Post-market Review of Pharmaceutical Benefits Scheme (PBS) listed medicines for pulmonary arterial hypertension (PAH)

Plain language summary

Background

Post-market reviews (PMRs) are routinely recommended by the Pharmaceutical Benefits Advisory Committee (PBAC). The role of a PMR is to understand how people currently use medicines for a particular disease or health matter compared to when the medicines were first listed on the Pharmaceutical Benefits Scheme (PBS).

Medicines are reviewed in the context of when and how they are used, and the Australian experience is compared to clinical guidelines and use in other countries. Input from expert technical advisers and consultation from consumers and healthcare professionals is part of the PMR process, so all aspects of usage are captured.

In July 2015 the Pharmaceutical Benefits Advisory Committee (PBAC) recommended to the Minister for Health that PMR be undertaken to assess the efficacy (treatment benefits) and cost-effectiveness of medicines for PAH. The PMR would include the existing PBS listings and consider where these might be extended to include other patients with PAH through comparison with international guidelines. International and Australian guidelines reference how severely the disease is experienced by patients through use of the PAH World Health Organization (WHO) Functional Class classification of symptoms (**Table 1**).

Table 1. PAH WHO Functional Class classification of symptoms

PAH WHO Functional Class*	Description of symptoms
1 (I)	No symptoms of PAH during physical activity or when at rest.
2 (II)	Symptoms occur during normal physical activity but not when at rest.
3 (III)	Symptoms occur during normal and minor physical activity but not when at rest.
4 (IV)	Symptoms occur with any physical activity and when at rest

*Functional Class 1, 2, 3 and 4 is referred to in international guidelines, and also the PBS criteria, using Roman Numerals (shown in brackets: I, II, III, IV). More information on the Classification of Pulmonary Hypertension can be found on the Pulmonary Hypertension Association of Australia (PHAA) website via the following link: PHA Australia - P Class (www.phaaustralia.com/page/74/p-class)

The Review

The overall aim of the PMR was to review the safety, treatment benefits, and cost-effectiveness of PBS-listed PAH medicines in the context of quality use of medicines and patient access to optimal treatment.

The PMR was conducted in accordance with the published PMR Framework. The opportunities for stakeholders to contribute to the PMR included:

(1) To provide submissions to address the PMR Terms of Reference and to comment on the draft Review Report.
(2) A consumer session held on 14 October 2017 attended by members of the Pulmonary Hypertension Association Australia.
(3) A stakeholder meeting held on 14 June 2019, attended by Reference Group members, medicine sponsors and clinicians to progress PBS restrictions for dual endothelin receptor antagonist (ERA) and phosphodiesterase type 5 inhibitor (PDE- 5i) medicine therapy at an acceptable price.

Table 2 notes the PBS medicines included in the PMR. Selexipag, first PBS-listed 1 February 2021, was not included in the PMR.

Table 2. PBS-listed PAH medicines included in the PMR*

Medicine Class	**PBS listed medicines generic drug name**
endothelin receptor antagonists (ERAs)	ambrisentan, bosentan monohydrate, macitentan
phosphodiesterase type 5 inhibitors (PDE-5i)	sildenafil citrate, tadalafil
prostanoids	epoprostenol sodium, iloprost trometamol
soluble guanylate cyclase stimulators (sGC stimulator)	riociguat

*The PBS listing criteria refer to either the medicine class (for example: ERA, PDE-5i, prostanoids or sGC stimulator) of the medicines generic name rather than its trade name) (for example: ambrisentan, rather than Volibris®

Outcomes

In November 2018, the Pharmaceutical Benefits Advisory Committee (PBAC) considered the Final Report for Post-market Review of Pulmonary Arterial Hypertension (PAH) medicines.

The PBAC November 2018 Outcome Statement and November 2018 Minutes detail the PBAC's consideration of the Review report and Review options.

The PBAC considered matters relating to its November 2018 recommendations at several meetings between March 2019 and March 2022.Access to further details from these meetings are available via the links in **Table 3.** The PBAC recommended changes to PBS restrictions for PAH medicines to improve patient access and align PBS restrictions more closely with clinical guidelines.

Table 3. PBAC meetings, outcomes, and minutes

PBAC meeting	**PBAC Outcomes**	**PBAC Minutes**
March 2019	March 2019 PBAC Outcomes	March 2019 PBAC Minutes
November 2019	November 2019 PBAC Outcomes	November 2019 PBAC Minutes

PBAC meeting	PBAC Outcomes	PBAC Minutes
September 2020	September 2020 PBAC Outcomes	September 2020 PBAC Minutes
March 2022	March 2022 PBAC Outcomes	March 2022 PBAC Minutes

Summary of Changes to PBS restrictions for medicines for PAH resulting from the PMR

A summary of the PBAC's recommended changes to the PBS restrictions for medicines specifically for PAH is shown in **Table 4 (page 4)**. All PBAC recommendations made under the PMR of PAH medicines have been implemented to the PBS.

What do these changes mean for consumers?

A summary of the updated (effective 1 December 2022) PBS-subsidised PAH medicines is shown in **Table 5 (page 5).** The table lists each medicine by WHO FC and therapy options and covers all changes made in response to the PMR findings.

Table 4. PBAC recommendations by meeting and date of implementation to the PBS*

PBAC Meeting	Recommendation	Date implemented to the PBS
March 2019 November 2019	Changes to PBS restriction for treatment with a single PAH medicine to better align with clinical guidelines: • the inclusion of additional PAH disease classifications • removal of the requirement to trial calcium channel blockers • strengthening the diagnostic role of right heart catherization.	1 May 2020
	Extension of access to PBS subsidised treatment with a single PAH medicine with an ERA or PDE-5i medicine for patients with PAH WHO FC II symptoms.	1 May 2020
November 2019 meeting	PBS subsidised access to treatment with more than one PAH medicine at the same time with ERAs and PDE-5 inhibitor medicines for patients with PAH with WHO FC III-IV symptoms.	1 October 2020
September 2020 meeting	Extend PBS subsidised access to treatment with a combination of epoprostenol (intravenous) or iloprost (inhaled) and sildenafil (or tadalafil at a comparable price) for patients with PAH, as initial treatment for patients with WHO FC IV symptoms and as a second treatment choice for patients with WHO FC III-symptoms.	1 March 2021
March 2022 meeting	Extend PBS subsidised access to treatment with a combination of epoprostenol (intravenous) or iloprost (inhaled) and ERA medicine, as the first treatment option for patients with WHO FC IV symptoms and as a second treatment choice for patients with WHO FC III symptoms.	1 December 2022
	Extend PBS subsidised access to treatment as a triple combination therapy with an ERA + epoprostenol (intravenous) or iloprost (inhaled) + PDE-5i for patients with PAH WHO FC IV symptoms.	1 December 2022

(PBS) Pharmaceutical Benefits Schedule, (PAH) pulmonary arterial hypertension, (WHO FC) World Health Organization Functional Class, (ERA) endothelin receptor antagonists, (PDE-5i) phosphodiesterase type 5 inhibitors. * Refer to Table 1 and Table 2 in this document for descriptions of PAH WHO Functional Class and PAH medicine class.

Note: Selexipag was PBS-listed 1 February 2021 for dual therapy and triple therapy in combination with an ERA or/and a PDE-5 inhibitor for patients with FC III or IV PAH symptoms.

Table 5. PBS listed PAH medicines by WHO Functional Class*

PAH medicines (all forms, strengths, listed brands)	**PAH Symptoms**	**Monotherapy** (Treatment with a single medicine)	**Dual Therapy** (Treatment with two medicines)	**Triple Therapy** (Treatment with three or more medicines)
Endothelin receptor antagonists (ERA)				
ambrisentan bosentan macitentan	WHO FC II	**√**	**×**	**×**
	WHO FC III	**√**	**√** with PDE-5i **√** with selexipag if PDE-5i contraindicated /intolerant **√** with prostanoid (Second line therapy)	**√** with PDE-5i + selexipag
	WHO FC IV	**√**	**√** with PDE-5i **√** with selexipag if PDE-5i contraindicated /intolerant **√** with prostanoid	**√** with PDE-5i + selexipag **√** with PDE-5i + prostanoid
Phosphodiesterase type 5 inhibitors (PDE-5i)				
sildenafil tadalafil	WHO FC II	**√**	**×**	**×**
	WHO FC III	**√**	**√** with ERA **√** with selexipag if ERA contraindicated /intolerant **√** with prostanoid (second line therapy)	**√** with ERA + selexipag
	WHO FC IV	**√**	**√** with ERA **√** with selexipag if ERA contraindicated /intolerant **√** with prostanoid	**√** with ERA + selexipag **√** with ERA + prostanoid
Soluble guanylate cyclase stimulators (sGC stimulator)				
riociguat	WHO FC II	**×**	**×**	**×**

PAH medicines (all forms, strengths, listed brands)	**PAH Symptoms**	**Monotherapy** (Treatment with a single medicine)	**Dual Therapy** (Treatment with two medicines)	**Triple Therapy** (Treatment with three or more medicines)
	WHO FC III	√	**×**	**×**
	WHO FC IV	√	**×**	**×**
Prostacyclin receptor agonist (oral)				
selexipag	WHO FC II	**×**	**×**	**×**
	WHO FC III	**×**	**√** with ERA if PDE-5i contraindicated /intolerant **√** with PDE-5i if ERA contraindicated /intolerant	**√** with ERA + PDE-5i
	WHO FC IV	**×**	**√** with ERA if PDE-5i contraindicated /intolerant **√** with PDE-5i if ERA contraindicated /intolerant	**√** with ERA + PDE-5i
Prostanoid (inhaled)				
iloprost	WHO FC II	**×**	**×**	**×**
	WHO FC III	**√** -Not for initial (first line) treatment use. Exception: initial (first line) treatment for drug and toxin induced PAH	**√** with ERA Not for initial (first line) treatment. Second treatment choice only **√** with PDE-5i Not for initial (first line) treatment. Second treatment choice only.	**×**
	WHO FC IV	**√**	**√** with ERA **√** with PDE-5i	**√** with ERA + PDE-5i
Prostanoid (intravenous)				
epoprostenol	WHO FC II	**×**	**×**	**×**
	WHO FC III	**√**	**√** with ERA	**×**

PAH medicines (all forms, strengths, listed brands)	**PAH Symptoms**	**Monotherapy** (Treatment with a single medicine)	**Dual Therapy** (Treatment with two medicines)	**Triple Therapy** (Treatment with three or more medicines)
		Not for initial (first line) treatment use. Second treatment choice only	Not for initial (first line) treatment. Second treatment choice only **√** with PDE-5i Not for initial (first line) treatment. Second treatment choice only	
	WHO FC IV	**√**	**√** with ERA **√** with PDE-5i	**√** with ERA + PDE-5i

ERA: endothelin receptor antagonist, PDE-5i: phosphodiesterase 5 inhibitor, sGC stimulator: soluble guanylate cyclase stimulator, WHO FC: World Health Organization Functional Class. * Refer to Table 1 and Table 2 in this document for descriptions of PAH WHO Functional Class and PAH medicine class.