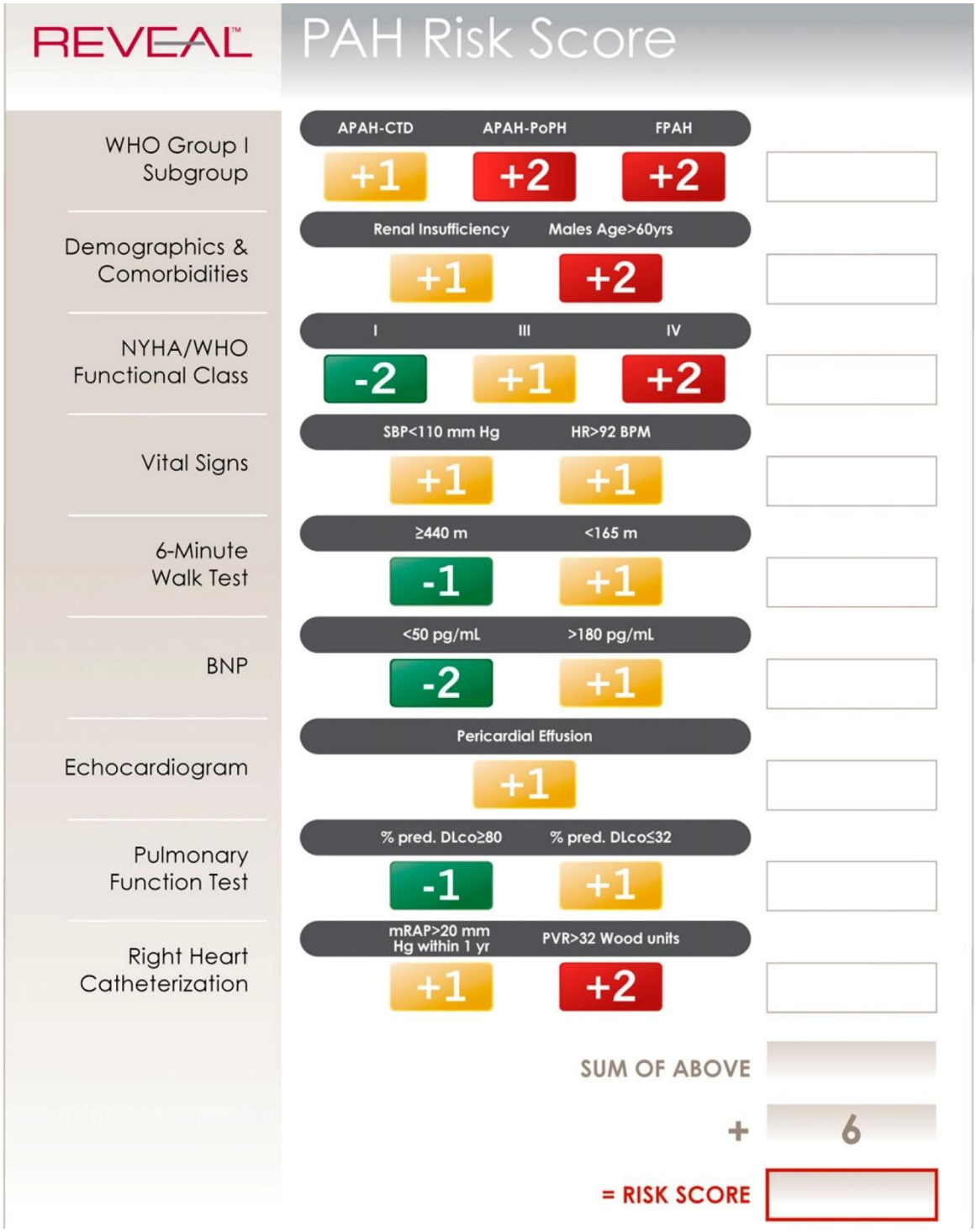


Figure 1.1 REVEAL risk score calculator

Note: Calculated risk scores can range from 0 (lowest risk) to 22 (highest risk). If N-terminal proBNP is available and BNP is not, listed cut points are replaced with < 300 pg/mL and > 1500 pg/mL.
APAH = associated pulmonary arterial hypertension; BNP = brain natriuretic peptide; BPM = beats per minute; CTD = connective tissue disease; DLco = diffusing capacity of lung for carbon monoxide; FPAH = familial pulmonary arterial hypertension; HR = heart rate; mRAP = mean right atrial pressure; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PoPH = portopulmonary hypertension; PVR = pulmonary vascular resistance; REVEAL Registry = Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management; SBP = systolic BP; WHO = World Health Organization.
Source: Benza *et al* 2012[33]

Definition of response and monitoring

The 2015 ESC/ERS Guidelines contains the key recommendations regarding type of tests and frequency of monitoring (Table 1.10 and Table 1.13) – these are based on those for determining patient risk factors and for setting therapeutic goals.

Table 1.13 ESC/ERS suggested assessments and timing for follow-up

Parameters	Baseline	Every 3-6 month	Every 6-12 month	3-6 month after therapy change	On clinical worsening
Medical assessment; determination of Functional class	+	+	+	+	+
ECG	+	+	+	+	+
6MWD + Borg Dyspnoea	+	+	+	+	+
CPET	+	-	+	-	+
ECHO	+	-	+	+	+
Basic lab	+	+	+	+	+
Extended lab	+	-	+	-	+
Arterial blood gas	+	-	+	+	+
RHC	+	-	+*	+*	+*

Basic lab: includes blood count, INR (if on warfarin), serum creatinine, sodium, potassium, aminotransferases (if on ERAs), bilirubin and BNP/NT-proBNP.
Extended lab: includes TSH (thyroid stimulating hormone), troponin, uric acid, iron status (iron, ferritin, soluble transferrin receptor) and other variables according to individual patient needs.
Notes: the intermediate (3-6 mo) interval to be adjusted according to patient need; RHC beyond baseline (*) to be considered but is recommended after therapy change; arterial blood gas can be replaced by oximetry/peripheral oxygen saturation in stable patients.
Source: Galie *et al* 2015[8]

The CADTH review[25] commented that WHO FC improvement may be a less reliable measure of response than clinical worsening, because WHO FC is a single outcome whereas clinical worsening is a composite of multiple factors. The review also commented that there is no minimally clinically important difference that can be defined for clinical worsening. Clinical worsening is understood to be a judgement made by the treating physician, based on the change in monitoring parameters over two or more consecutive visits.

Guidelines recommend that patients should be considered primarily according to progress against therapeutic goals and their risk of poor prognosis when making treatment decisions (an approach that uses WHO Functional Class as a component). Treatment goals are defined as target improvements in specific variables to improve the patient's prognosis or risk category. A patient already on PAH treatment could be low or intermediate risk, with stable disease but with unmet treatment goals. According to guideline recommendations this is sufficient evidence to add another PAH medicine.

1.4.4 PAH treatment centres

The 2015 ESC/ERS Guidelines state "*The interpretation of these [PAH testing] investigations requires, at the very least, expertise in cardiology, imaging and respiratory medicine and may best be discussed at a multidisciplinary team meeting*." A similar statement is included in the US 2014 CHEST guideline[8, 19].

The CADTH review also stated *"[The Canadian Drug Expert Committee] acknowledges that medical specialists working in PH clinics are best suited to prescribe these medications for adults with PAH, given the nature of the disease as well as the complexity and costs of drug regimens"*[25].

The authors of the paediatric guideline concur, stating further that *"children with PH should be evaluated and treated in comprehensive, multidisciplinary clinics at specialised paediatric centres"*[22].

Minimum criteria for referral centres for treatment of PAH patients should be[8]:

- No fewer than 200 adults patients seen per centre per year of which at least half have a final diagnosis of PAH. In countries such as Australia having a population larger than 10◦million, the number should be greater than 300 patients per centre per year;
- The centre should at any time be following at least 50 patients with PAH or CTEPH;
- At least two PAH or CTEPH referrals per month;
- The patient should be seen by a multi-profession team including cardiology and respiratory medicine physicians, clinical nurse specialist, radiologists, psychological and social work support, and other appropriate on-call expertise;
- The centre to perform 20 vasoreactivity tests per year.

1.5 PBS restrictions and TGA indications

1.5.1 TGA indications

Current ARTG registered PAH medicines

Medications registered for PAH in Australia are listed in Table 1.14 with an overview of their approved indications for use in terms of WHO Functional Classes and combination use. Information on paediatric use is also included as this was a significant area where the registered indications, PBS restrictions and clinical guidelines do not align.

Text of registered indications as it appears in the PI for each medicine is reproduced in Table 1.15. The approved indications are either for the whole of Group 1 of the WHO PH classification or for the individual subtypes.

Table 1.14 Overview of registered indications for PAH medicines

Treatment	Aetiology / PAH subtypes	WHO FC	Combination therapy	Children
Macitentan	IPAH, HPAH, PAH-CTD or PAH-CHD	II,III, IV	Yes, approved PAH treatments (PDE-5 inhibitors or prostanoids)	Limited data in children aged 12 and above, none in children <12 years
Bosentan	IPAH, HPAH, PAH-CTD or PAH-CHD	II,III, IV	Clinical benefit of the combination of bosentan and epoprostenol has not been demonstrated Use with sildenafil should be avoided due altered PK	Yes
Ambrisentan	As monotherapy: IPAH, PAH-CTD; With tadalafil: all WHO Group 1 / PAH	Mono: unspecified Combo: II,III, IV	Yes, with tadalafil (WHO Group 1, II/III/IV PAH)	No
Sildenafil	PAH (efficacy has been shown in IPAH and PAH-CTD)	II,III	Concomitant use of riociguat with PDE-5 inhibitors is contraindicated. Efficacy of sildenafil has not been evaluated in patients currently on bosentan.	No
Tadalafil	PAH (efficacy has been shown in IPAH and PAH-CTD)	II,III	Concomitant use of riociguat with PDE-5 inhibitors is contraindicated	No
Riociguat	IPAH, HPAH, PAH-CTD or PAH-CHD	II,III, IV	Yes, approved PAH treatments (ERAs or prostanoids). Concomitant use of riociguat with PDE-5 inhibitors is contraindicated	No
Iloprost	IPAH, PAH-DT, PAH-CTD	Moderate or severe stage	Not mentioned	No
Epoprostenol	IPAH, HPAH, PAH-CTD	III,IV	Not mentioned	No
Selexipag	*IPAH, HPAH, PAH-CTD or PAH-CHD, PAH-DT*	*II,III, IV*	*Yes, patients insufficiently controlled with an ERA and/or a PDE-5 inhibitor*	*No*

ERA = endothelin receptor antagonist; FC = Functional Class; HPAH = heritable pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; 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-DT = drug/toxin-induced pulmonary arterial hypertension; PDE-5 = phosphodiesterase type 5;

Note: selexipag (in grey) is approved but not PBS listed and is not in scope for this Post-Market Review.

Source: Relevant product information documents

Table 1.15 PAH medicines – TGA wording of registered indications

Medicine	Brand	PI Version Date	Registered Indications – extract from Product Information
Bosentan	Tracleer®	15 February 2016	*TRACLEER® is indicated for the treatment of* • *idiopathic pulmonary arterial hypertension* • *familial pulmonary arterial hypertension* • *pulmonary arterial hypertension associated with scleroderma or* • *pulmonary arterial hypertension associated with congenital systemic to pulmonary shunts including Eisenmenger physiology* *in patients with WHO functional Class II, III or IV symptoms.*
Ambrisentan	Volibris®	16 February 2016	*VOLIBRIS® is indicated for the treatment of:* • *idiopathic pulmonary arterial hypertension (PAH),* • *pulmonary arterial hypertension associated with connective tissue disease (PAH-CTD),* • *in patients with WHO functional class II, III or IV symptoms.* *VOLIBRIS® in combination with Tadalafil is indicated for the treatment of WHO Group 1 pulmonary arterial hypertension in patients with WHO functional class II, III or IV symptoms.*
Macitentan	Opsumit®	25 August 2016	*OPSUMIT®, as monotherapy or in combination with approved PAH treatments (phosphodiesterase-5 inhibitors or inhaled prostanoids), is indicated for the treatment of:* • *idiopathic pulmonary arterial hypertension* • *heritable pulmonary arterial hypertension* • *pulmonary arterial hypertension associated with connective tissue disease* • *pulmonary arterial hypertension associated with congenital heart disease with repaired shunts*

Medicine	Brand	PI Version Date	Registered Indications – extract from Product Information
			in patients with WHO Functional class II, III or IV symptoms.
Sildenafil	Revatio®	21 December 2015	*REVATIO® tablets are indicated for the treatment of patients with pulmonary arterial hypertension classified as WHO functional classes II and III, to improve exercise capacity. Efficacy has been shown in primary pulmonary hypertension and pulmonary hypertension associated with connective tissue disease.* *REVATIO® solution for injection is for the treatment of adult patients with pulmonary arterial hypertension who are currently prescribed oral REVATIO® and who are temporarily unable to take oral therapy, but are otherwise clinically and haemodynamically stable.* *The efficacy of REVATIO® has not been established in patients currently on bosentan therapy (see PRECAUTIONS).*
Tadalafil	Adcirca®	18 December 2015	*ADCIRCA® is indicated in adults for the treatment of pulmonary arterial hypertension (PAH) classified as WHO functional class II and III, to improve exercise capacity. Efficacy has been shown in idiopathic PAH (IPAH) and in PAH related to collagen vascular disease.*
Riociguat	Adempas®	17 March 2017	*Pulmonary arterial hypertension* *ADEMPAS®, as monotherapy or in combination with approved PAH treatments (endothelin receptor antagonists or inhaled or subcutaneous prostanoids), is indicated for the treatment of:* • *idiopathic pulmonary arterial hypertension* • *heritable pulmonary arterial hypertension* • *pulmonary arterial hypertension associated with connective tissue diseases or* • *pulmonary arterial hypertension associated with congenital heart disease* *in adult patients with WHO functional Class II, lll or IV symptoms.* *Chronic thromboembolic pulmonary hypertension* *ADEMPAS® is indicated for the treatment of:* *• Persistent or recurrent chronic thromboembolic pulmonary hypertension (CTEPH) after surgical treatment or* *• inoperable CTEPH* *in adult patients with WHO functional Class II, lll or IV symptoms.*

Medicine	Brand	PI Version Date	Registered Indications – extract from Product Information
Epoprostenol	Flolan®	3 February 2016	*FLOLAN® is indicated for the long-term treatment, via continuous intravenous infusion, in WHO functional Class III or Class IV patients with:* • *idiopathic pulmonary arterial hypertension* • *familial pulmonary arterial hypertension* • *pulmonary arterial hypertension associated with the scleroderma spectrum of diseases.*
Iloprost	Ventavis®	16 June 2017	*Treatment of patients with primary pulmonary hypertension or secondary pulmonary hypertension due to connective tissue disease or drug-induced, in moderate or severe stages of the disease. In addition, treatment of moderate or severe secondary pulmonary hypertension due to chronic pulmonary thromboembolism, where surgery is not possible.*
Selexipag	*Uptravi®*	*14 July 2016*	*UPTRAVI® is indicated for the treatment of:* *• idiopathic pulmonary arterial hypertension* *• heritable pulmonary arterial hypertension* *• pulmonary arterial hypertension associated with connective tissue disease* *• pulmonary arterial hypertension associated with congenital heart disease with repaired shunts* *• pulmonary arterial hypertension associated with drugs and toxins* *in patients with WHO functional class II, III or IV symptoms.* *Selexipag can be used in combination therapy in patients insufficiently controlled with an endothelin receptor antagonist (ERA) and/or a phosphodiesterase type 5 (PDE 5) inhibitor, or as monotherapy in patients who are not candidates for these therapies.*

Source: Relevant product information documents

Further details from the current Product Information (PI) for each PAH medicine relevant to this review are given in the Appendices:

- Statements regarding use in combination with other PAH medicines, whether they be registered indications, warnings or contraindications: Appendix 1, Table 1.20.
- Statements regarding use to treat children: Appendix 1, Table 1.21.

Information from the PI relevant to the key issues for this review is summarised in the following sections, also highlighting any key issues that appear in the corresponding product information for these medicines in Europe or the USA.

All PAH medicines currently listed on the PBS are ARTG registered for treatment of patients with WHO FC II PAH, except epoprostenol and iloprost (Class III and IV only). The PDE-5 inhibitors are only approved to treat Class II and III. The other oral medicines are approved for classes II, III and IV. The registered indication for iloprost makes no reference to WHO Functional Class but refers instead to moderate or severe disease. This is assumed to correspond more or less to Class III or Class IV PAH.

Calcium Channel Blockers for PAH

None of the CCBs registered on the ARTG are approved for treatment of PAH. Diltiazem, nifedipine and amlodipine are registered for systemic hypertension and stable angina. Use of high dose CCBs in PAH patients is off-label, although this clinical practice has occurred since at least the early 1990s given the absence of targeted PAH medicines at the time. The situation is the same in overseas markets. The Australian PIs for CCBs do not mention treatment of PAH patients, in particular the high dose regimens recommended for PAH treatment or adverse events associated with it.

PAH guideline dose recommendations and safety warnings for high dose CCB therapy are in Table 1.8 Guideline recommendations regarding high dose CCBs.

Information in the Product Information regarding combination use of PAH medicines

PI statements regarding use in combination with other PAH medicines, including registered indications, warnings and contraindications, are presented in Appendix 1, Table 1.20.

Three PAH medicines are approved in Australia for add-on or combination use:

- Ambrisentan + tadalafil
- Macitentan + PDE-5 inhibitors or inhaled prostanoids
- Riociguat + ERAs or inhaled or subcutaneous prostanoids.

Use in combination with tadalafil is a registered indication for ambrisentan and this is reflected in supporting information in the PI. The PI for tadalafil is silent on this particular combination and makes no mention of ambrisentan.

The PIs of PAH medicines contain several warnings and contraindications regarding certain combinations:

- Contraindication: Riociguat + PDE-5 inhibitors (tadalafil; sildenafil), due to high risk of hypotensive effects, especially syncope, and lack of incremental clinical benefit.
- Precaution: Bosentan + sildenafil, due to the altered pharmacokinetics of both drugs when co-administered.

Riociguat is contraindicated for co-administration with both sildenafil and tadalafil as it may lead to symptomatic hypotension including syncope. This is a contraindication not merely a precaution. The PI states this is due to: (1) the high rate of discontinuations due to hypotension in patients receiving this combination, along with; (2) the lack of evidence for any clinical benefit compared with monotherapy (sildenafil).

The approved indications for macitentan and riociguat refer to use in combination with inhaled and/ or subcutaneous prostanoids, specified by their route of administration. Only one inhaled prostanoid is available in Australia (iloprost), and no subcutaneous prostanoids.

The two prostanoids and riociguat each involve a dose initiation phase, with monitoring for adverse effects / haemodynamic variables and dose titration accordingly. In principle, patients should be stabilised on one agent first before commencing with dosing of the second. A 2017 report by Strange *et al*[14] defined initiation of two PAH medicines within 30 days as initial combination therapy though it is unknown if this is representative of current clinical practice in Australia.

<u>Drug interactions between ERAs and PDE-5 inhibitors</u>

Both ambrisentan and macitentan are approved for use with one or more PDE-5 inhibitors. Bosentan is not approved in Australia for any combination use.

Bosentan has been shown to interact with sildenafil, altering the pharmacokinetics of both molecules[35]. A study in healthy volunteers resulted in a 63% decrease in sildenafil AUC and a 50% increase in bosentan AUC. In effect, without dose adjustment patients are overdosed on bosentan (which could result in increased side effects especially to do with bleeding or hepatotoxicity) but underdosed with sildenafil (potentially resulting in a less-than-clinically effective dose).

These PK effects have been observed in other studies of patients (for example Paul *et al* 2005[36]). According to the sildenafil PI, the effect is likely due to induction by bosentan of cytochrome P450 enzymes that metabolise sildenafil, specifically CYP3A4.

Nevertheless, bosentan + sildenafil is a common combination therapy used to treat PAH patients in Australia. This is reportedly driven by the low cost of sildenafil if added as second agent via a private script (e.g. Moonen *et al* 2017[12]). It is not known if/how physicians are managing the PK effects when giving sildenafil and bosentan in combination (for example, through dose adjustment or monitoring).

Interactions between bosentan and tadalafil have also been studied – the PI for tadalafil reports that co-administration with bosentan also results in a 42% decrease in tadalafil systemic exposure but not for bosentan or its metabolites. Although this information is included in the tadalafil PI, there is no recommendation against combination use of these two PAH medicines specifically.

There is no similar warning in the bosentan PI, though there is a guarded statement in the PRECAUTIONS under 'theoretical interactions'. The PI states *"TRACLEER® is an inducer of the cytochrome P450 isoenzymes CYP2C9 and CYP3A4.[…] plasma concentrations of drugs metabolized by these isoenzymes will be decreased when TRACLEER® is co-administered"*. Note that this includes sildenafil and tadalafil. Although this is described as a theoretical interaction, for tadalafil, this has been confirmed in patients[35].

These PK effects have not been reproduced with other ERAs. The ambrisentan PI states "Co-administration of ambrisentan with a phosphodiesterase inhibitor, either sildenafil or tadalafil (both substrates of CYP 3A4) in healthy volunteers did not significantly affect the pharmacokinetics of ambrisentan or the phosphodiesterase inhibitor".

Co-administration of ambrisentan with tadalafil does however lead to a modest increase in anaemia and peripheral oedema compared with monotherapy of either agent.

A modest elevation of sildenafil is observed on co-administration with macitentan, though the macitentan PI states that this was not considered clinically relevant. Furthermore, and although this is not in the macitentan PI, the European product information states that macitentan is not an inducer or an inhibitor of any cytochrome P450 enzymes (Summary of Product Characteristics (SmPC) dated 8 February 2017[37]).

Paediatric use

Of the TGA approved medicines for PAH, only bosentan is registered to treat PAH in children. The PIs for the other PAH medicines contain recommendations against treatment of children. Macitentan's PI also states "*There is no data available on the effects of macitentan on growth and development in paediatric patients. There is limited clinical experience in paediatric patients aged 12 and above*".

PI statements regarding use to treat children are presented in Appendix 1, Table 1.21 for each of the PAH medicines.

1.5.2 PBS prescribing restrictions

The PBS restrictions for PAH medicines were introduced in the Background to this report:

The current PBS listings have these general features:

- All PAH medicines are listed for treatment of both WHO FC III and Class IV disease, with these exceptions:
- The PDE-5 inhibitors are listed for WHO FC Class III treatment only;
- The prostanoids are listed for treatment of Class III patients in second line (except iloprost for drug-induced PAH), their use treating Class IV disease is first line.
- All PAH medicines are listed for treatment of IPAH, heritable PAH, drug and toxin induced PAH and PAH-CTD.
- Only bosentan, macitentan and riociguat are listed for PAH-CHD. These three drugs are listed for the same suite of indications. Neither epoprostenol nor iloprost are listed for PAH due to CHD.
- All PAH clinical criteria are silent regarding age group, in effect allowing for treatment of children (i.e. under 18 years old).
- Since 2014 the current restrictions have referred to three subtypes as a group (*B.4.5.3 Recent amendments to* PBS Restrictions), IPAH, anorexigen-induced PAH and hereditable PAH, to replace the older term “primary pulmonary hypertension”.
- A further subtype, ‘drug-induced PAH’ is specific to iloprost, and is separate to ‘anorexigen-induced PAH’ in the iloprost restriction. This enables use of iloprost as first line treatment in WHO FC III patients with this subtype. Note below that iloprost is the only PAH medicine that is TGA approved with clinical evidence for drug-induced PAH.

A grid showing current ARTG indications and PBS listings in terms of PAH subtype is given in Table 1.16 (not taking WHO FC into account).

- ‘☑✚’ shows medicines where the TGA indication matches the PBS restriction, noting that grey ticks indicate that the clinical evidence base is in a different subtype;
- ‘✖⭘’ indicates where the medicine is neither registered nor PBS listed for that indication. This only applies to PAH-CHD (for ambrisentan monotherapy; iloprost and epoprostenol). By this measure, congenital heart disease patients have fewer treatment options compared with other subtypes;

- '✖✚' indicates that the indication is not registered but is PBS listed for that medicine. This applies to the majority of listings for drug induced PAH, and also iloprost for heritable PAH and ambrisentan monotherapy for PAH-CTD.

Table 1.16 Alignment of ARTG indications with PBS listings (not accounting for WHO FC)

Treatment	IPAH	HPAH	PAH-CTD	PAH-CHD	PAH-DT
Macitentan	☑✚	☑✚	☑✚	☑✚	✖✚
Ambrisentan: monotherapy	☑✚	✖✚	☑✚	✖✪	✖✚
Ambrisentan: with tadalafil[a]	☑	☑	☑	☑	☑
Bosentan	☑✚	☑✚	☑✚	☑✚	✖✚
Sildenafil[b]	☑✚	☑✚	☑✚	☑✪	☑✚
Tadalafil[b]	☑✚	☑✚	☑✚	☑✪	☑✚
Riociguat	☑✚	☑✚	☑✚	☑✚	✖✚
Iloprost	☑✚	✖✚	☑✚	✖✪	☑✚
Epoprostenol	☑✚	☑✚	☑✚	✖✪	✖✚

☑ = ARTG registered indication; ✖ = not an ARTG registered indication; ✚ = PBS indication; ✪ = not PBS listed for this indication
a: Ambrisentan with tadalafil (strikethrough)l is not permitted on the PBS
b: Sildenafil and tadalafil are indicated for PAH in general (in grey) – efficacy shown only in IPAH and PAH-CTD (in black)

Further details of the PAH restrictions are tabulated with comments in Appendix 1:

Table 1.22 Clinical criteria and prescribing instructions common to all PAH items

Table 1.23 PAH initial treatment: clinical criteria and prescribing instructions

Table 1.24 PAH continuing treatment: clinical criteria and prescribing instructions

Table 1.25 Administrative information in PAH items

Architecture of current PAH items on the PBS

All PAH drugs are listed under Section 100 of the Schedule as Highly Specialised Drugs – these are 'hospital only' items. PAH items are also 'complex authority required' (CAR), that involve application to the Services Australia Complex Drugs.

Each restriction has core clinical criteria that must be satisfied for each patient, and requirements in prescribing instructions that prescribers must address in a written application which require a patient narrative and/or diagnostic results.

Complex written authorities are typically imposed on those PBS listings where some or all of the following issues apply:

- The medicine is new and clinical practice is still adapting to accommodate it;

- The medicine requires prescribing by specialists with particular experience or training in the patient group that not all specialists in that area may have;
- There is a high risk to the Commonwealth of use outside the patient group that PBAC considers to be cost-effective ('leakage'); and
- The price of the drug is high (and listing is accompanied by a risk share agreement between the Sponsor and the Commonwealth).

Within each PBS item, separate restrictions are included for different purposes that cover initial treatment, switching, grandfathering, balance of supply (where the dispensed quantity has been insufficient), continuing treatment and cessation of treatment (to allow for dose reduction). There are in some cases further distinctions within each of those purposes; for example where initial patients fall into different PAH types or WHO FC. A detailed break-down of items in terms of these features is Appendix 1.D Details of PAH restrictions.

'Balance of supply' and 'subsequent continuing' treatment applications can be made by telephone ('telephone authorities') but all 'initial' treatment and 'first continuing' treatment applications must be in writing.

The three types of PAH initial treatment items are for the following purposes (with the exception of epoprostenol):

- 'Initial 1' that requires trial and failure of vasodilator treatment with CCBs in Class III patients with mean right atrial pressure of 8 mmHg or less;
- 'Initial 2' in which prior vasodilator treatment with CCBs is not required, but only in Class III patients whose mean right atrial pressure is greater than 8 mmHg, or Class IV patients (where listed for that agent and indication), and
- 'Initial 2 or 3' which provides for re-commencement or switching between PAH medicines (under certain circumstances only).

At least one report in the medical literature refers to the "administrative and repeat testing burden" of the current PBS restrictions, but notes that the introduction of the 'subsequent continuing' restriction does reduce this (evidence of response no longer required to be provided in writing in patients who have demonstrated a response to initial and first continuing treatment)[13]. Another paper which reported the initial experience of the first multi-disciplinary regional PAH clinic in Australia describes 'submission of PBS-related paperwork' as one of the key functions of the rheumatology nurse for their PAH clinic[38].

All applications for complex drugs are handled by the Services Australia office responsible for Complex Drugs (located in Hobart) – both written and telephone applications. Services Australia practices in administering these items were not within the scope of this review.

1.5.3 PAH therapy recommendations

The PBS restriction requirements (in terms of therapy with PAH medicines) are presented with commentary in Table 1.17. Those specific to vasodilator therapy with CCBs are in Table 1.18. Selected issues are discussed further below. Restriction requirements and commentary regarding diagnostic and monitoring criteria are in Table 1.19.

More complete text of the restriction elements is in the more detailed tables in Appendix 1.D (Table 1.22; Table 1.23; Table 1.24; Table 1.25), along with a number of minor comments not included herein.

Treatment of patients with PAH medicines according to WHO FC status

Current PBS requirement

The current PAH restrictions are subject to the following clinical criteria:

Patient must have WHO Functional Class III, OR

Patient must have WHO Functional Class IV

In addition, different PAH items reflect these principles:

- PDE-5 inhibitor restrictions are for WHO FC III only, consistent with TGA status.
- Epoprostenol is listed first line for WHO FC IV and second line for WHO FC III.
- Iloprost is listed to treat drug-induced PAH in WHO FC III patients, other indications are for WHO FC IV patients.

Guideline recommendations

Current guidelines recommend that treatment of patients who have WHO FC II disease with oral PAH medicines is recommended as standard of care. Those who are eligible to receive high dose CCBs are only a small subset of PAH patients. Also:

- Oral PAH medicines should be used in patients with WHO functional Class II disease. This is the standard of care in these patients.
- In line with the registered clinical indications, prostacyclin analogues (prostanoids) are not recommended for the treatment of WHO FC II patients, and typically not for patients with WHO FC III status in the absence of high risk factors. However, patients with advanced PAH or presence high risk factors should be treated with treatment including a prostanoid, without reference to line of therapy.
- PDE-5 inhibitors are recommended for patients with WHO FC IV disease but the evidence base is weaker.

Use of PAH medicines in combination

Current PBS requirement

The current PBS restrictions specify that treatment must be the sole PBS-subsidised PAH agent for this condition. This is distinct from 'as monotherapy', which appears in PBS restrictions for other medicines (and precludes any co-administration at all).

Patients who fail to demonstrate a response must cease therapy with that medicine.

Guideline recommendations

Monotherapy remains indicated for treatment naïve PAH patients, with the exception of certain patients who may benefit from initial combination treatment, primarily those with more advanced PAH or with signs of poor prognosis.

Sequential combination therapy is recommended as standard of care in patients already on PAH medicines but who are failing to meet their therapeutic targets or those who have poor prognostic / high risk factors. Use is recommended of up to three PAH medicines, each from a different drug class. This suggests patients who fail to respond should continue the current treatment, in contrast with the current requirement to cease therapy with that medicine.

Current TGA indications for combination therapy, contraindications and a discussion of potential drug interactions between PAH medicines are in **Information in the PI regarding combination use of PAH medicines**.

Table 1.17 Restriction criteria considered in this review

Clinical Criteria or Prescribing Instruction	Guideline Recommendations	Consistent with Guidelines?
The PAH restrictions cover the subsidised conditions as follows: IPAH Anorexigen-induced PAH Hereditable PAH Drug-induced PAH PAH secondary to connective tissue disease including scleroderma PAH associated with a congenital systemic-to-pulmonary shunt (including Eisenmenger physiology)	Discussed in *PAH treatment algorithm*	Yes or partially. All the PAH subtypes or aetiologies eligible for PBS funded treatment fall within Group 1 of the WHO classification, with the exception of PAH associated with schistosomiasis, HIV infection or portal hypertension which are not covered as the PBAC has not considered submissions for these subtypes. Treatment recommendations for all Group 1 conditions are broadly similar with regard to choice of PAH medicines including PAH due to HIV or portal hypertension. Schistosomiasis does not occur in Australia except in travellers returning from incident areas such as Brazil. See separate comments regarding current *PAH classification and terminology.*
[Clinical criteria no longer specify adults or any age group restrictions]	See *Paediatric use*.	Yes, though no age-appropriate pharmaceutical forms or dosage strengths are listed for young children. See *Paediatric use*.
Patient must have WHO Functional Class III [PAH subtypes], OR Patient must have WHO Functional Class IV [PAH subtypes]	See Table 1.7 Guideline recommendations supporting the therapy pathways.	No. See *Treatment of patients with PAH medicines according to WHO FC status*
The treatment must be the sole PBS-subsidised PAH agent for this condition	See Table 1.7.	No. See *Use of PAH medicines in combination*
Patients who fail to demonstrate a response to PBS-subsidised treatment with this agent at the time where an assessment is required must cease PBS-subsidised therapy with this agent.	See Table 1.7.	No. See *Use of PAH medicines in combination*
The maximum quantity authorised will be limited to provide sufficient supply for 1 month of treatment, based on the	–	Comment: As with most PBS listings for chronic conditions, each PAH authority application is intended to provide six months' treatment, that is, a maximum quantity of one month's supply per script plus five repeats. The PAH listings include a statement that one month's

dosage recommendations in the TGA approved Product Information. A maximum of 5 repeats will be authorised.		treatment must be defined according to the information in the approved TGA Product Information. Normally this would be left to prescribers to manage in the course of clinical practice. It is not stated how this should be defined for PAH items that allow for (or are silent on) paediatric use but where the PI only provides dosing information for adults. In cases where the proposed amount is insufficient, prescribers must use a balance of supply item to prescribe the remainder to make up the total for a 6 month course. Many of the PAH medicines require dose adjustment or dose titration, but it is not known whether this leads to repeated use of the balance of supply items in practice. The guidelines make almost no dosing recommendations, with the exception of those discussed in the text regarding sildenafil – see *Dosage* *Current PBS requirement* The current PBS restrictions specify that doses to inform maximum quantities for prescribing are limited to the recommended dose in the approved PI. <u>Guideline recommendations</u> The majority of guideline recommendations are to do with choice of agent rather than the dose. The 2015 ESC/ERS Guidelines report doses that are approved by regulators or that have been effective in clinical trials, but makes no dosing or dose adjustment recommendations aside from those regarding use of sildenafil in children. The CHEST guideline[19] also makes few comments with respect to dose adjustments – the only one of note relates to sildenafil in adults (below). Note regarding sildenafil dosage (adults) and *Use of sildenafil for PAH in children* (children)
PAH agents are not PBS-subsidised for patients with pulmonary hypertension secondary to interstitial lung disease associated with connective tissue disease, where the total lung capacity is less than 70% of predicted.	–	Yes, however, it is not clear why this but not other ‘non-Group 1’ PH conditions are included in this note. PH due to interstitial lung disease is a WHO Group 3 condition. It is one of a number of conditions, such as CTEPH, PPHN or PH due to left heart disease, for which treatment recommendations are different to those for WHO Group 1 causes of PAH. No other conditions are included in this restriction note. This statement dates from the original March 2004 listing of bosentan.

Table 1.18 PBS criteria for vasodilator therapy with CCBs

Clinical or Prescribing Instruction	Guideline Recommendations	Consistent with Guidelines?
Initial 1: Patient must have a mean right atrial pressure of 8 mmHg or less as measured by right heart catheterisation (RHC);OR Patient must have right ventricular function assessed by echocardiography (ECHO) where a RHC cannot be performed on clinical grounds Initial 2: Patient must have a mean right atrial pressure of greater than 8 mmHg, as measured by right heart catheterisation (RHC) OR Patient must have WHO Functional Class III [PAH sub-type] with right ventricular function assessed by echocardiography (ECHO) where a RHC cannot be performed on clinical grounds.	Guideline recommendations in Table 1.8.	No. The 8 mmHg RAP by RHC is being used as an eligibility criterion for vasodilator treatment with CCBs – this is not recommended. The 8mmHg threshold in the PBS restrictions is one of a range of clinical features of low risk patients (the normal range is 1-6 mmHg). Though only in WHO FC I or II PAH would this be consistent with an assessment of low risk (the PBS restrictions cite this value in reference to WHO FC III patients). The mRAP of any value is not recommended as a sole basis for making any treatment decisions and it is not a criterion for determining whether CCBs are indicated. The alternative measure specified is the assessment of right ventricular function by echocardiography. Neither of these criteria are recommended to determine eligibility for vasodilator therapy with CCBs.
Response to prior vasodilator treatment with CCBs is defined as follows: For patients with 2 or more baseline tests, response to treatment is defined as 2 or more tests demonstrating stability or improvement of disease, as assessed by a physician from a designated hospital. For patients with a RHC composite assessment alone at baseline, response to treatment is defined as a RHC result demonstrating stability or improvement of disease, as assessed by a physician from a designated hospital. For patients with an ECHO composite assessment alone at baseline, response to treatment is defined as an ECHO result demonstrating stability or improvement of disease, as assessed by a physician from a designated hospital. For patients aged less than 18 years, response to treatment is defined as at least one of the baseline tests demonstrating	Guideline recommendations in Table 1.8.	Partially. These are the same criteria as definition of a response to PAH agent. Assessment of response would not be limited to RHC, but would include monitoring parameters given in Table 1.8. Patients without RHC at baseline would not be eligible to receive vasodilator treatment with CCBs as RHC is required to administer the acute vasoreactivity test to establish if patients are likely to respond to CCBs. However, somewhat different criteria apply for high dose CCBs. Patient should demonstrate near normalisation of symptoms.

stability or improvement of disease, as assessed by a physician from a designated hospital.		
Patient must have failed to respond to 6 or more weeks of appropriate vasodilator treatment with CCBs unless intolerance or a contraindication to such treatment exists.	See Table 1.8.	No/unclear. The 2015 ESC/ERS Guidelines recommend complete re-assessment at 3-6 months. If the purpose of this vasodilator trial is solely to rule out CCBs and proceed to PAH medicines, 6 weeks may not be adequate.
Details of prior vasodilator treatment with CCBs, including the dose and duration of treatment, must be provided at the time of application. Where the patient has an adverse event to a CCB or where vasodilator treatment with CCBs is contraindicated, details of the nature of the adverse event or contraindication according to the TGA approved Product Information must also be provided with the application.	–	No. It is not clear what criteria the dose and duration reported here would be measured against. This is off-label use for CCBs. The TGA Product Information does not cover adverse events or contraindications relevant to high dose CCB treatment for PAH (though it is likely to be overlapping with those for lower dose therapy for angina or heart failure). Contraindications may exist that would not be outlined in the current PI.

Dosage

Current PBS requirement

The current PBS restrictions specify that doses to inform maximum quantities for prescribing are limited to the recommended dose in the approved PI.

Guideline recommendations

The majority of guideline recommendations are to do with choice of agent rather than the dose. The 2015 ESC/ERS Guidelines report doses that are approved by regulators or that have been effective in clinical trials, but makes no dosing or dose adjustment recommendations aside from those regarding use of sildenafil in children.

The CHEST guideline[19] also makes few comments with respect to dose adjustments – the only one of note relates to sildenafil in adults (below).

Note regarding sildenafil dosage

The sildenafil PI features clinical data from a number of studies where doses of 80 mg or more were administered to patients. Sildenafil is being used overseas at doses in adults beyond the approved recommended dose (20 mg three times a day) and it is likely that doses up to 100 mg tid are being prescribed for PAH in Australia.

In the UK, the NHS Commissioning guidance in the guidelines search (see *Guidelines*) states that the following doses will be funded for sildenafil in patients with PH:

i) As Viagra tablets (unlicensed indication): for dose escalation 25-100 mg tid
ii) As Revatio® tablets: for use only at licensed dose of 20 mg tid

The CADTH made a similar observation in its 2015 report, that clinicians in Canada would start with 20 mg tid but increase the dose to 80 mg tid or more in practice[25].

The Australian PI states that *"no greater efficacy was achieved [in clinical trials] with doses higher than 20 mg tid."* Sildenafil is frequently described in the PAH literature as having a comparatively mild toxicity profile, but it is unknown if this would apply to long-term dosing at high levels. The 2015 ESC/ERS Guidelines[8] contain no recommendations regarding doses higher than 20 mg tid however, the CHEST guideline[19] does suggest exploring higher doses:

"Titration of therapy up to 80 mg tid has been done in clinical trials and a dose response in hemodynamic response has been noted. In patients who fail to demonstrate and maintain an adequate clinical response to 20 mg sildenafil tid, we recommend consideration of increasing the dose in 20 mg increments to a maximum of 80 mg tid or adding another agent".

Paediatric use

Current PBS requirement

All the current PBS restrictions provide for treatment of paediatric patients. The clinical criteria are silent on the age group and though adults were specified in some items in the past, this has since been removed. Further, the definition of response to treatment for all PAH medicines listed provides criteria specific to patients under 18 years.

At least some of the PBS restrictions refer to dosing and adverse events criteria in the PI of relevant PAH medicines. With the exception of bosentan it is not clear that the PIs would reflect the correct information for children.

Guideline recommendations

The 2015 ESC/ERS Guidelines state that: *Sildenafil has shown efficacy and has been approved in Europe for children 1–17 years of age. Increased mortality using high doses has raised concerns; therefore high doses should not be used in children (high individual doses of sildenafil on a three daily dosing not recommended: 10 mg/dose with a bodyweight of 8-20 kg, 20 mg/dose in children with a bodyweight >20 kg or 1 mg/kg/dose in infants and small children).*

The CHEST Guideline states that it makes no recommendations for children, referring instead to the Ivy et al., guideline[23].

Pharmaceutical forms

PAH medicines that are available as tablets (ERAs, PDE-5 inhibitors and riociguat (also selexipag)) would need to be compounded by the pharmacist for children unable to swallow a tablet or where appropriate low-dose strengths are unavailable. Compounded medicines are not eligible for PBS subsidy and must be obtained on a private script (or through schemes that may be available through treating hospitals). Few community pharmacies offer compounding and for those that do, the typical cost per script for a compounded oral suspension can be $70-$90 per script.

Private scripts do not contribute to safety net thresholds nor are they eligible for concessions. Alternatively, the PBS-subsidised tablets may be crushed and suspended for each dose by the patient's carer (if an age-appropriate tablet strength is available). Pharmaceutical forms suitable for paediatric administration that are available overseas, such as oral solutions, are not on the market in Australia. Product information for Europe and the USA show that, in both regions, sildenafil is available as powder for oral suspension and bosentan is available as a dispersible tablet. The bosentan dispersible tablet is a lower strength 32 mg tablet that is also 'quadrisectable' into 8 mg portions to enable dosing of young children with a correspondingly small body weight.

Other PI statements regarding children

The current Australian PI for riociguat states that it has not been studied in children and is therefore not recommended. The European Public Assessment Report (EPAR, 23 January 2014) goes further, and comments that effects of riociguat on bone growth have been observed in both mouse and rat toxicology studies. The EPAR advises *"The implications of the adverse effects on bone encountered in growing rats on paediatric patients in whom the epiphysis is not yet closed are not clear. Until more is known, the use of riociguat in children and in growing adolescents should be avoided"*.

Use of sildenafil for PAH in children

During preparation of this report it became evident there is a large volume of published literature regarding use of sildenafil in children with PAH.

In 2011 Pfizer sought to extend the indication for sildenafil to include children (1-17 years) and made applications to the TGA[39] and regulatory authorities overseas.

Pfizer's application to the TGA proposed extemporaneous compounding of a 10 mg/mL oral solution for children unable to swallow a tablet, prepared from 62 x 20 mg Revatio® tablets (the Australian public assessment report (AusPAR) notes that the same solution could also be prepared using only 12 x 100 mg Viagra tablets). The application was subsequently withdrawn and Revatio® remains approved for use only in adults in Australia.

Pfizer's application to the US Food and Drug Administration (FDA) was for a similar indication but different oral dosage form. Three paediatric clinical trials including one open label extension study have been performed to investigate sildenafil (as Revatio®) in children with PAH. These studies found a trend toward increased risk of mortality in children. In addition, this trend was dose-related and associated with long-term use. There was also a suggestion that doses without the risk of these consequences may not be clinically effective. In 2012 the FDA issued a safety warning in relation to this finding[40] and required warnings to be included in the Product Label with clinical trial data in the Prescribing Information (equivalent to the Product Information). The FDA initiated a full safety and clinical review which it referred to its Paediatric Advisory Committee (meeting of 24 March 2015)[41]. The outcome of this review is that paediatric powder for oral solution remains approved but the extension of indication is not.

The current US Product Label states "Increased mortality with increasing doses in pediatric patients. Not recommended for use in pediatric patients." The FDA has since defended its decision, stating that "health care professionals must consider whether the benefits of treatment with the drug are likely to outweigh its potential risks for each patient."[42]

In Europe, the European Medicines Agency (EMA) took a different view and approved sildenafil for PAH in children. The recommended dose in children weighing ≤ 20 kg is 10 mg tid and for patients > 20 kg it is 20 mg tid (the same as the adult dose). The SmPC notes the

mortality risk and warns that higher doses should not be used. Equivalent information is not contained in the Australian PI.

On a related point, Pfizer submitted to the EMA two clinical trials performed in children with its IV sildenafil formulation (one in children post-surgery with heart defects and a second in neonates with PPHN)[43]. As the clinical data are in the public domain and the IV form is now registered in Australia, it is possible that IV sildenafil would be used off-label for these indications.

Prior vasodilator therapy with CCBs

Current PBS requirement

The current PAH restrictions (Table 1.18) require a trial and failure of vasodilator therapy with CCBs prior to commencement on PAH medicines in all WHO FC III patients whose (mRAP by RHC is 8 mmHg or less. This is not required for access to PBS epoprostenol, but applies to iloprost (drug-induced PAH only) and the oral PAH medicines (for all PAH subtypes except PAH-CHD). This requirement does not apply to patients with WHO FC IV disease, or those exceeding the mRAP threshold. The 2015 DUSC review noted that PHSANZ has previously queried this value as a criterion for CCBs treatment. Further comments are in Table 1.18.

Since the requirement for a trial of CCBs was first introduced (with the listing of bosentan in March 2004), the clinical place for both CCBs and PAH medicines has changed. High dose CCB therapy is indicated only in a limited patient subset due to safety concerns whereas oral PAH medicines have become the mainstay of clinical practice.

Guideline recommendations

According to guidelines reviewed, high dose CCB treatment is indicated for WHO FC II or lower risk WHO FC III patients with IPAH, heritable PAH (HPAH) and drug-induced PAH (see Table 1.8). Recommendations were limited to only three drugs, diltiazem, nifedipine and amlodipine, and did not extend to any other CCBs. Patients with the suitable PAH subtypes that are likely to benefit from CCBs must be assessed by acute vasoreactivity testing. CCBs should not be used in the absence of a demonstrated positive result to acute vasoreactivity challenge. Patients with no positive vasoreactivity test, those with other types of PAH, and in higher risk categories, should be commenced on targeted PAH medicines.

The 2015 ESC/ERS guidelines[8] observe that in all other forms of PAH, vasoreactivity results can be misleading, responders are rare and that only one in ten IPAH patients are likely to benefit from CCB treatment. It stated further that CCBs were not appropriate for patients with Eisenmenger physiology. No guidelines recommend CCBs for PAH-CTD.

There is a risk of hypotensive adverse events from high dose CCBs in unsuitable patients. The severity of potential hypotensive effects on the one hand and the lack of benefit in unsuitable patients on the other has led to strongly worded guideline recommendations on

the circumstances in which CCBs are indicated, due to the risks to patient safety (Table 1.7). Further details including contraindications to CCBs and also to vasoreactivity testing, haemodynamic definition of response are in Table 1.7.

Pricing context

Dihydropyridine CCBs (felodipine, lercanidipine, nifedipine, amlodipine), and the benzothiazapine drug diltiazem, are unrestricted benefits with a DPMQ per script (for approximately one month's treatment) that is well under the current patient co-payment threshold of $39.50 (as of 1 January 2018).

At the time that the first PAH drug bosentan was listed on the PBS in March 2004, CCBs were already listed as unrestricted benefits, and dihydropyridine derivatives were priced as a therapeutic group (that is, the price was set by the lowest price medicine in the group based on the Therapeutic Group Premium Policy). Although these medicines were marginally more expensive in March 2004 than their present day listings, these CCBs still cost no more than $40 per script at that time. In contrast, when it was first listed in 2004 the DPMQ for bosentan was $4035. DPMQs for PAH medicines (current at December 2017) are given in Appendix 1.B, Table B.9.

There have previously been Special Pricing Arrangements in place for several of the PAH medicines including ambrisentan bosentan and iloprost, however currently only riociguat continues to have a Special Pricing Arrangement. The main reason for the Commonwealth to enter into a Special Pricing Arrangement for the supply of a medicine is so that Australia is able to have access to medicines at a lower cost-effective price without affecting the price for the product in other markets resulting in a 'published' versus 'effective' pricing component. The difference between the published price in the Schedule of Pharmaceutical Benefits and the price actually paid by the Commonwealth (the 'effective' price), is managed through a rebate arrangement.

Table 1.19 Restriction criteria for diagnostic tests and monitoring considered in this review

Clinical or Prescribing Instruction	Guideline Recommendations	Consistent with Guidelines?
[PAH sub-type] defined as follows: (i) mean pulmonary artery pressure (mPAP) greater than 25 mmHg at rest and pulmonary artery wedge pressure (PAWP) less than 15 mmHg;	See PAH haemodynamic definition in Table 1.9.	Yes – this reflects the current haemodynamic definition for PAH diagnosis and has been recently updated (see *B.4.5.3 Recent amendments to* PBS Restrictions).
[PAH sub-type] defined as follows: (ii) where a right heart catheter (RHC) cannot be performed on clinical grounds, right ventricular systolic pressure (RVSP), assessed by echocardiography (ECHO), greater than 40 mmHg, with normal left ventricular function.	See PAH haemodynamic definition; RHC contra-indications and Clinical features suggestive of PAH in Table 1.9.	No. It is unlikely that the echocardiographic criterion (ii) is current. The current guidelines recommend measurement of peak TRV as the key echocardiographic variable predictive of PAH. If RHC is contraindicated, clinical features suggestive of PAH on echocardiography are given in Table 1.9 Guideline diagnostic recommendations for PAH and while a number of similar parameters are cited, RVSP is not among them.
The restrictions no longer require mPAP obtained during exercise.	–	Yes. This has recently been removed from the PAH restrictions (see *B.4.5.3 Recent amendments to* PBS Restrictions). This reflects a corresponding move away from exercise testing in the guidelines.
Test requirements to establish baseline for initiation of treatment are as follows: • A right heart catheter (RHC) composite assessment • An echocardiograph (ECHO) composite assessment, • A 6 minute walk test (6MWT).	See Table 1.10.	Partially. RHC is the gold standard for diagnosis and is essential for diagnosis and baseline characteristics. If RHC results are available, evidence of echocardiography may not be required as it should also have been as part of the work-up for RHC. The 6MWD criterion reflects the use of this measure as an endpoint for clinical trials in PAH but this parameter is not diagnostic of PAH and is only one of a panel of baseline assessments. This parameter is not considered prognostic in children, though it may prove informative for monitoring of exercise capacity in some children. Also discussed in main text.
Where it is not possible to perform all 3 tests above on clinical grounds, the following list outlines the preferred test combination, in	See RHC contraindications and Clinical	No. Echocardiography should be performed prior to RHC thus availability of RHC without echocardiography would be unusual. Given that ECHO is a non-invasive imaging test conducted at rest there are relatively few obstacles to conducting this in a PAH patient.

descending order, for the purposes of initiation of PBS-subsidised treatment: (1) RHC plus ECHO composite assessments; (2) RHC composite assessment plus 6MWT; (3) RHC composite assessment only. In circumstances where a RHC cannot be performed on clinical grounds, applications may be submitted for consideration based on the results of the following test combinations, which are listed in descending order of preference: (1) ECHO composite assessment plus 6MWT; (2) ECHO composite assessment only. Where fewer than 3 tests are able to be performed on clinical grounds, a patient specific reason outlining why the particular test(s) could not be conducted must be provided with the authority application.	features suggestive of PAH in Table 1.9.	These requirements remain largely unchanged from their first appearance with the listing of bosentan in March 2004. RHC is considered essential for diagnosis of PAH (based on reading of the guidelines), there are some contraindications but it is unlikely that many patients will be diagnosed without RHC. If RHC is contraindicated however, clinical features suggestive of PAH on echocardiography are given in Table 1.9 Guideline diagnostic recommendations for PAH. See comments above regarding 6MWD – see also main text.
Patient must have been assessed […] to have achieved a response to the PBS-subsidised initial course of treatment.	See Table 1.9 and specifically frequency of assessments in Table 1.13.	The need for a response – yes, but the timing of evaluation – unclear. Response evaluation is driven by the 6-month duration of treatment for each authority application, rather than by clinical need. Dose titration, monitoring, differing therapy goals and long lead times for outpatient clinic appointments may make this difficult to achieve for some patients.
Response to a PAH agent is defined as follows: For patients with two or more baseline tests, response to treatment is defined as two or more tests demonstrating stability or improvement of disease, as assessed by a physician from a designated hospital. For patients with a RHC composite assessment alone at baseline, response to treatment is defined as a RHC result	See recommendations in Table 1.10.	Partially. Assessment of response would not be limited to RHC, but would include monitoring parameters given in Table 1.12. See above comments about relationship between RHC and echocardiography. The requirements for demonstration of a response have a certain logic (if 2 baseline tests, then 2 tests to show response; if RHC baseline only, then RHC only to show response etc), but these have no basis in the available PAH guidelines. It would useful to understand from treating specialists whether certain tests are ever unavailable or unsuitable for specific patients in light of the imperative to assess response in time to make the next authority application.

demonstrating stability or improvement of disease, as assessed by a physician from a designated hospital. For patients with an ECHO composite assessment alone at baseline, response to treatment is defined as an ECHO result demonstrating stability or improvement of disease, as assessed by a physician from a designated hospital. For patients aged less than 18 years, response to treatment is defined as at least one of the baseline tests demonstrating stability or improvement of disease, as assessed by a physician from a designated hospital.		
Patient must have been assessed by a physician at a designated hospital.	See discussion in *Treatment setting and PAH treatment centres*	Unclear. The large number of centres in the list of designated hospitals (and submission from PHSANZ to this review) suggests many centres are likely to be unable to meet guideline requirements in terms of numbers of PAH patients treated to meet a 'critical mass' of PAH expertise. The number of patients seen at each centre were not available for this review.

Source: Table compiled for this review

1.5.4 PAH diagnostic and monitoring recommendations

Haemodynamic criteria, definition of response and monitoring requirements

Current PBS requirement

Current diagnostic and monitoring criteria in the PBS restrictions are given in Table 1.19 along with comments regarding their currency compared with the guidelines. Key issues are discussed below – a small number of relatively minor issues are covered in the table alone.

Diagnostic recommendations for eligibility to receive vasodilator therapy with CCBs have been considered above, along with the treatment recommendations for CCBs (Table 1.18).

Guideline Recommendations

Guideline recommendations for diagnosis of PAH (Table 1.9) and monitoring of patients (Table 1.10) have been cross-referenced in the tables with the PBS restriction requirements.

The PAH restrictions contain diagnostic requirements that must be satisfied either to meet the definition of PAH, or the definition of response to treatment. A number of these date from the original listing of bosentan in March 2004. Some key values and terms have been updated in response to requests from PHSANZ; others are unchanged since 2004.

A minimum set of criteria to determine treatment decisions (based on a synthesis of the guideline recommendations) is presented in the synthesis section, noting that these are somewhat different to the three key tests required for access to PBS medicines.

Role of RHC and Echocardiography in PAH diagnosis

The guidelines recommend echocardiography, prior to RHC to establish a likelihood of PAH based on TRV and other factors suggestive of PAH (Table 1.9). It is unlikely that RHC would be performed without first administering an echocardiograph as an essential preliminary test to establish whether RHC should be performed and to determine parameters for measurement during RHC. RHC is then definitive for the diagnosis and is used to measure a number of parameters in addition to the measurement of PAP (such as SvO_2, cardiac output, evidence of right ventricular deterioration) which provide a prognostic picture of the patient.

The current PAH restrictions specify RHC, echocardiography and 6MWD as required assessments to establish the patient's baseline measurements. However only RHC is definitive for a PAH diagnosis – it should be conducted as the final test after all the non-invasive assessment are complete.

It is unknown how many Australian patients would be contraindicated for RHC such that an initial diagnostic RHC was unavailable. The PBS restrictions state that if RHC is not possible, the right ventricular systolic pressure (RVSP) should be estimated by echocardiography to be at least greater than 40 mmHg, with normal left ventricular function. This alternative has been a feature of PAH restrictions since the original listing for bosentan in March 2004.

This criterion is included in the 2009 AHA consensus statement as a criterion warranting further investigation (high suspicion of PAH[20]) but it is not diagnostic of PAH and this criterion for decision-making is not reflected in any of the more recent guidelines. In the past, RVSP was a surrogate used to estimate pulmonary artery systolic pressure (PASP)[44] as the two values were typically equivalent, noting that mPAP is a mean value, whereas PASP is at the peak.

However, the 2015 ESC/ERS Guidelines[8] recommend that the main variable measured by chest ECHO should be TRV and not the estimated PASP. TRV should instead be used for assigning the echocardiographic probability of PH. A recommendation for either of these parameters on echocardiography as diagnostic of PAH was not found in any of the supporting guidelines on imaging. The current 2015 ESC/ERS Guidelines recommend measurement of peak TRV and other factors suggestive of PAH (see Table 1.9) as the key haemodynamic variable predictive of PAH.

This report has not considered other means of imaging. Cardiac magnetic resonance imaging (MRI) may be informative in diagnosis and assessment of PAH patients, but it is not among the principle recommended methods (nor is it subsidised through Medicare for this use in Australia).

Role of 6MWD in PAH diagnosis and monitoring

The 6MWD as a measure of exercise capacity is considered a useful prognostic test both at baseline and for monitoring. It is recommended as one of a suite of factors that should be monitored during the patient's treatment, however there is no absolute distance that is applicable for all patients[8] (Table 1.10). The prominence in the PAH restriction may reflect the importance of 6MWD as an endpoint in clinical trial data at the time. If 6MWD is not administered, another measure of exercise capacity should be obtained –cardiopulmonary exercise testing can substitute for 6MWD according to guidelines. There are many other tests and test parameters that are equally informative but that are not cited in the restrictions (BNP or NT-proBNP, blood gases; dyspnoea score, cardiac output) some of these may also be measured during RHC.

Bagga *et al*[38] observed that "ongoing PBS-subsidized supply of medication is dependent on a less than 20% deterioration in 6MWD and PAP on transthoracic echocardiography". This information was reportedly specified in the then Medicare PAH Physician's Guide which is no longer available and Services Australia has confirmed that such a document is no longer in use. Services Australia stated that it is up to the prescriber to justify their assessment of the patient's status.

In children, the 6MWD is still recommended at baseline but as a point of comparison for monitoring and follow-up[8,23]. Children generally walk further than adults on the test and the distance ranges quoted for adults in low versus high risk categories for this outcome are not considered relevant for children. As such 6MWD is not a prognostic factor for children, but in older children it can be used to assess changes in exercise tolerance over time.

1.5.5 Other issues

Treatment setting and PAH treatment centres

Current PBS requirement

PAH drugs may only be prescribed within the hospital system and the specific hospital must be one of the designated hospitals accepted by Services Australia for PAH prescribing. As of January 2018, 61 centres were included in the Services Australia list of designated hospitals. The centres represent both public and private hospitals.

Unlike some other s100 HSD complex authority required drugs, the prescriber specialties are not explicit. Given s100 HSD items are 'hospital only' listings, this excludes general practitioners.

Guideline recommendations

Recommendations for staff, facilities and numbers of patients seen per year for PAH treatment centres are given in Section *PAH treatment centres*. It is not known whether these objectives are achievable for regional and rural centres in Australia, however it would be more likely that a tertiary referral centre in the capital cities could meet these criteria.

This is a much larger number than would be expected even allowing for geographical constraints and equity of access concerns. Numbers of PAH centres are much lower in other countries such as the United Kingdom (eight) and Ireland (one)[45]; Sweden (eight)[46] and Canada (16 PAH centres plus four for paediatric patients)[47].

Although figures of PAH patients treated per designated hospital per year were not available for this review, it is not consistent with PAH epidemiology that these centres would all be seeing the number of patients to meet international guidance of a minimum 300 referred patients (including 50 paediatric patients) per centre per year in order to maintain expertise in PAH diagnosis, care and prescribing practices. Furthermore, recommendations for RHC, vasoreactivity testing and other invasive procedures and imaging are predicated on these being performed in expert tertiary referral centres, focused on PH/PAH care, and seeing the specified minimum number of patients per month to maintain a core of expertise such that any complications leading to morbidity and mortality are within the ranges outlined in international guidelines.

The current list of Services Australia designated centres does not identify which centres are outpatient clinics that see some PAH patients as a small portion of their total intake and those that are tertiary referral centres that specialise in PAH and related conditions.

In submissions to this post-market review, both PHSANZ and TSANZ comment that what constitutes a designated centre would benefit from review.

The websites for both the Pulmonary Hypertension Association of Australia and the Pulmonary Hypertension Network Australia differentiate between PH specialist or treatment centres on the one hand and 'prescribing centres' on the other. Both websites provide the Services Australia list of designated hospitals (the prescribing centres) as a list separate to the much smaller list of

centres in which patients can receive PH treatment[48-50]. This would benefit from feedback from these and other relevant organisations in case this information is incomplete, or out of date.

No information on PAH patient numbers or PBS prescriptions per designated hospital was available. Services Australia confirmed that the criteria for designation includes access to or affiliation with another centre that provides cardiac catheterisation. There was no information available to determine if the centres in the Services Australia list are meeting the current guidance on numbers of patients referred and treated per centre per year (including paediatric patients), or numbers of RHC procedures.

PAH classification and terminology

Current PBS requirement

- The different PAH subtypes specified in the current PBS restrictions (see Background, in Table B.6) are:
- Idiopathic pulmonary arterial hypertension
- Anorexigen-induced pulmonary arterial hypertension
- Hereditable pulmonary arterial hypertension
- Drug-induced pulmonary arterial hypertension
- Pulmonary arterial hypertension secondary to connective tissue disease including scleroderma
- Pulmonary arterial hypertension associated with a congenital systemic-to-pulmonary shunt (including Eisenmenger physiology)

This represents all the subtypes – and the terminology used – in the current PAH items.

Current WHO Classification

As the WHO classification scheme for PH and PAH has been changed and updated, so the approved PAH indications and the PBS restrictions have appeared to describe different PAH subtypes. The current terminology is understood to either encompass or be interchangeable with the previously used descriptions.

The current WHO classification[9] provides that:

- The terminology ‘drug or toxin induced’ PAH has replaced ‘anorexigen induced’ PAH
- PAH with a genetic or familial component is referred to as ‘heritable’ PAH
- Connective tissue disease is defined as including scleroderma

Congenital conditions causing PAH, but still encompassed by WHO Group 1 PH / PAH classification, are not limited to those characterised by a systemic-to-pulmonary shunt.

Some notes are given below.

Drug and toxin induced PAH
With regard to drug-induced PAH, PBS restrictions refer in some cases to 'anorexigen-induced' PAH, whereas the restrictions for iloprost refer to 'drug-induced' PAH and also 'anorexigen-induced' PAH. The most recent WHO classification refers to 'drug and toxin induced' PAH. These are not distinct patient groups but the same group described according to the prevailing terminology. There are few anorectics associated with PAH remaining on the market in Australia, thus a reference to anorexigen-induced PAH may be interpreted by clinicians as 'drug or toxin induced' irrespective of the causative agent.

PAH due to congenital heart disease
Previous classifications for PAH have referred to PAH associated with "congenital systemic-to-pulmonary shunts" (which includes Eisenmenger physiology). In the current 2013 classification, this subtype is referred to more simply as "congenital heart diseases" with the groups falling under that category described in considerable detail in the 2013 revised PAH classification[9] and is now broader than previous classifications.

Heritable PAH
The term 'hereditable' used in the current PBS restrictions is a conflation of 'hereditary' and 'heritable'. It does not reflect terminology in the international guidelines or PAH classification ('heritable PAH'), nor is it in common use in the scientific literature.

1.6 Synthesis of findings

1.6.1 Guidelines for PAH

Nine clinical practice guidelines for PAH were considered relevant to this review (Table 1.4), covering diagnosis and treatment of PAH, the international classification scheme and recommendations for paediatric patients. The two key documents used for this review were the 2015 European Society of Cardiology /European Respiratory Society joint Guidelines for the diagnosis and treatment of pulmonary hypertension[8] and the CHEST guideline and expert panel report: Pharmacologic therapy for pulmonary arterial hypertension in adults[19]. Of the two, the European document can be considered definitive except where noted. Further guidance regarding diagnostic and monitoring of PAH patients, treatment of PAH in children and other matters including PAH disease classification was obtained from the other documents presented with the key findings in Table 1.4.

There are no PH or PAH clinical guidelines for Australia or New Zealand.

Based on the Guideline recommendations and taking into account patient risk factors, the key treatment recommendations are as follows:

- Patients with WHO FC I should be monitored and treatment commenced on signs of clinical worsening.
- Oral PAH medicines are standard of care for PAH, particularly for WHO FC II and III.

- Prostanoids are recommended primarily for more severe disease (WHO FC III and IV) and are not recommended for WHO FC II patients.
- Monotherapy with oral PAH medicines remains indicated for treatment naïve patients except those with high risk factors for whom initial combination therapy may be appropriate.
- Sequential combination or add-on therapy involving addition of another PAH agent to existing PAH therapy is standard of care after inadequate response or clinical worsening.
- Current clinical algorithms consider patients in terms of patient risk factors as well as WHO FC.
- High dose CCBs are indicated in a small sub-set of patients having a positive vasoreactivity response during RHC and who have certain Group 1 subtypes (IPAH, heritable PAH and drug and toxin-induced PAH).

Treatment pathways capturing these recommendations have been presented in Table 1.5 (patients receiving monotherapy) and Table 1.6 (patients receiving combination therapy).

1.6.2 Alignment of TGA, PBS and guideline requirements

Alignment of therapeutic recommendations

A summary table of the alignment in these three areas has been presented with the key findings in Table 1.1. Further to this:

- PAH is defined as all WHO Group 1 PH conditions. Guideline recommendations are broadly similar for treatment across the Group 1 PAH subtypes. With the exception of drug and toxin induced PAH, the subtypes in the TGA indications align reasonably well with current PBS restrictions.
- Patients with Group 1 conditions PAH-HIV or PAH associated with portal hypertension (PAH-PH) are currently excluded from access to PAH medicines on the PBS.
- PBS restrictions do not cover currently recommended use in WHO FC II which is considered standard of care. Current recommendations for treatment according to WHO FC are largely consistent with TGA registered indications for PAH medicines. The main exception is the PDE-5 inhibitors which are not TGA approved for WHO FC IV but are likely to be used in combination regimens for all functional classes of PAH.
- Some but not all recommendations for combination use are supported by the TGA indications, limited to those medicines approved more recently. Older products (bosentan, prostanoids, sildenafil) are not registered for combination treatment. No combination use of PAH medicines is permitted within the current PBS restrictions.
- The current PBS restrictions do not permit PBS funded combination therapy. The February 2015 DUSC report on "Pulmonary arterial hypertension (PAH) medicines utilisation analysis" indicates that, in practice, combination therapy is achieved by adding low cost private prescription sildenafil to another of the PBS subsidised drugs[51].
- Patients with PAH-CHD have fewer treatment options than for other Group 1 subtypes. Neither of the prostanoids and only three of the oral medicines (bosentan, macitentan, riociguat) are TGA approved/PBS listed for these patients. The 2015 ESC/ERS Guidelines

recommendations for PAH-CHD are consensus-based due to lack of evidence in this subtype[8].

- Patient groups currently unable to access any PBS subsidised PAH treatment, or PBS treatment that meets the guideline recommendations, have been presented with the key findings in Table 1.1.
- Some combinations of PAH medicines are contraindicated for safety. A number of other potential drug interactions should be taken into account, in particular interaction between bosentan and sildenafil.
- Treatment recommendations are similar between adults and children and this is reflected in the PAH restrictions on the PBS. However, only bosentan is approved in Australia for treatment of children with PAH. Sildenafil is most likely being used off-label for children in Australia as it is in the USA, although it is approved in Europe for children 1-17 years old with PAH. Modified dosing is recommended to manage an increased mortality risk that has been observed on long-term dosing.
- The current PBS restrictions provide for treatment of paediatric patients but only one of the registered drugs within the scope of this review is explicitly approved in Australia for paediatric use (bosentan). Pharmaceutical forms suitable for paediatric administration are available overseas, such as powder for oral solution or dispersible tablets, but are not on the market in Australia. The lack of an appropriate pharmaceutical form can effectively exclude patients from PBS subsidy as compounded medicines are only available as private scripts.
- Patients not satisfying guideline criteria for CCBs are at risk of serious hypotensive events and administration of CCBs in such patients is strongly discouraged. The recommended patient groups and diagnostic criteria are not consistent with requirements of the current restrictions. High dose CCB therapy is off-label use, the PIs for diltiazem, nifedipine and amlodipine do not cover dosing or safety information for PAH patients.

Alignment of diagnostic tests and patient assessments

A summary table of the alignment between PBS and guideline diagnostic requirements has been presented with the key findings in Table 1.1.

The results of RHC, 6MWD and echocardiography are currently used as assessments for PBS treatment eligibility but certain PBS requirements do not match guideline diagnostic recommendations.

According to current guidelines, RHC is the gold standard for diagnosis of PAH and is essential unless explicitly contraindicated. This is consistent with the PBS restrictions; however its purpose in the guidelines appears to be distinct to that for echocardiography and 6MWD:

- Doppler echocardiography is recommended prior to RHC to establish a likelihood of PAH based on TRV and other factors suggestive of PAH. Echocardiography is not recommended for diagnosis of PAH as it is unable to confirm PAH in patients where the TRV is not measurable.
- It is unlikely that RHC would be performed without first administering echocardiography as an essential preliminary test to establish whether RHC should be performed and to determine parameters for measurement during RHC.

- There is no suggestion in the guidance reviewed that echocardiography should be used as a substitute for RHC. There are some contraindications for RHC, but RHC should be performed if at all possible given the magnitude of the diagnosis, as well as safety implications for inappropriate treatment. The echocardiography recommendations are very much focused on determination of right heart variables as a means to screen patients who should receive RHC, which is associated with morbidity and mortality risks and should not be administered unless absolutely necessary.
- Current recommendations suggest 6MWD should be one of a panel of assessments administered at baseline and during follow-up to monitor clinical status (and disease risk factors) but that 6MWD does not on its own form the basis for treatment decisions. It is not clear that this is consistent with the purpose of the 6MWD as it currently stands in the PBS restrictions.

In addition to the diagnosis of PAH, RHC is used to determine other baseline (prognostic) parameters such as PAWP, SvO_2, RAP, PVR and cardiac output. Similarly, features such as TAPSE and presence/absence of pericardial effusion form part of the ECHO composite assessment. Each of these outcomes, along with 6MWD, form part of a panel of parameters taken at baseline used to determine the patient's prognosis or risk of PAH deterioration.

Current guidance recommends that each PAH patient's risk category or prognostic factors should be based on a panel of assessments performed at baseline, then repeated during follow-up to track progress against therapeutic goals and to evaluate response to treatment. There is no one definitive set of parameters recommended for baseline assessments. The published algorithms and recommendations suggest that the assessment of the patient's risk is equally important as WHO functional class in determining PAH treatment.

The three assessments currently required by the PAH restrictions contribute to the patient's baseline measurements but do not fulfil all of them.

Assessment of the patient's PAH risk using this approach is a key part of treatment decisions as recommended in current guidance. However, an assessment of patient prognosis or risk is not currently required for PBS subsidy although guidelines indicate it fulfils a similar purpose to WHO FC in making PAH treatment decisions.

There was no minimum set of test criteria recommended by the guidelines as the basis of treatment decisions. Nevertheless, in the context of criteria needed for authority to prescribe, a distillation of essential criteria to determine treatment could be:

- Positive diagnosis by RHC
- WHO FC
- Patient prognosis / risk of PAH deterioration

Key decision criteria for patients already on treatment (or untreated Class I patients):

- Disease status – improvement, stability, or sustained deterioration (clinical worsening); and
- Whether or not treatment goals are being met.

- Input from treating PAH specialists would be essential to confirm these criteria are appropriate.

The current guidelines suggest that inadequate treatment response should include clinical worsening but also failure to improve or minimal improvement against therapeutic goals. Maintenance of disease status may not be appropriate in patients with milder disease. This is up to the judgement of the treating specialist.

Several tests or criteria are specified in the PBS restrictions as the basis for treatment decisions that do not match guideline recommendations. This applies to:

- The current criterion for determining which patients should receive vasodilators with CCBs (the threshold criterion of 8 mmHg RAP by RHC). Eligibility should instead be determined by acute vasoreactivity testing using a different criterion (Table 1.8);
- The current echocardiography criterion diagnostic of PAH in cases where RHC is unavailable (40 mmHg RVSP). It is recommended that probability of PAH by echocardiography should instead be determined by TRV and/or other echocardiographic features suggestive of PAH. This would be sufficient for a diagnosis of PAH only in cases where RHC is clearly contraindicated.

1.6.3 Other Issues

It is likely that only a modest number of centres amongst the 61 listed as designated hospitals for PBS-subsidised PAH treatment would be meeting guideline requirements. It is recommended that a centre should be treating a critical mass of PAH patients (300 patients referred for diagnosis and treatment per centre per year – *PAH treatment centres*) in order to maintain expertise and quality of care.

The terminology used in the current PBS restrictions does not reflect the current classification of different PAH subtypes and it is not clear how these would be interpreted in current clinical practice.

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Appendix 1.B Further ARTG and PBS information for PAH medicines

Table B.7 PAH Brands Registered in Australia

Drug	Registered Brands†	TGA Sponsor	PBS Listed
Bosentan	***Tracleer®**; Bosentan Actelion	Actelion	Yes
	Bosentan CW; Bosentan CH; Bosentan AN	Amneal	No
	Bosentan Dr Reddy's; Bosentan Reddy's; APO-Bosentan; **Bosentan-DRLA**	Dr Reddy's Laboratories	Yes
	Usenta	Tolmar	No
	Bosentan Sun; **Bosentan RBX**; Bosentan RAN	Sun Pharma	Yes
	Bosentan Sandoz	Sandoz	Yes
	Bosentan INTAS; Bosentan ASTRON	Accord Healthcare	No
	Bosleer	Arrow Pharmaceuticals	Yes
	Bosentan GH	Generic Health	No
	Bosentan APOTEX; GENRX Bosentan	Apotex	Yes
	Bosentan ALPHAPHARM; **Bosentan MYLAN**	Alphapharm	Yes
	BOSENTAN CA; BOSENCIP; BOSENTAN CIPLA; BOSENTAS;	Cipla	No
Sitaxentan	**Thelin®; withdrawn from market 10 December 2010 – no longer registered*	*Pfizer / Encysive Pharmaceuticals*	*Delisted*
Ambrisentan	***Volibris®**	GlaxoSmithKline	Yes
	CIPLA Ambrisentan; AMBRIS Ambrisentan; AMBRICIP Ambrisentan	Cipla	No
Macitentan	**Opsumit®**	Actelion	Yes
Sildenafil	***Revatio®**	Pfizer	Yes (tablet only)

Drug	Registered Brands†	TGA Sponsor	PBS Listed
	APO-Sildenafil PHT; CHEMMART SILDENAFIL PHT; TERRY WHITE CHEMISTS SILDENAFIL PHT	Apotex	Yes
	SILDENAFIL-DRx; SYZUM-DRLA Sildenafil; MECFIL Sildenafil; ALSIOZ Sildenafil; CAVEROZ Sildenafil	Dr Reddy's Laboratories	Yes
	Sildenafil AN PHT 20	Amneal	Yes
	Sildenafil Sandoz PHT 20; SILDACCORD PHT; SILDANIL PHT 20	Accord Healthcare	Yes
	DENSIL sildenafil; SILVIO sildenafil; SILDENAFIL ACTAVIS PAH	Medis Pharma	No
	SILDENAFIL AN PHT 20	Arrow Pharma	No
	PHARMACOR SILDENAFIL PHT 20	Pharmacor	No
Tadalafil	***Adcirca®**	Eli Lilly	Yes
Riociguat	***Adempas®**	Bayer	Yes
Epoprostenol	***Flolan®**	GlaxoSmithKline	Yes
	Veletri®	Actelion	Yes
	Epoprostenol MYX	Mayne Pharma	No
Iloprost	***Ventavis®**	Bayer	Yes
Treprostinil	*Remodulin®; withdrawn from market after November 2016 (exact date unknown) – no longer registered*	*Orphan Australia*	*No*
Selexipag	*Uptravi®*	*Actelion*	*No*

†PBS Listed brands are **bold; *** Indicates first brand to be registered on ARTG (primary search of 13 December 2017)
Source: Relevant product Information for each brand; www.pbs.gov.au

Table B.8 History of PBAC Considerations for PAH Medicines

Drug	Proposed PBS listing	PBAC Meeting	PBAC decision Reasons
Endothelin receptor antagonist			
Bosentan	Treatment of IPAH or PAH associated with scleroderma in patients with WHO FC III or IV severity	December 2002	Rejected Unacceptable and uncertain cost-effectiveness.
	Re-submission (as above)	June 2003	Rejected Uncertainty in the clinical benefit, in terms of the extent in any gain in survival, and uncertain and unacceptable cost-effectiveness.
	Re-submission (as above)	September 2003	Rejected Uncertain and unacceptable cost-effectiveness.
	Re-submission (as above)	December 2003	Recommended listing on basis of acceptable, but high, cost-effectiveness ratio. [redacted]
	Extend listing to include PAH associated with congenital systemic-to-pulmonary shunts including Eisenmenger physiology	March 2008	Recommended listing Acceptable cost-effectiveness compared with standard care (evidence is presented at i) below).
	Minor submission from PHSANZ requesting amendment of the current 'continuing treatment' restriction	July 2015	Recommended that that the current "continuing treatment (all patients)" restriction be replaced by a "continuing treatment – new patient" restriction (written authority); and a subsequent "continuing treatment" restriction (telephone authority) without a requirement to provide evidence of response to the most recent treatment course.
Ambrisentan	Treatment of IPAH or PAH-CTD in patients with a WHO FC III-IV severity	July 2009	Recommended listing as Section 100 HSD Program Public and Private Hospital Authority Required Cost minimisation basis to bosentan. Equi-effective doses are ambrisentan 5 mg daily and bosentan 125 mg bid (evidence is presented at ii) below).
Macitentan	Treatment of WHO FC III or IV IPAH, PAH-CTD or PAH-CHD	March 2014	Recommended listing Cost minimisation basis to bosentan. Equi-effective doses are macitentan 10 mg once daily versus bosentan 62.5 mg twice daily for 4 weeks, then a maintenance dose of 125 mg twice daily.

Drug	Proposed PBS listing	PBAC Meeting	PBAC decision Reasons
	Minor submission from PHSANZ requesting amendment of the current 'continuing treatment' restriction	July 2015	Recommended that that the current "continuing treatment (all patients)" restriction be replaced by a "continuing treatment – new patient" restriction (written authority); and a subsequent "continuing treatment" restriction (telephone authority) without a requirement to provide evidence of response to the most recent treatment course.
Sitaxentan	Treatment of IPAH in patients with WHO FC III symptoms, and PAH-CTD	July 2007	Recommended listing as a Section 100 HSD Program Public and Private Hospital Authority Cost minimisation basis to bosentan. Equi-effective doses are sitaxentan 100 mg daily and bosentan 125 mg bid (evidence is presented at iii) below).
Phosphodiesterase inhibitors			
Sildenafil	Treatment of IPAH or PAH-CTD in patients with WHO FC III	November 2006	Recommended listing Sildenafil is no worse than bosentan in terms of effectiveness and has similar toxicity. The equi-effective doses are sildenafil 20 mg three times daily (tid) and bosentan 62.5 mg bid for 4 weeks followed by a maintenance dose of 125 mg bid (evidence is presented at iv) below).
Tadalafil	Treatment of WHO FC III IPAH and PAH-CTD	November 2011	Recommended listing as Section 100 HSD Program Public and Private Hospital Authority Required Cost minimisation basis compared with sildenafil. The equi-effective doses are tadalafil 40 mg once daily and sildenafil 20 mg tid (evidence is presented at v) below).
Prostanoids			
Iloprost	Treatment of IPAH, drug-induced PAH or PAH-CTD	November 2004	Recommended Section 100 listing [redacted]
		March 2008	Recommended removal of the word "adult" and amendment to the iloprost listing as appropriate to allow use in paediatric patients.
		March 2009	Recommended an amendment to the restrictions for iloprost to limit availability to second-line use in patients with WHO Class III IPAH or PAH-CTD who had failed to respond to a prior PBS-subsidised therapy.

Drug	Proposed PBS listing	PBAC Meeting	PBAC decision Reasons
Epoprostenol	Treatment of WHO FC III or IV IPAH patients who met certain criteria and had failed to respond to treatment with bosentan or where bosentan was contraindicated or was ceased due to intolerable adverse events	July 2004	Rejected Section 100 listing Unacceptable cost-effectiveness.
	Treatment of adult and paediatric patients with FC III or IV IPAH (similar to bosentan listing)	March 2005	Rejected a first line section 100 listing Uncertainty about the determination of equi-effective doses and uncertainty about the resulting cost minimisation analysis.
	Re-submission (as above)	March 2006	Recommended listing Cost minimisation based on an indirect comparison showing epoprostenol is therapeutically no worse than bosentan. The equi-effective doses are epoprostenol, commencing at an average dose of 11.9ng/kg/min over the first 3 months of treatment and escalating linearly in steps to an average dose of 27.2ng/kg/min at 3 years, and bosentan 125 mg bid (evidence is presented at vi) below).
		March 2009	Recommended changes in the restrictions of epoprostenol to allow only second-line use for PAH treatment.
	Second-line therapy for WHO FC III PAH-CTD and first-line therapy for WHO FC IV PAH-CTD	November 2011	Recommended listing Cost minimisation based on comparison between iloprost and bosentan. The equi-effective doses are estimated to be epoprostenol, commencing at a dose of 2.2ng/kg/min, with an average dose of 11.2 ng/kg/min at week 12, increasing linearly in steps to an average dose of 47.4 ng/kg/min at 3 years; bosentan 62.5 mg orally bid for 4 weeks, then a maintenance dose of 125 mg bid; and iloprost 2.5-5 µg nebulised 6-9 times per day, giving a mean of 7.5 x 20 µg per day (evidence is presented at vii) below).
	Minor submission from PHSANZ requesting amendment of the current ‘continuing treatment’ restriction	July 2015	Recommended that that the current “continuing treatment (all patients)” restriction be replaced by a “continuing treatment – new patient” restriction (written authority); and a subsequent “continuing treatment” restriction (telephone authority) without a requirement to provide evidence of response to the most recent treatment course.

Drug	Proposed PBS listing	PBAC Meeting	PBAC decision Reasons
Treprostinil	Treatment of IPAH or PAH-CTD, in patients with disease of WHO FC III or IV severity.	November 2005	Recommended listing Cost minimisation based on indirect comparison involving placebo as the common reference indicated that, overall, treprostinil was no worse than bosentan. The equi-effective doses were trepostinil sodium 9.3 ng/kg/min via continuous subcutaneous infusion and bosentan 125 mg *bid*. The PBAC considered that the listing of trepostinil would provide an additional treatment option to patients with a different mode of administration - that is, by subcutaneous infusion (evidence is presented at viii) below).
sGC stimulator			
Riociguat	Treatment of WHO FC III or IV IPAH or PAH-CTD or PAH-CHD	March 2014	Recommended listing Cost minimisation basis to bosentan. Equi-effective doses are: ○ Individual titration of riociguat (1 mg tid to 2.5 mg tid) and bosentan 62.5 mg bid or 125 mg bid. ○ Individual titration of riociguat (1 mg tid to 2.5 mg tid) and sildenafil 20 mg tid.
Non-prostanoid prostacyclin receptor agonist			
Selexipag	Treatment of WHO FC III or IV IPAH, drug or toxin-induced PAH, heritable PAH, or PAH-CTD, PAH-CHD or PAH-HIV, in patient with inadequate clinical response to ERA or PDE-5 inhibitor	March 2016	Rejected listing The magnitude of clinical benefit was unclear, and that the estimate of cost-effectiveness as presented in the submission was difficult to interpret The ICER was high.
	As above, apart from as a component of triple therapy, not dual therapy	March 2017	Rejected a first line section 100 listing The ICERs remained difficult to interpret, and were highly likely to be too high.

Table B.9 PAH item numbers, DPMQs, authorities and treatment phases (Prices current for 1 December 2017 Schedule)

Drug	Items	Listings	DPMQ	Treatment Phase	Authority
BOSENTAN 62.5, 125 mg tablet, pack of 60	5618Q, 5619R, 6429J, 6430K	S100 HSD Public S100 HSD Private	$2295.43 $2342.58	Initial 1 (new patients)	Written
				Initial 2 (new patients)	Written
				Initial 3 (change or re-commencement of therapy for all patients)	Written
				Initial 1 or Initial 2 (new patients) or Initial 3 (change or re-commencement of therapy for all patients) or First Continuing treatment - Balance of supply	Telephone
				First Continuing treatment	Written
				Subsequent Continuing treatment	Telephone
				Cessation of treatment (all patients) (62.5 mg strength only)	Telephone
AMBRISENTAN 5, 10 mg tablet, pack of 30	5607D, 5608E, 9648T, 9649W	S100 HSD Public S100 HSD Private	$2732.65 $2779.80	Initial 1 (new patients)	Written
				Initial 2 (new patients)	Written
				Initial 3 (change or re-commencement of therapy for all patients)	Written
				Initial 1 or Initial 2 (new patients) or Initial 3 (change or re-commencement of therapy for all patients) or First Continuing treatment - Balance of supply	Telephone
				First Continuing treatment	Written
				Subsequent Continuing treatment	Telephone
MACITENTAN 10 mg tablet, pack of 30	10134J, 10136L	S100 HSD Public S100 HSD Private	$2876.47 $2923.62	Initial 1 (new patients)	Written
				Initial 2 (new patients)	Written
				Initial 3 (change or re-commencement of therapy for all patients)	Written
				Initial 1 or Initial 2 (new patients) or Initial 3 (change or re-commencement of therapy for all patients) or First Continuing treatment - Balance of supply	Telephone
				First Continuing treatment	Written
				Subsequent Continuing treatment	Telephone
SILDENAFIL 20 mg tablet, pack of 90	9547L, 9605M	S100 HSD Public S100 HSD Private	$319.72 $339.66	Treatment Phase: Initial 1 (new patients)	Written
				Initial 2 (new patients)	Written
				Initial 3 (change or re-commencement of therapy for all patients)	Written
				Initial 1 or Initial 2 (new patients) or Initial 3 (change or re-commencement of therapy for all patients) or First Continuing treatment - Balance of supply	Telephone
				First Continuing treatment	Written
				Subsequent Continuing treatment	Telephone

Drug	Items	Listings	DPMQ	Treatment Phase	Authority
TADALAFIL 20 mg tablet, pack of 56	1304P, 1308W	S100 HSD Public S100 HSD Private	$796.60 $835.61	Initial 1 (new patients)	Written
				Initial 2 (new patients)	Written
				Initial 3 (change or re-commencement of therapy for all patients)	Written
				Initial 1 or Initial 2 (new patients) or Initial 3 (change or re-commencement of therapy for all patients) or First Continuing treatment - Balance of supply	Telephone
				First Continuing treatment	Written
				Subsequent Continuing treatment	Telephone
EPOPROSTENOL 500 µg, 1.5 mg injection, 1 vial (Veletri®) OR 1.5 mg injection + diluent, 1 pack (Flolan®)	10111E, 10117L, 10129D, 10130E, 11065J, 11069N, 11082G, 11090Q	S100 HSD Public S100 HSD Private S100 HSD Public S100 HSD Private	$33.28 (500 µg) $43.76 (500 µg) $66.55 (1.5 mg) $77.70 (1.5 mg)	Initial 1 (new patients)	Written
				Initial 2 (change or re-commencement of therapy for all patients)	Written
				Initial 1 (new patients) or Initial 2 (change or re-commencement of therapy for all patients) or First Continuing treatment - Balance of supply	Telephone
				First Continuing treatment	Written
				Subsequent Continuing treatment	Telephone
ILOPROST 20µg/2mL inhalation solution, 30x2mL ampoules	5751Q 6456T	S100 HSD Public S100 HSD Private	$408.88 $432.39	Initial 1 (new patients)	Written
				Initial 2 (new patients)	Written
				Initial 3 (change or re-commencement of therapy for all patients)	Written
				Initial 1 or Initial 2 (new patients) or Initial 3 (change or re-commencement of therapy for all patients) or First Continuing treatment - Balance of supply	Telephone
				First Continuing treatment	Written
				Subsequent Continuing treatment	Telephone
RIOCIGUAT 500 µg, 1.0, 1.5, 2.0, 2.5 mg tablet, pack of 42 or 84	11040C 11031N 11059C 11058B 11054T 11028K 11053R 11060D 11047K	S100 HSD Public S100 HSD Private S100 HSD Public S100 HSD Private S100 HSD Public S100 HSD Private S100 HSD Public S100 HSD Private S100 HSD Public	$1717.71 (500 µg/42) $1764.86 (500 µg/42) $3435.42 (500 µg/84) $3482.57 (500 µg/84) $1717.71 (1.0 mg/42) $1764.86 (1.0 mg/42) $3435.42 (1.0 mg/84) $3482.57 (1.0 mg/84) $1717.71 (1.5 mg/42)	Initial 1 (new patients)	Written
				Initial 2 (new patients)	Written
				Initial 3 (change or re-commencement of therapy for all patients)	Written
				Initial 1 or Initial 2 (new patients) or Initial 3 (change or re-commencement of therapy for all patients) or First Continuing treatment - Balance of supply	Telephone
				First Continuing treatment	Written
				Subsequent Continuing treatment	Telephone
				Initial 4 (Grandfathered patients)	Written

Drug	Items	Listings	DPMQ	Treatment Phase	Authority
	11046J	S100 HSD Private	$1764.86 (1.5 mg/42)	Initial 5 (Grandfathered patients)	Written
	11048L	S100 HSD Public	$3435.42 (1.5 mg/84)		
	11061E	S100 HSD Private	$3482.57 (1.5 mg/84)		
	11038Y	S100 HSD Public	$1717.71 (2.0 mg/42)		
	11045H	S100 HSD Private	$1764.86 (2.0 mg/42)		
	11039B	S100 HSD Public	$3435.42 (2.0 mg/84)		
	11030M	S100 HSD Private	$3482.57 (2.0 mg/84)		
	11057Y	S100 HSD Public	$1717.71 (2.5 mg/42)		
	11052Q	S100 HSD Private	$1764.86 (2.5 mg/42)		
	11024F	S100 HSD Public	$3435.42 (2.5 mg/84)		
	11035T	S100 HSD Private	$3482.57 (2.5 mg/84)		

Source: www.pbs.gov.au; Correct as of 1 December 2017.

Table 1.20 PAH Medicines – PI references to use in combination with other PAH medicines

Medicine	Brand	PI Date	Combination Therapy
Bosentan	Tracleer®	15 February 2016	*CLINICAL TRIALS:* *Combination with epoprostenol – The combination of TRACLEER® and epoprostenol has been investigated in two studies: AC-052-355 (BREATHE-2) and AC-052-356 (BREATHE-3). AC-052-355 was a multi-centre, randomised, double-blind, parallel-group trial of TRACLEER® versus placebo in 33 patients with severe pulmonary arterial hypertension who were receiving concomitant epoprostenol therapy. AC-052-356 was an open-label, non-controlled trial; 10 of the 19 paediatric patients were on concomitant TRACLEER® and epoprostenol therapy during the 12–week trial. The safety profile of the combination was not different from the one expected with each component and the combination therapy was well tolerated in children and adults. The clinical benefit of the combination has not been demonstrated.* *PRECAUTIONS:* *Use in patients receiving epoprostenol – In a randomised, double blind trial (BREATHE-2), 32 patients were commenced on epoprostenol, to which bosentan (n=22) or placebo (n=11) was added two days later. The treatments were then carried out for 16 weeks. The trial failed to show any significant clinical benefit (6 minute walk, dyspnoea score, WHO functional class) or pharmacodynamic effect. The co-administration of bosentan with epoprostenol is, therefore, not recommended.* *Interactions with Other Medicines – Concomitant administration of TRACLEER® and epoprostenol has shown to be safe and efficacious in a clinical study with paediatric PPH/PAH patients. The pharmacokinetics were similar to those in adult patients and healthy subjects in other studies.* *Effects of bosentan on other drugs – Co-administration of TRACLEER® 125 mg twice daily (steady state) with sildenafil 80 mg three times a day (at steady state) concomitantly administered during 6 days in healthy volunteers resulted in a 63% decrease of the sildenafil AUC and a 50% increase of the bosentan AUC. Caution is recommended in case of co-administration. The reduction in sildenafil plasma concentration with co-administration of bosentan has also been reported in a study of patients with primary arterial hypertension.*
Ambrisentan	Volibris®	16 February 2016	*PHARMACOLOGY:* *The effect of 7-day dosing of sildenafil (20 mg three times daily) on the pharmacokinetics of a single dose of ambrisentan, and the effects of 7-day dosing of ambrisentan (10 mg once daily) on the pharmacokinetics of a single dose of sildenafil were investigated in 19 healthy adults. With the exception of a 13% increase (90% CI: 99.6% - 129.1%) in sildenafil Cmax following co-administration with ambrisentan, there were no other changes in the pharmacokinetic parameters of sildenafil, N-desmethyl-sildenafil and ambrisentan. This slight increase in sildenafil Cmax is not considered clinically relevant (see Interactions with Other Medicines).* *INDICATIONS:* *VOLIBRIS® in combination with Tadalafil is indicated for the treatment of WHO Group 1 pulmonary arterial hypertension in patients with WHO functional class II, III or IV symptoms.*

Medicine	Brand	PI Date	Combination Therapy
			Extensive clinical information to support the registered indication combination therapy of ambrisentan + tadalafil is included in the PI and is not reproduced here. *INTERACTIONS WITH OTHER MEDICINES:* *Sildenafil & Tadalafil – Co-administration of ambrisentan with a phosphodiesterase inhibitor, either sildenafil or tadalafil (both substrates of CYP 3A4) in healthy volunteers did not significantly affect the pharmacokinetics of ambrisentan or the phosphodiesterase inhibitor (see Metabolism).*
Macitentan	Opsumit®	25 August 2016	*INDICATIONS:* *OPSUMIT®, as monotherapy or in combination with approved PAH treatments (phosphodiesterase-5 inhibitors or inhaled prostanoids) … [indicated for the same suite of indications for monotherapy and combination therapy]* *PRECAUTIONS:* *The efficacy and safety of macitentan when co-administered with epoprostenol has not been specifically studied in controlled clinical trials.* The PI contains no warning about use with other ERAs but makes a general statement that "*Caution should be exercised when OPSUMIT® is used concomitantly with medicinal products known to be associated with hepatic injury as the additive effects of OPSUMIT® with these agents are not known.* *INTERACTIONS WITH OTHER MEDICINES:* *Sildenafil: At steady-state, the exposure to sildenafil 20 mg t.i.d. was increased by 15% during concomitant administration of macitentan 10 mg once daily. Sildenafil, a CYP3A4 substrate, did not affect the pharmacokinetics of macitentan, while there was a 15% reduction in the exposure to the active metabolite of macitentan. These changes are not considered clinically relevant. In a placebo-controlled trial in patients with PAH, the efficacy and safety of macitentan in combination with sildenafil were demonstrated.*
Sildenafil	Revatio®	21 December 2015	*INDICATIONS:* *The efficacy of REVATIO® has not been established in patients currently on bosentan therapy (see PRECAUTIONS).* *CONTRAINDICATIONS:* *Co-administration of PDE-5 inhibitors, including REVATIO®, with guanylate cyclase stimulators, such as riociguat, is contraindicated as it may potentially lead to symptomatic hypotension.* *PRECAUTIONS:* *Co-administration with bosentan – In a study of PAH patients (primary PAH and secondary PAH associated with CTD) on bosentan therapy, no incremental benefit (6MWD) of sildenafil co-administered with bosentan was demonstrated over bosentan alone. The mean result of the combination of sildenafil and bosentan was numerically worse than bosentan alone in patients with PAH associated with CTD but numerically better than bosentan alone in patients with primary PAH. Physicians should assess the clinical response when sildenafil is*

Medicine	Brand	PI Date	Combination Therapy
			used in combination with bosentan in primary PAH. Co-administration of sildenafil and bosentan in patients with PAH associated with CTD is not recommended (see INTERACTIONS WITH OTHER MEDICINES). *Concomitant use with other PDE-5 inhibitors – The safety and efficacy of sildenafil when co-administered with other PDE-5 inhibitor products has not been studied in PAH patients and such concomitant use is not recommended.* *INTERACTIONS WITH OTHER MEDICINES:* *Effect of Other Medicines on REVATIO® – In a study of healthy male volunteers co-administration of the endothelin antagonist bosentan, which is a moderate inducer of CYP3A4, CYP2C9 and possibly of CYP2C19, at steady state (125 mg twice a day) with oral sildenafil at steady state (80 mg three times a day) resulted in a 62.6% decrease of sildenafil AUC and a 55.4% decrease in sildenafil Cmax. The same effect was also observed with lower doses of sildenafil (20 mg three times a day) and bosentan therapy (62.5 mg – 125 mg twice daily). The combination of both drugs did not lead to clinically significant changes of blood pressure (supine and standing).* *Effect of Other Medicines on REVATIO® – Riociguat: Preclinical studies showed an additive systemic blood pressure lowering effect when PDE-5 inhibitors were combined with riociguat. In clinical studies, riociguat has been shown to augment the hypotensive effects of sildenafil. There was no evidence of favourable clinical effect of the combination in the population studied. Concomitant use of riociguat with PDE-5 inhibitors, including sildenafil, is contraindicated as it may potentially lead to symptomatic hypotension (see CONTRAINDICATIONS).* *Effect of REVATIO® on Other Medicines – In a study of healthy volunteers oral sildenafil at steady state (80 mg three times a day) resulted in a 49.8% increase in bosentan AUC and a 42% increase in bosentan Cmax (125 mg twice daily). The same effect was also observed with lower doses of sildenafil (20 three times a day) and bosentan therapy (62.5 mg – 125 mg twice a day).* *Co-administration with other PAH treatments – The safety and efficacy of sildenafil when co-administered with medicines for PAH other than epoprostenol has not been studied in controlled clinical trials. Caution is recommended in the case of co-administration. The safety and efficacy of REVATIO® when co-administered with other PDE-5 inhibitors has not been studied in pulmonary arterial hypertension patients.*
Tadalafil	Adcirca®	18 December 2015	*CONTRAINDICATIONS:* *Guanylate Cyclase Stimulators – The combination of tadalafil and guanylate cyclase stimulators, such as riociguat, is contraindicated because it may lead to symptomatic hypotension.* *PRECAUTIONS* *The efficacy and safety of tadalafil co-administered with prostacyclin or its analogues has not been studied in controlled clinical trials. Therefore, caution is recommended in case of co-administration.*

Medicine	Brand	PI Date	Combination Therapy
			The efficacy of tadalafil in patients already on bosentan therapy has not been conclusively demonstrated (see PRECAUTIONS – Interactions with Other Medicines and CLINICAL TRIALS). *The safety and efficacy of combinations of ADCIRCA® and other PDE-5 inhibitors or other treatments for erectile dysfunction have not been studied. Therefore patients should be informed not to take ADCIRCA® with these medications.* *Endothelin-1 receptor antagonists (e.g. bosentan) – Bosentan (125 mg twice daily), a substrate of CYP2C9 and CYP3A4 and a moderate inducer of CYP3A4, CYP2C9 and possibly CYP2C19, reduced tadalafil (40 mg once per day) systemic exposure by 42% and Cmax by 27% following multiple dose co-administration. The efficacy of tadalafil in patients already on bosentan therapy has not been conclusively demonstrated (see PRECAUTIONS and CLINICAL TRIALS). Tadalafil did not affect the exposure (AUC and Cmax) of bosentan or its metabolites. The safety and efficacy of combinations of ADCIRCA® and other endothelin-1 receptor antagonists have not been studied.* *Other PDE-5 inhibitors – The safety and efficacy of combinations of ADCIRCA® and other PDE-5 inhibitors have not been studied. Therefore, the use of such combinations is not recommended.* *Riociguat – Preclinical studies showed an additive systemic blood pressure lowering effect when PDE-5 inhibitors were combined with riociguat. In clinical studies, riociguat has been shown to augment the hypotensive effects of PDE-5 inhibitors. There was no evidence of favourable clinical effect of the combination in the population studied. Concomitant use of riociguat with PDE-5 inhibitors, including tadalafil, is contraindicated as it may potentially lead to symptomatic hypotension (see CONTRAINDICATIONS).*
Riociguat	Adempas®	17 March 2017	*INDICATIONS:* *Pulmonary arterial hypertension – ADEMPAS®, as monotherapy or in combination with approved PAH treatments (endothelin receptor antagonists or inhaled or subcutaneous prostanoids) ….* [applies to all the registered PAH indications for riociguat] *CONTRAINDICATIONS:* *Co-administration of ADEMPAS® with specific PDE-5-inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline) is contraindicated (see INTERACTIONS WITH OTHER MEDICINES, Pharmacodynamic Interactions).* *PRECAUTIONS:* *The efficacy and safety of riociguat when co-administered with epoprostenol has not been established.* *INTERACTIONS WITH OTHER MEDICINES:* *Pharmacokinetic Interactions – Bosentan, reported to be a moderate inducer of CYP3A4, led to a decrease of riociguat steady-state plasma concentrations in PAH patients by 27% without compromising the efficacy of the combination (see INDICATIONS and CLINICAL TRIALS, Treatment of Pulmonary Arterial Hypertension).*

Medicine	Brand	PI Date	Combination Therapy
			Pharmacodynamic Interactions – PDE-5 inhibitors *Riociguat and PDE-5-inhibitors are modulators of intra-cellular cGMP through different modes of action, but both act as vasodilators clinically. When cGMP is elevated by combining both principles, an additive effect on systemic blood pressure is anticipated (see CONTRAINDICATIONS).* *Preclinical studies in animal models showed additive systemic blood pressure lowering effect when riociguat was combined with either sildenafil or vardenafil. With increased doses, over additive effects on systemic blood pressure were observed in some cases.* *In some patients, concomitant use of these two medicine classes can lower blood pressure significantly leading to symptomatic hypotension (see CONTRAINDICATIONS).* *In an exploratory interaction study in 7 patients with PAH on stable sildenafil treatment (20 mg three times daily) and single doses of riociguat (0.5 mg and 1 mg sequentially) showed additive haemodynamic effects. Doses above 1 mg riociguat were not investigated in this study.* *A 12 week combination study in 18 patients with PAH on stable sildenafil treatment (20 mg three times daily) and riociguat (1.0 mg – 2.5 mg three times daily) compared to sildenafil alone was performed. In the long term extension part (non-controlled) the concomitant use of sildenafil and riociguat resulted in a high rate of discontinuation, predominately due to hypotension. There was no evidence of a favourable clinical effect of the combination in the population studied.* *Concomitant administration of ADEMPAS® with PDE-5-inhibitors (such as sildenafil, tadalafil, vardenafil) or non-specific PDE inhibitors (such as dypyridamole or theophylline) is contraindicated (see CONTRAINDICATIONS).*
Epoprostenol	Flolan®	3 February 2016	The PI contains no recommendations or warnings about use of epoprostenol with other PAH medicines. The only potentially relevant statement is in the PRECAUTIONS that *"The vasodilator effects of FLOLAN® may augment or be augmented by concomitant use of other vasodilators."*
Iloprost	Ventavis®	16 June 2017	*INTERACTIONS WITH OTHER MEDICINES* *Iloprost may increase the antihypertensive effect of vasodilating and antihypertensive agents. Caution is recommended in case of co-administration of VENTAVIS® with vasodilating or antihypertensive agents as dose adjustment might be required.* *DOSAGE AND ADMINISTRATION:* *Incompatibilities – In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.*

Source: Relevant product information

Table 1.21 PAH medicines – paediatric use instructions and warnings

Medicine	Brand	PI Version Date	Paediatric Use Instructions
Macitentan	Opsumit®	25 August 2016	*PRECAUTIONS: Paediatric population – The safety and efficacy of OPSUMIT® in children below the age of 12 years have not yet been established. There is no data available on the effects of macitentan on growth and development in paediatric patients. There is limited clinical experience in paediatric patients aged 12 and above.* *DOSAGE AND ADMINISTRATION: Dosage adjustment in paediatric population – There is limited clinical experience in paediatric patients aged 12 and above therefore caution is advised; the recommended dose is 10 mg once daily in patients aged 12 and above and with body weight > 40kg. The safety and efficacy of OPSUMIT® in children below the age of 12 years have not yet been established.*
Bosentan	Tracleer®	15 February 2016	*PRECAUTIONS: Paediatric Use – Various doses of TRACLEER® have been assessed in a clinical study in paediatric patients with PPH or PAH related to congenital systemic to pulmonary communications, either as monotherapy or combined with epoprostenol (see CLINICAL TRIALS). The results indicate that the doses used were effective and appropriate in terms of safety and pharmacokinetics (see DOSAGE AND ADMINISTRATION – Dosage Adjustment in Children).* *DOSAGE AND ADMINISTRATION: Dosage Adjustment in Children – There is limited experience with the use of TRACLEER® in children based on a pharmacokinetic study conducted in 19 children with PAH (see PHARMACOKINETICS and CLINICAL TRIALS). The pharmacokinetic findings showed that systemic exposure in children with PAH was lower than in adults with PAH. Although the number of patients studied in each dose group was generally insufficient to establish the optimal dosing regimen, the following doses are recommended in children aged 3 years and over:* *Body weight 10 to 20 kg: Starting dose (First 4 weeks) 31.25 mg ONCE daily; Maintenance dose (Week 5 onwards) 31.25 mg twice daily* *Body weight >20 to 40 kg: Starting dose (First 4 weeks) 31.25 mg twice daily; Maintenance dose (Week 5 onwards) 62.5 mg twice daily* *Body weight >40 kg: Starting dose (First 4 weeks) 62.5 mg twice daily; Maintenance dose (Week 5 onwards) 125 mg twice daily*
Ambrisentan	Volibris®	16 February 2016	*PRECAUTIONS: Children – Ambrisentan has not been studied in children. Refer to Dosage and Administration.* *DOSAGE AND ADMINISTRATION: Children – The safety and efficacy of VOLIBRIS® have not been established in patients less than 18 years of age, and therefore its use in this age group is not recommended.*
Sildenafil	Revatio®	21 December 2015	*PRECAUTIONS: Paediatric Use – REVATIO® is not indicated for use in children under 18 years of age.*

Medicine	Brand	PI Version Date	Paediatric Use Instructions
			DOSAGE AND ADMINISTRATION: Use in Children (<18 Years) – REVATIO® is not indicated for use in children <18 years of age.
Tadalafil	Adcirca®	18 December 2015	*DOSAGE AND ADMINISTRATION: Use in children and adolescents – ADCIRCA® should not be used in individuals below 18 years of age.*
Riociguat	Riociguat	17 March 2017	*PRECAUTIONS: Paediatric Use – The safety and efficacy of ADEMPAS® have not yet been studied in patients below 18 years. No data are available. Therefore, ADEMPAS® is not recommended in paediatrics.* *DOSAGE AND ADMINISTRATION: Paediatric Use – The safety and efficacy of ADEMPAS® have not yet been studied in patients below 18 years. No data are available. Therefore, ADEMPAS® is not recommended for use in paediatric patients.*
Iloprost	Ventavis®	16 June 2017	*PRECAUTIONS: Paediatric use – The experience in children and adolescents (patients below 18 years of age) is limited. Therefore VENTAVIS® is not recommended for use in this population (see DOSAGE AND ADMINISTRATION).* *DOSAGE AND ADMINISTRATION: Paediatric patients/ Children and adolescents (below 18 years of age) – The experience in children and adolescents (patients below 18 years of age) is limited. Therefore VENTAVIS® is not recommended for use in this population (see PRECAUTIONS).*
Epoprostenol	Flolan®	3 February 2016	*PRECAUTIONS: Paediatric Use – There is limited information on the use of FLOLAN® for PAH in children.* *DOSAGE AND ADMINISTRATION: Children – There is limited information on the use of FLOLAN® for PPH* in children.*
Selexipag	*Selexipag*	*14 July 2016*	*PRECAUTIONS: Paediatric – The safety and efficacy of UPTRAV®I in children (<18 years) has not been established.*

*PPH = primary pulmonary hypertension is an older term for PAH
Source: Relevant product information

Appendix 1.C Published treatment and diagnostic algorithms

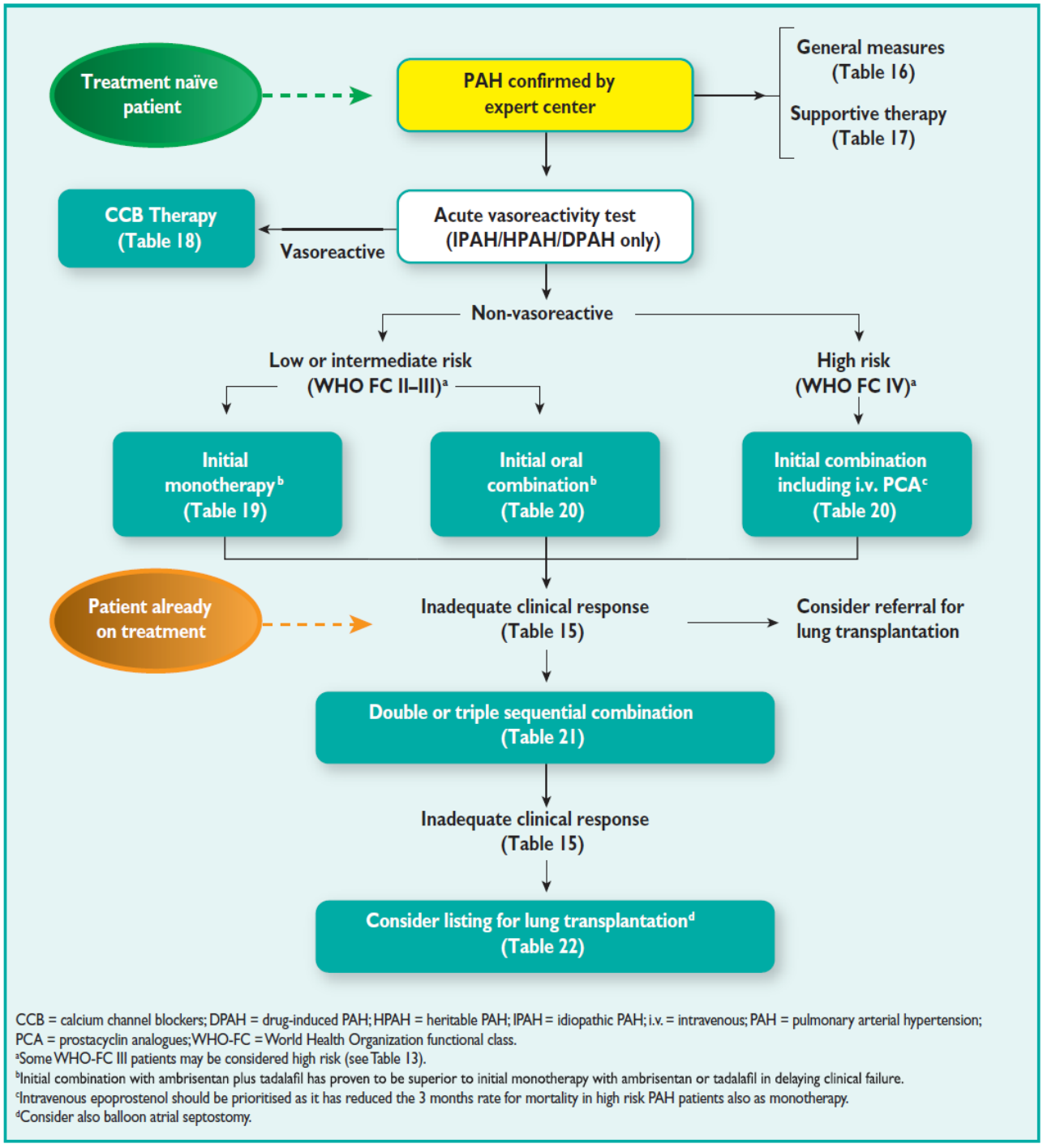


Figure 1.2 Treatment algorithm for PAH 2015 ESC/ERS Guidelines

Source: 2015 ESC/ERS Guidelines[8]

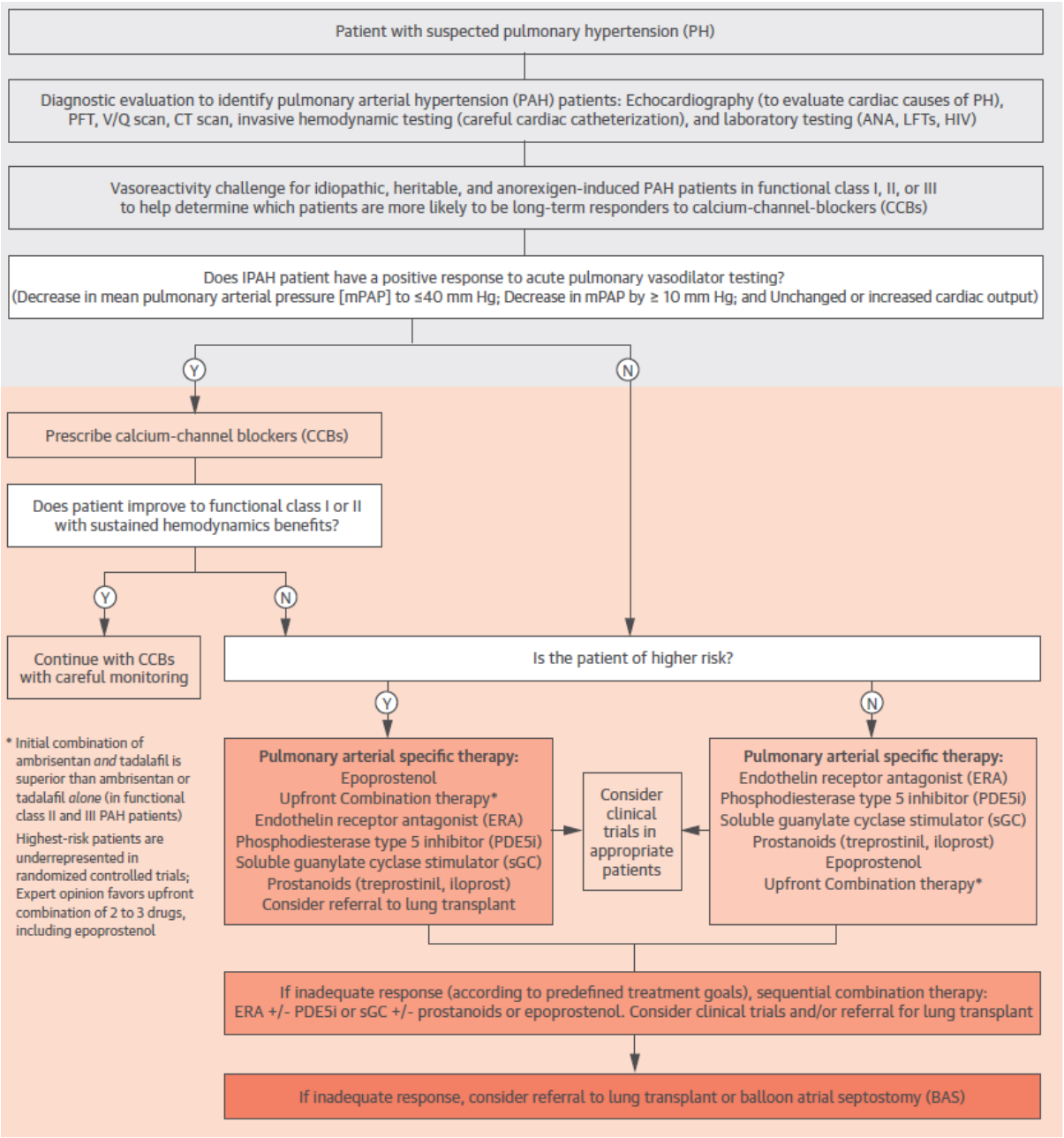
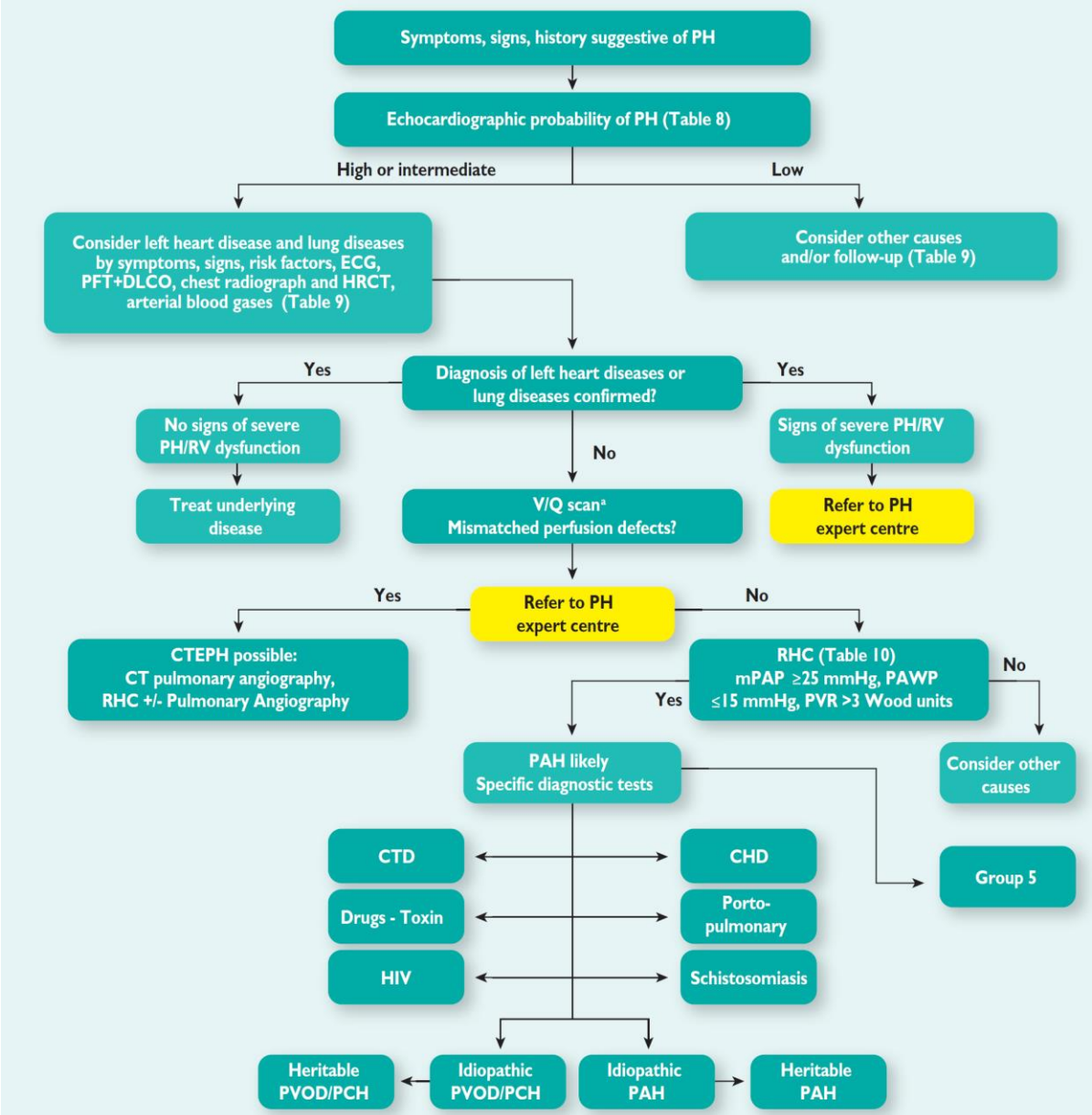


Figure 1.3 Treatment algorithm from McLaughlin et al (2015)

Source: McLaughlin *et al* 2015[29]



CHD = congenital heart diseases; CT = computed tomography; CTD = connective tissue disease; CTEPH = chronic thromboembolic pulmonary hypertension; DLCO = carbon monoxide diffusing capacity; ECG = electrocardiogram; HIV = Human immunodeficiency virus; HR-CT = high resolution CT; mPAP = mean pulmonary arterial pressure; PA = pulmonary angiography; PAH = pulmonary arterial hypertension; PAWP = pulmonary artery wedge pressure; PFT = pulmonary function tests; PH = pulmonary hypertension; PVOD/PCH = pulmonary veno-occlusive disease or pulmonary capillary hemangiomathosis; PVR = pulmonary vascular resistance; RHC = right heart catheterisation; RV = right ventricular; V/Q = ventilation/perfusion.

[a]CT pulmonary angiography alone may miss diagnosis of chronic thromboembolic pulmonary hypertension.

Figure 1.4 Diagnostic algorithm for PAH, 2015 ESC/ERS Guidelines

Source: ESC/European Guideline[8]

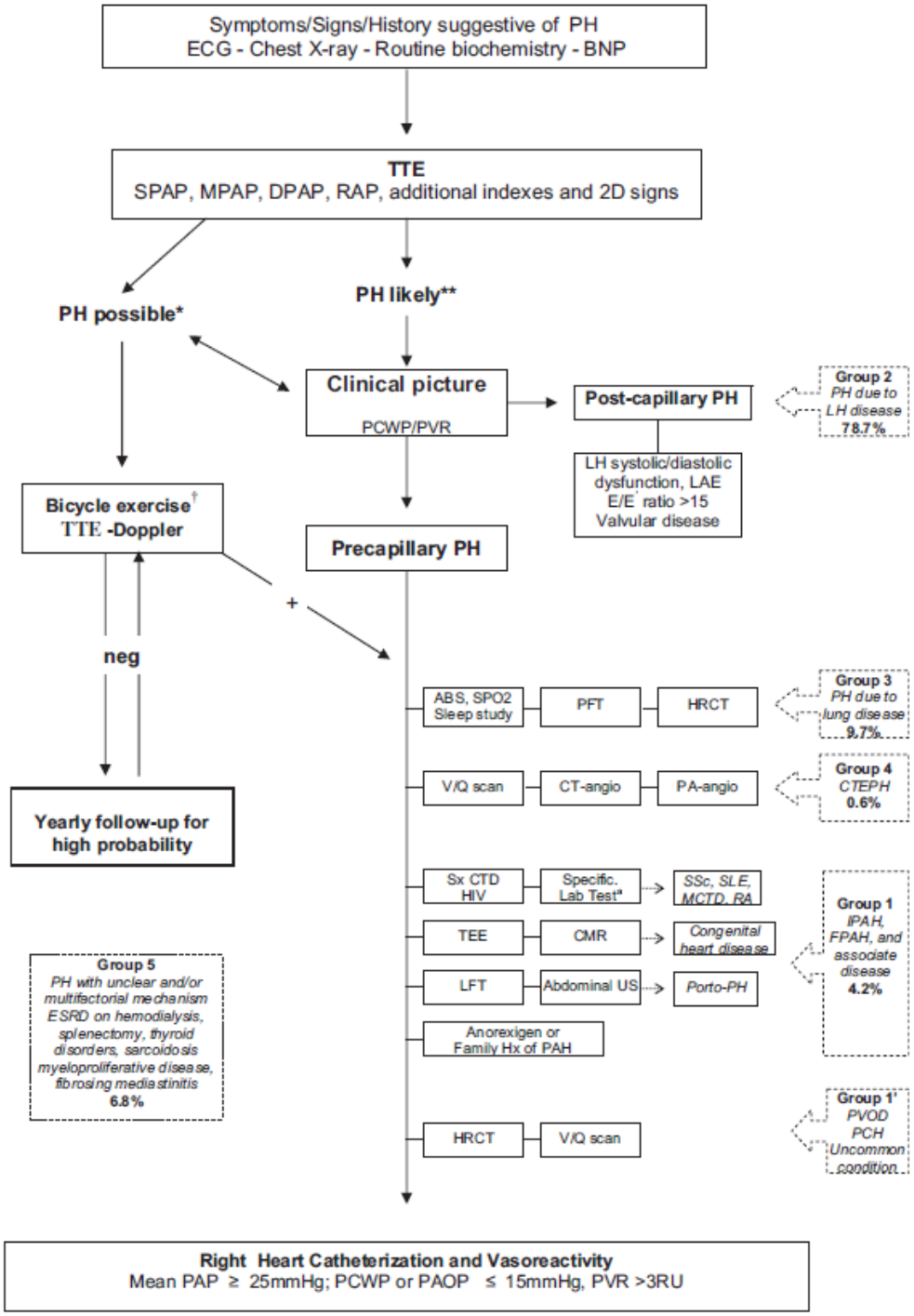


Figure 1.5 Diagnostic algorithm for PAH

Source: Bossone *et al* 2013[30]

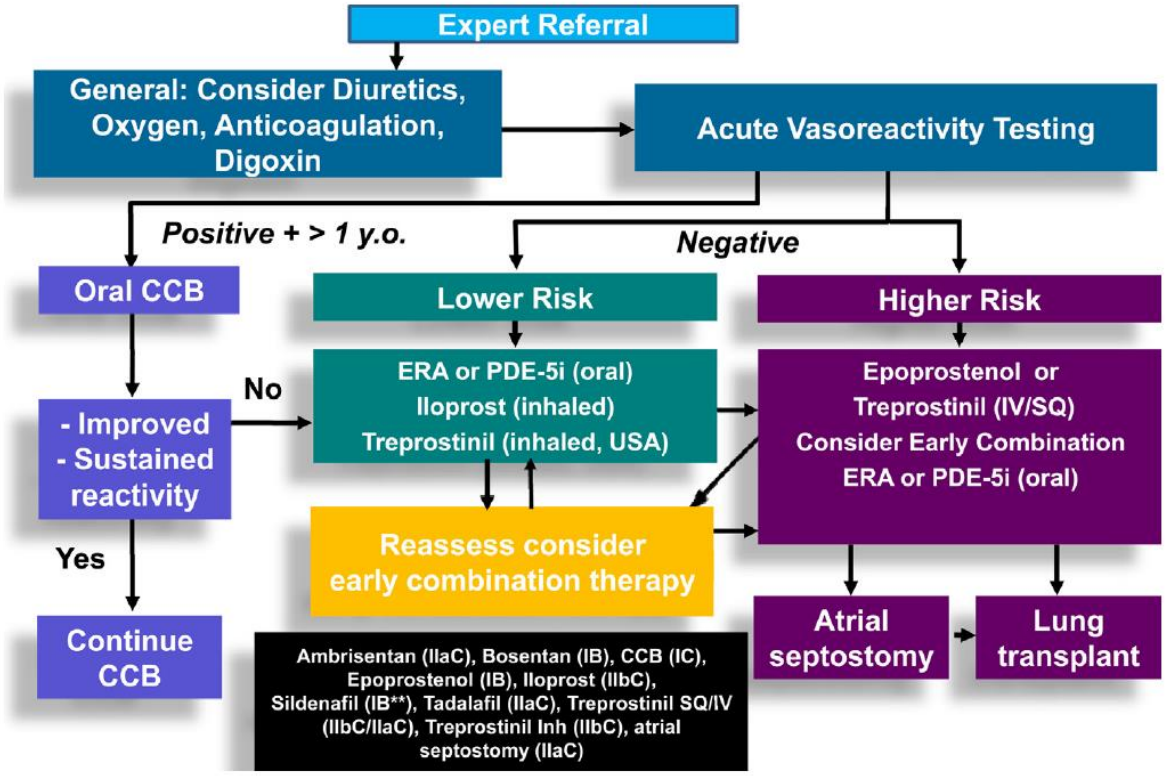


Figure 1.6 Treatment algorithm for Paediatric PAH (World Symposium)

Source: Ivy *et al* 2013[23]

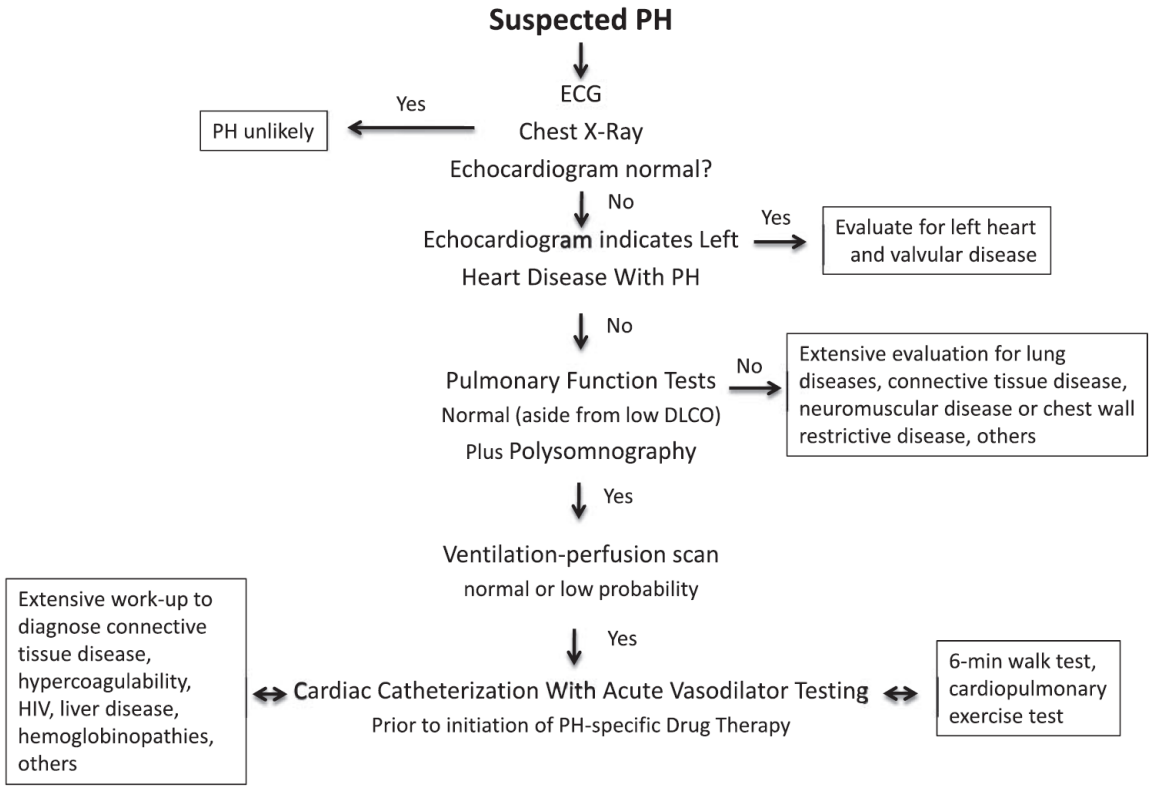


Figure 1.7 Diagnostic algorithm for Paediatric PAH

Source: Abman *et al* 2015[22]

Appendix 1.D Details of PAH restrictions

Table 1.22 Clinical criteria and prescribing instructions common to all PAH items

Current PBS Restriction	Comment
Clinical criterion ('initial 1'; 'initial 2'; also 'subsequent continuing'): Patient must have been assessed by a physician at a designated hospital Clinical criterion ('first continuing'): Patient must have been assessed by a physician from a designated hospital to have achieved a response to the PBS-subsidised initial course of treatment Note: Refer to the Department of Human Services website at www.humanservices.gov.au for a list of designated hospitals.	Unlike some other s100 HSD complex authority required drugs, the prescriber specialties are not explicit. However, given s100 HSD items are 'hospital only' listings, this excludes general practitioners. It is expected that respiratory physicians, cardiologists, some rheumatologists and a small number of paediatricians with expertise in heart conditions would need to be able to prescribe PAH medicines. A comparison of these centres against guideline criteria for numbers of PAH patients per year was not possible as these data were not available. Although not a clinical criterion for 'initial 3'; the definition of response required to previous therapy includes an assessment by a physician at a designated hospital. (Appears in all restrictions except balance of supply) https://www.humanservices.gov.au/organisations/health-professionals/enablers/pulmonary-arterial-hypertension-designated-centres (Appears in all restrictions except balance of supply)
Clinical criterion (all restrictions): The treatment must be the sole PBS-subsidised PAH agent for this condition.	Discussed in main body.
Prescribing instruction: The term 'PAH agents' refers to bosentan monohydrate, iloprost trometamol, epoprostenol sodium, sildenafil citrate, ambrisentan, tadalafil, macitentan, and riociguat.	This is a list of all drugs listed on the PBS for PAH – this did not include riociguat when it was only listed for chronic thromboembolic pulmonary hypertension (CTEPH). (Appears in all restrictions except balance of supply).
Prescribing Instruction: PAH agents are not PBS-subsidised for patients with pulmonary hypertension secondary to interstitial lung disease associated with connective tissue disease, where the total lung capacity is less than 70% of predicted.	This instruction appears in all restrictions, in all PAH items. Discussed in main body.

Source: www.pbs.gov.au

Table 1.23 PAH initial treatment: clinical criteria and prescribing instructions

Current PBS Restriction	Comment
Clinical criterion ('initial 1' and 'initial 2'): Patient must not have received prior PBS-subsidised treatment with a pulmonary arterial hypertension (PAH) agent	It is not clear which treatment circumstance is applicable for patients having failed the first PAH agent that need to switch to a different drug.
Clinical criterion ('initial 1' and 'initial 2'): *WHO Functional Class + PAH types – this criterion varies between PAH agents and individual restrictions.*	Terminology should reflect the most recent WHO classification – discussed in main text.
Clinical criterion ('initial 1'): Patient must have a mean right atrial pressure of 8 mmHg or less as measured by right heart catheterisation (RHC); OR Patient must have right ventricular function assessed by echocardiography (ECHO) where a RHC cannot be performed on clinical grounds Clinical criterion ('initial 2'): Patient must have WHO Functional Class III [PAH sub-type] and a mean right atrial pressure of greater than 8 mmHg, as measured by right heart catheterisation (RHC); OR Patient must have WHO Functional Class III [PAH sub-type] with right ventricular function assessed by echocardiography (ECHO) where a RHC cannot be performed on clinical grounds; OR Patient must have WHO Functional Class IV [PAH sub-type, including PAH-CHD]	Discussed in main text. The 'initial 1' and 'initial 2 criteria distinguish between patients who should first fail vasodilator treatment with CCBs and 'initial 2' patients who can commence PAH treatment without a trial. The PAH sub-type varies from one agent to the next.
Clinical criteria (initial 2/3 change or recommencement – prostanoids): Patient must have [PAH subtypes] and must wish to re-commence PBS-subsidised therapy with this agent after a break in therapy and must have demonstrated a response to their most recent course of PBS-subsidised treatment with this agent; OR Patient must have [PAH subtypes] and must have received prior treatment with a PBS-subsidised PAH agent other than this agent; OR Patient must have[PAH subtypes] and must have failed to respond to a prior PBS-subsidised PAH agent,	This wording appears in prostanoid restrictions. Prostanoid restrictions have an additional circumstance for change to a different PAH agent compared to the oral agents, that the patient must have failed prior PBS-subsidised treatment. This is intended to reflect the use in second line Class III patients.

Current PBS Restriction	Comment
Clinical criteria (initial 2/3 change or recommencement – oral agents): Patient must have [PAH subtypes] and must wish to re-commence PBS-subsidised therapy with this agent after a break in therapy and must have demonstrated a response to their most recent course of PBS-subsidised treatment with this agent; OR Patient must have [PAH subtypes] and whose most recent course of PBS-subsidised treatment was with a PAH agent other than this agent,	This wording appears in oral agents restrictions – no reference to treatment failure with prior PBS-subsidised agent (which is used in prostanoid restrictions to specify second line treatment for Class III patients).
Clinical criterion ('initial 1'): Patient must have failed to respond to 6 or more weeks of appropriate vasodilator treatment (*with CCBs*) unless intolerance or a contraindication to such treatment exists.	See main text. This is not a criterion for epoprostenol, but applies to iloprost and the oral PAH medicines.
Prescribing instruction ('initial 1'): Response to prior vasodilator treatment (*with CCBs*) is defined as follows: For patients with 2 or more baseline tests, response to treatment is defined as 2 or more tests demonstrating stability or improvement of disease, as assessed by a physician from a designated hospital. For patients with a RHC composite assessment alone at baseline, response to treatment is defined as a RHC result demonstrating stability or improvement of disease, as assessed by a physician from a designated hospital. For patients with an ECHO composite assessment alone at baseline, response to treatment is defined as an ECHO result demonstrating stability or improvement of disease, as assessed by a physician from a designated hospital. For patients aged less than 18 years, response to treatment is defined as at least one of the baseline tests demonstrating stability or improvement of disease, as assessed by a physician from a designated hospital.	These are the same tests as required for response to targeted PAH treatment. Discussed in main text. This appears for all PAH medicines that have a requirement for a trial of vasodilators with CCBs (i.e. all except epoprostenol)

Current PBS Restriction	Comment
Prescribing instructions ('initial 1'; 'initial 2'): [PAH sub-type] defined as follows: (i) mean pulmonary artery pressure (mPAP) greater than 25 mmHg at rest and pulmonary artery wedge pressure (PAWP) less than 15 mmHg; or (ii) where a right heart catheter (RHC) cannot be performed on clinical grounds, right ventricular systolic pressure (RVSP), assessed by echocardiography (ECHO), greater than 40 mmHg, with normal left ventricular function.	The same haemodynamic criteria apply regardless of the type of PAH under consideration. The RHC criterion i(i) s consistent with guidelines but it is unlikely that the echocardiographic criterion (ii) is current, as neither RVSP nor the similar value PASP are considered diagnostic of PAH nor do they represent best practice for identifying diagnostic features of PAH in the absence of RHC. The current guidelines recommend measurement of peak TRV as the key cardiographic variable predictive of PAH. In the absence of measureable TRV, clinical features suggestive of PAH are given in Table 1.9.
Prescribing instructions ('initial 1'): Test requirements to establish baseline for initiation of treatment are as follows: A right heart catheter (RHC) composite assessment An echocardiograph (ECHO) composite assessment, A 6 minute walk test (6MWT)	Discussed above in main body text.
Prescribing instructions ('initial 1'; 'initial 2'): Where it is not possible to perform all 3 tests above on clinical grounds, the following list outlines the preferred test combination, in descending order, for the purposes of initiation of PBS-subsidised treatment: (1) RHC plus ECHO composite assessments; (2) RHC composite assessment plus 6MWT; (3) RHC composite assessment only. In circumstances where a RHC cannot be performed on clinical grounds, applications may be submitted for consideration based on the results of the following test combinations, which are listed in descending order of preference: (1) ECHO composite assessment plus 6MWT; (2) ECHO composite assessment only. Where fewer than 3 tests are able to be performed on clinical grounds, a patient specific reason outlining why the particular test(s) could not be conducted must be provided with the authority application.	This is not consistent with current guidelines that recommend although RHC is the gold standard for diagnosis, transthoracic echocardiography is the key non-invasive test that establishes if PAH is likely and thus if RHC is indicated. Both are essential. On the other hand 6MWT is only one of many functional assessments that need to be performed at baseline but are not essential for diagnosis. Further discussion is above in main body text.

Current PBS Restriction	Comment
Prescribing instructions ('initial 1'): Details of prior vasodilator treatment (*with CCBs*), 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 (*with a CCB*) or where vasodilator treatment (*with CCBs*) 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.	Discussed in main body.
Prescribing Instruction ('initial 1'; 'initial 2''; 'initial 3'): Approvals for the first authority prescription will be limited to 1 month of therapy with the 62.5◦mg strength tablet, with the quantity approved based on the dosage recommendations in the Therapeutic Goods Administration (TGA) approved Product Information. No repeats will be authorised for this prescription. The second authority prescription may be written for either the 62.5 mg tablet or the 125 mg tablet strengths. Approvals for the second authority prescription will be limited to 1 month of treatment, with the quantity approved based on the dosage recommendations in the TGA-approved Product Information, and a maximum of 4 repeats. Note ('initial 1'; 'initial 2''; 'initial 3'): Where the 62.5 mg tablet strength is required for the second authority prescription, please contact the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday) for further advice. The approved second authority prescription will be returned to the prescriber by the Department of Human Services two weeks after the date of the approval of the first authority prescription, to allow for the uninterrupted completion of the six months initial treatment course. The Department of Human Services will contact prescribers prior to dispatch of the second authority prescription to confirm the tablet strength required for the patient.	Bosentan only, relates to initial and maintenance dosing phases.
Prescribing Instruction: The assessment of the patient's response to the initial 6 month course of treatment should be made following the preceding 5 months of treatment, in order to allow sufficient time for a response to be demonstrated.	See comments regarding timing of monitoring and follow-up assessments in main body text.

Current PBS Restriction	Comment
Prescribing instruction ('initial 1'; 'initial 2'; 'initial 3'; 'first continuing'): Patients who fail to demonstrate a response to PBS-subsidised treatment with this agent at the time where an assessment is required must cease PBS-subsidised therapy with this agent.	See main text.
Prescribing instruction ('initial 3'): Swapping between PAH agents: Patients can access PAH agents through the PBS according to the relevant restrictions. Once these patients are approved initial treatment with 1 of these 8 drugs, they may swap between PAH agents at any time without having to re-qualify for treatment with the alternate agent. This means that patients may commence treatment with the alternate agent, subject to that agent's restriction, irrespective of the severity of their disease at the time the application to swap therapy is submitted. It also means that no new baseline measurements will be necessary. New baselines may be submitted where the patient has failed to respond to their current treatment. Eligible patients may only swap between PAH agents if they have not failed prior PBS-subsidised treatment with that agent. For eligible patients, applications to swap between the 8 PAH agents must be made under the relevant initial treatment restriction. Patients should be assessed for response to the treatment they are ceasing at the time the application to swap therapy is being made. Patients who fail to demonstrate a response or for whom no assessment results are submitted with the application to swap therapy may not re-commence PBS-subsidised treatment with the drug they are ceasing. Note: Applications for patients who wish to swap to an alternate PAH agent should be accompanied by the previously approved authority prescription, or remaining repeats, for the treatment the patient is ceasing.	Swapping is intended for patients who have taken a break from treatment but were responding, or whose previous PAH treatment was with a different agent. The guidelines reviewed contain essentially no recommendations on switching.
Clinical criterion ('Initial 4' – Grandfathered patients) Patient must have previously received treatment with this drug for this condition prior to 1 February 2017 Clinical criterion ('Initial 4' – Grandfathered patients) Patient must be receiving treatment with this drug at the time of application	Grandfathered access for patients otherwise identical to 'initial 1'. Not considered in this review.

Current PBS Restriction	Comment
Clinical criterion ('Initial 5' – Grandfathered patients) Patient must have previously received treatment with this drug for this condition prior to 1 February 2017 Clinical criterion ('Initial 5' – Grandfathered patients) Patient must be receiving treatment with this drug at the time of application	Grandfathered access for patients otherwise identical to 'initial 2'. Not considered in this review.

Source: www.pbs.gov.au

Table 1.24 PAH continuing treatment: clinical criteria and prescribing instructions

Current PBS Restriction	Comment
Clinical criterion ('first continuing'): Patient must have received a PBS-subsidised initial course of treatment with this agent for this condition Clinical criterion ('subsequent continuing'): Patient must have received a PBS-subsidised treatment under First Continuing treatment with this agent for this condition; OR Patient must have previously received PBS-subsidised treatment under this criteria with this agent for this condition	—
Clinical criterion ('balance of supply'): Patient must have received insufficient therapy with this agent under the Initial 1 (new patients) restriction to complete a maximum of six months of treatment; OR Patient must have received insufficient therapy with this agent under the Initial 2 (new patients) restriction to complete a maximum of six months of treatment; OR Patient must have received insufficient therapy with this agent under the Initial 3 (change or re-commencement of therapy for all patients) restriction to complete a maximum of six months of treatment; OR Patient must have received insufficient therapy with this agent under the First Continuing treatment restriction to complete a maximum of six months of treatment,	As with all PBS items for treatment of chronic conditions, one script should provide one month's supply with repeats sufficient for a total of 6 months' treatment in total.
Clinical criterion ('balance of supply'): The treatment must provide no more than the balance of up to six months treatment available under one of the above restrictions.	As with all PBS items for treatment of chronic conditions, one script should provide one month's supply with repeats sufficient for a total of 6 months' treatment in total.

Current PBS Restriction	Comment
Prescribing instruction ('first continuing'): Test requirements to establish response to treatment for continuation of treatment are as follows: The following list outlines the preferred test combination, in descending order, for the purposes of continuation of PBS-subsidised treatment: (1) RHC plus ECHO composite assessments plus 6MWT; (2) RHC plus ECHO composite assessments; (3) RHC composite assessment plus 6MWT; (4) ECHO composite assessment plus 6MWT; (5) RHC composite assessment only; (6) ECHO composite assessment only.	This offers the possibility to skip RHC if ECHO and 6MWT are in hand and if all three tests were conducted at baseline. This is discussed above in the main body text.
The results of the same tests as conducted at baseline should be provided with the written First Continuing treatment application, except for patients who were able to undergo all 3 tests at baseline, and whose subsequent ECHO and 6MWT results demonstrate disease stability or improvement, in which case RHC can be omitted. In all other patients, where the same test(s) conducted at baseline cannot be performed for assessment of response on clinical grounds, a patient specific reason why the test(s) could not be conducted must be provided with the application.	
Prescribing instructions ('initial 2/3 change or recommencement'; 'first continuing): Response to a PAH agent is defined as follows: For patients with two or more baseline tests, response to treatment is defined as two or more tests demonstrating stability or improvement of disease, as assessed by a physician from a designated hospital. For patients with a RHC composite assessment alone at baseline, response to treatment is defined as a RHC result demonstrating stability or improvement of disease, as assessed by a physician from a designated hospital. For patients with an ECHO composite assessment alone at baseline, response to treatment is defined as an ECHO result demonstrating stability or improvement of disease, as assessed by a physician from a designated hospital.	Discussed in main text.

Current PBS Restriction	Comment
For patients aged less than 18 years, response to treatment is defined as at least one of the baseline tests demonstrating stability or improvement of disease, as assessed by a physician from a designated hospital.	This wording appears in all the change/recommencement and all the first continuing restrictions for PAH agents,
Prescribing instruction ('first continuing'; 'subsequent continuing'): The maximum quantity authorised will be limited to provide sufficient supply for 1 month of treatment, based on the dosage recommendations in the Therapeutic Goods Administration (TGA) approved Product Information. A maximum of 5 repeats will be authorised.	Discussed in main text.
Prescribing instruction ('first continuing'): An application for First Continuing treatment with a PAH agent should be made prior to the completion of the Initial 6 month treatment course to ensure continuity for those patients who respond to treatment, as assessed by the treating physician. Prescribing instruction ('subsequent continuing'): An application for Subsequent Continuing treatment with a PAH agents should be made prior to the completion of the First Continuing treatment course to ensure continuity of treatment.	—

Source: www.pbs.gov.au

Table 1.25 Administrative information in PAH items

Current PBS Restriction	Comment
Prescribing Instruction: Applications for authorisation must be in writing and must include: (1) two completed authority prescription forms; and (2) a completed Pulmonary Arterial Hypertension PBS Authority Application - Supporting Information form which includes results from the three tests below, where available: (i) RHC composite assessment; and (ii) ECHO composite assessment; and (iii) 6 Minute Walk Test (6MWT); and (3) a signed patient acknowledgement.	—
Prescribing Instruction: The test results provided must not be more than 2 months old at the time of application	—
Note ('initial 1'; 'initial 2'; 'initial 3'; 'first continuing'): Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001	Written applications are required for all initial treatment the first continuing treatment restrictions.

Current PBS Restriction	Comment
Note ('balance of supply'; 'subsequent continuing'): Applications for authorisation under this criterion may be made by telephone by contacting the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Written applications for authorisation under this criterion should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001	Telephone authority applications are only permitted for 'balance of supply' and 'subsequent continuing' restrictions.
Prescribing Instruction: A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria. Note: No applications for increased repeats will be authorised.	Riociguat grandfathered access items only. Not considered in this review.
Note: Special Pricing Arrangements apply.	Iloprost only.

Source: www.pbs.gov.au